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A Dissertation And Review Of Current Knowledge On Aspects Relating To The Use Of Remifentanil To Cover The Tunnelling Phase Of Ventriculoperitoneal Shunt Insertion In Paediatrics

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Chapter 1:

A Review Of The Clinical Condition "Hydrocephalus"

Contents Of This Chapter:

1. INTRODUCTION

Definition

Hydrocephalus is a hydrodynamic disorder of the cerebrospinal fluid that leads to an increase in the volume occupied by this fluid in the central nervous system.

Other conditions may mimic it, i.e. cerebral atrophy or focal destructive lesions, if a loss of cerebral tissue leaves vacant space that is passively filled with cerebrospinal fluid. These conditions are not the result of altered hydrodynamics and are thus excluded from the group.

Incidence

The worldwide incidence of hydrocephalus is unknown and varies according to the health care from country to country. Congenital hydrocephalus has a quoted incidence of three per one thousand live births.

Approximately one hundred thousand shunts are implanted per year in developed counties.

The incidence of hydrocephalus has a bimodal distribution curve, with one peak in infancy, related to the various forms of congenital malformations and another peak in adult years, mostly related to so-called normal pressure hydrocephalus. Adult hydrocephalus represents about forty percent of the total number of cases. In children the average revision rate for a valve is approximately twice that in adults. Thus an estimate of the number of new paediatric hydrocephalic patients treated each year is about twenty thousand worldwide. This figure is, happily, decreasing.

2. CEREBROSPINAL FLUID PHYSIOLOGY

Cerebrospinal fluid production

Eighty percent of cerebrospinal fluid is ultra-filtered and actively secreted by the choroid plexus into the ventricles at the level of the non-tight junction of the capillary endothelial wall (McComb 1983). The plexus is a very secure blood brain barrier. The fluid secretion rate is continuous and stable under normal conditions (twenty one millilitres per hour in adults and children). There are no specific data on neonates, but the plexus is relatively bigger in this age group (Welch 1975).

Other functions of the plexus include active transportation of solutes and purification processes. Chronic increases in intra-cranial pressure (as occurs in hydrocephalus) reduce cerebrospinal fluid formation and may cause atrophy of the plexus.

The other twenty per cent of cerebrospinal fluid is produced by the ependyma.

Cerebrospinal fluid flow

From its ventricular origin, cerebrospinal fluid flows in a bi-directional manner, that is, with both retrograde and anterograde direction. It is pulsatile and dependent on the cardiac pulsation and central nervous system displacement.

Cerebrospinal fluid resorption

The fluid is resorbed, passively, at the arachnoid villi in the venous sinuses, depending on pressure gradients between subarachnoid space and the sinus. There appears to be both a vacuolar transport system and some lymphatic drainage responsible for this process. The resorption rate is a linear function of pressure above a pressure threshold that is equal to the venous sinus pressure (approximately five centimetres of water in the supine adult). There is also some evidence for the potential role of the central canal of the spinal cord in children in this resorption process.

Intra-cranial Pressure

Intra-cranial pressure, defined as the cerebrospinal fluid hydrostatic pressure, results from the active secretion of cerebrospinal fluid and the resistances that oppose its flow and passive resorption in the venous system. It thus represents the equilibrium point where resorption equals secretion and is directly related to venous sinus pressure and passively follows its variations. This explains the postural changes noted. In the recumbent, resting child and adult, pressures are about twelve centimetres of water. In the newborn and during infancy, values are less and are quoted as starting at two to four centimetres of water in neonates (Welch 1980).

3. DIAGNOSIS

The clinical picture will depend on age of patient, the nature and degree of the underlying pathology and the speed of onset of the hydrodynamic disturbance and the associated neurological and endocrine disturbances.

Suspicion should be high in the presence of known associated conditions.

During infancy, an abnormally rapid head growth is the most common sign (Nellhaus 1968). It always occurs in hydrocephalus occurring before the age of two years, irrespective of the cause.

Macrocrania is another important sign and may be accompanied by features of raised intra-cranial pressure. In infants this includes a bulging anterior fontanelle, disjunction of the sutures, thin, shiny scalp with visible veins and the setting sun eye phenomenon.

Sixth and third nerve palsies may also be seen and carry the potential risk of amblyopia by disturbing binocular vision

Signs of acute intra-cranial hypertension are more frequent in older children with rigid skulls.

Chronic intra-cranial hypertension in addition may cause developmental delays, headaches, memory loss and behavioural changes. Later signs include motor disturbance and endocrine imbalances.

Differential diagnoses of hydrocephalus include: non-pathological big heads (familial macrocrania), normal rapid skull growth of the premature infant, chronic subdural causing intra-cranial hypertension.

Investigations:

Transfontaneller ultrasound examination across an open anterior fontanelle can visualise ventricular dilation, but cannot ascertain the cause (Bejar 1980).

Computerised tomogram (CT) scanning can illustrate the ventricular dilation, the topography and the concurrent dilation of the subarachnoid spaces (Albanese 1982). The total number of scans through the ocular globes should be limited to decrease the risk of cataract formation.

Magnetic Resonance Imaging (MRI) Scanning is the examination of choice. It provides greater morphological definition. It also allows a pathophysiological approach to understanding the underlying hydrodynamic disorder through analysis of the cerebrospinal fluid flow (cine-phase contrast studies).

Chronic intra-cranial pressure monitoring can also be done, non-invasively in infants, through the anterior fontanelle, or invasively in older children.

Other investigations occasionally of use include Doppler assessment of cerebral blood flow, lumbar puncture and angiography.

4. MANAGEMENT:

If the pathology manifests before closure of the cranial sutures, the condition presents with an increase in intra-cranial volume and treatment is semi-elective. When the sutures are closed, raised intra-cranial pressure may compromise cerebral perfusion and treatment is then urgent.

Management is still today guided by individual neurosurgical preference. The development of implantable shunt devices was a major breakthrough in treatment (Nulsen 1951) but has led to a whole new range of problems, i.e. the management of shunt complications (McLaurin 1982). This

has lead to commercial competition and a wide array of implantable devices. There is also a need for associated forms of treatment to complement the use of implantable devices.

Medical treatment to decrease cerebrospinal fluid volume:

Acetazolamide and frusemide decrease cerebrospinal fluid formation and isosorbide increases its resorption. These agents can be used as a temporary measure whilst awaiting either the insertion of a shunt or the resolution of the underlying pathology. They are ineffective in the long-term management of hydrocephalus and may induce metabolic complications.

External drainage of cerebrospinal fluid:

External drainage may be achieved by a ventricular catheter or by repeated cerebrospinal fluid taps performed with subcutaneous ventricular access. These are also temporary measures whilst awaiting the resolution of the underlying condition or the insertion of a shunt when sepsis has cleared. This treatment requires close observation and carries the risk of contamination.

These measures save a significant number of patients from a permanent shunt. They also allow time for clearing of clot or debris in patients who will receive a shunt.

Alternatives to shunting:

Alternatives exist mainly when there is an obstacle within the ventricles, including the outlet of the fourth (aqueductal stenosis, posterior fossa tumour, arachnoid cysts). These treatments should be considered first, even if they are less straightforward than simple shunt insertion.

Treatment of underlying cause is the best therapeutic strategy. Treatment of hypervitaminosis A, resection of a mass, correction of a malformation etc. A promising example is the use of thrombolytics in cases of post haemorrhagic hydrocephalus. Urokinase instilled into the ventricles appears to reduce the requirement for shunt placement (Hudgins 1994). Unfortunately normal fluid flow is not always established due to secondary alterations and multifactorial aetiology. Historically some patients were "shunted" prior to receiving "aetiological treatment" to control intra-cranial pressures pre-op, but this practice has been abandoned since the realisation that it induces shunt dependency in patients who would otherwise no longer be hydrocephalic.

Membrane fenestration is an alternative to treatment of the underlying cause. In cases of alteration of cerebrospinal fluid flow in the posterior fossa or aqueduct stenosis, this can establish an alternative route for flow toward the subarachnoid spaces (Hoffman 1981). This is usually performed endoscopically via a coronal burr-hole and perforations can be made by laser, coagulation, radiofrequency or balloon catheter techniques (Heilman 1991).

Shunts:

At present seventy five percent of cases of hydrocephalus require a shunt (DiRocco 1987), the other twenty five percent can be managed by other means. The aim is to establish a communication between the cerebrospinal fluid (ventricular or lumbar) and a drainage cavity (peritoneum, right atrium, pleura). The choice of cavities varies with each case, depending on age, aetiology and previous sepsis. The peritoneal cavity is the preferred drainage site in children, because it enables the implantation of an important length of drainage catheter to allow for growth and predisposes to less severe infectious complications than does the use of the right atrium.

The perfect shunt does not exist. Careful consideration and planning is necessary before committing a patient to a lifelong relationship with an imperfect device. Shunt selection is influenced both by attempts to prevent skin complications and by hydrodynamic requirements. Shunt selection is, in reality, remarkably anecdotal and may be driven by cost, personal experience, marketing techniques etc.

Numerous differing shunts exist, but they can be classified, from the hydrodynamic point of view, into two categories.

Shunts consist of proximal tubing, a valve system and distal tubing. Other components may be added. Components are made of silicone elastomer with barium impregnation, polycarbonate, polyethylene, polysulfone and various metals. Antibiotics may in the future be impregnated into the shunt matrix. A multicentre prospective trial is presently in progress in South Africa.

The proximal tube components may vary in size, stiffness, length and shape and tip characteristics (flanged or not).

The valve varies in location, profile, pressure-flow characteristics (pressure regulating, siphon resistive or flow regulating).

The distal tubing is coated. A pure platinum cured silicone outer wall seems less prone to promoting calcification than does barium-impregnated tubing. At least twenty-five centimetres has to be inserted to allow for growth and to allow for lengthening procedures without adverse sequelae.

The connections between elements vary in shape, mode of securing, size and material used. Reservoirs are rarely used today due to the risk of contamination.

Shunt characteristics, including configuration, hydrodynamic properties and material amount to a compromise between ease of insertion and risk of disconnection, risk of early or late obstruction, expense and ease and cost of manufacture.

The surgical technique influences the risk of contamination. Other factors include operating theatre "traffic", timing of surgery, number of procedures performed per day.

Post-operative care of patients with shunts:

High care nursing should be considered for all small babies or any with patient with problems. Special care should be given to prevention of skin problems leading to shunt contamination and avoidance of pressure over the valve system.

5. ANAESTHESIA FOR SHUNT INSERTION:

Ventriculoperitoneal shunt insertion involves the positioning of an inert, silicone drain from the lateral ventricle to the peritoneal cavity under general anaesthesia. There are three stages; the first two involve incisions over scalp and abdomen for drain placement and the third is to tunnel a conduit for the connecting catheter from the scalp incision to the abdomen. This runs subcutaneously and allows the flow of cerebrospinal fluid from ventricle to the peritoneal cavity where the cerebrospinal fluid is absorbed.

ANAESTHESIA

General goals for the anaesthetist

One of the fundamental principles of providing good anaesthetic care is that the Anaesthetist should attempt to maintain his patient's tissue metabolism in spite of the threat posed to this by both the underlying pathophysiology and the clinical interventions. In order to achieve this, a stable physiological environment is required; in particular, tissue perfusion, oxygenation, substrate supply, attenuation of the stress response and temperature control are basic goals.

It is well recognised that this clinical "Holy Grail" is not always possible, but with developing knowledge, improving techniques and the availability of new drugs with specific pharmacological profiles, the Anaesthetist is better placed to achieve these ends.

Specific goals in this scenario

Principles of good anaesthetic practice in this particular situation include peri-operative attention to any associated anomalies, anaesthesia for the small child, optimisation and maintenance of cerebral perfusion pressure, attenuation of the stress response to minimise autonomic, neuroendocrine, metabolic, catabolic and immunosuppressive sequelae, and finally rapid recovery with no respiratory depression or interference with neurological assessment post operatively.

Thus good anaesthetic care should include general anaesthesia, positive pressure ventilation, attention to cerebral perfusion, local anaesthesia to the scalp and abdominal sites and adequate analgesia to cover the subcutaneous tunnelling phase, without causing post-operative respiratory depression or delayed recovery.

Present day practice- room for improvement

Intra-operative pain management of the third, tunnelling, stage has, however, always been felt to be suboptimal. This is both because of a poor historical understanding of the nature of paediatric pain and because of a fear of the side effects of opioids in small children.

Whilst analgesia is provided by infiltration with local anaesthetic and vasoconstrictor for the scalp and abdominal sites, subcutaneous tunnelling, which is possibly the most painful part and is performed towards the end of the procedure (about twenty to thirty minutes in straightforward cases), is performed without specific analgesia, for fear of post operative respiratory depression and delayed recovery. This is especially critical in the presence of a potentially depressed level of consciousness due to intra-cranial pathology and in sick neonates with a poorly developed respiratory drive. The usual practice is to briefly increase the concentration of inspired volatile agent. This has the inherent problem, however, of being difficult to titrate to effect, because of exponential wash-in and wash-out curves of both anaesthetic circuit and patient. This means extreme difficulty with manipulating brain isoflurane levels to coincide with isolated events. It may thus lead to either inadequate cover and / or unacceptable cardiovascular depression and may therefore compromise cerebral perfusion in a patient whose cerebral perfusion pressure is already at risk.

It is also inherently inappropriate to use an anaesthetic agent when an analgesic is required.

Previous misconceptions about the nature of paediatric pain

Popular dogma in the not too distant past has suggested that neonates, infants and young children do not feel pain, as do adults; their responses were thought to be "decorticate in nature", with little associated stress response.

Aynsley-Green and Anand have both written that even small premature babies do have the neurophysiological and anatomical development to feel and respond to painful stimuli. Anand was the first to suggest that unattenuated pain and stress worsens outcome and that preventing pain and stress improves outcome.

There is now overwhelming evidence to show that all of the neurophysiological components required for pain perception begin to develop by the seventh week of gestation and are significantly developed by mid gestation in the human foetus (Fitzgerald) and are functionally active by the time that viable preterm birth occurs.

Fitzgerald & Gibson, in 1994, proposed that pain may be experienced by babies in a heightened fashion due to a lack of descending inhibition and because immature nociceptors are less specific, have lower thresholds and have larger receptive fields and because there is immature synaptic processing by small children and neonates.

A further point to make is that metabolic stability is that much harder to achieve in the newborn for many reasons. These include a greater surface area to volume ratio, necessitating greater heat production; a larger brain to body weight ratio, with increased obligatory glucose requirements; the need to maintain somatic growth; much smaller reserves of fat, carbohydrate and protein; the metabolic adaptation to extra-uterine life and enteral nutrition and the maturation of metabolic enzymes and the other chemical mechanisms controlling these systems.

Anand has succinctly and clearly stated that hormonal and metabolic changes are greater in magnitude and shorter in duration in term infants than in adults undergoing similar surgery. Immature enzyme activity and decreased lipid stores increase tissue breakdown in preterm infants post operatively.

Pain may also cause many other harmful pathophysiological changes. Endorphin release may cause changes in blood pressure and respiratory demands; thus energy expenditure may increase. Pain is also known to cause changes in regional blood flow, respiratory parameters and oxygenation.

In addition, unattenuated stress predisposes to catabolism and immunocompromise. Ward showed both depressed circulating concentrations of lymphocytes and impaired "in vitro" lymphocyte function in infants and children undergoing a stress response post operatively. Shunt infection being a common and serious complication of the procedure and is thought to usually involve

bacteria that infect intra-operatively (the association between poor control of the stress response and shunt infection is a theoretical one and very little work has been published specifically on this matter.)

Anand states that acute or chronic pain and stress in the preterm neonate may also be associated with a resulting prolonged period of hyperalgesia (also Andrews), with an increased incidence of early intraventricular haemorrhage, with ischaemic changes leading to periventricular leukomalacia and may in fact cause long term neurobehavioural and developmental sequelae. It may delay social milestones and feeding. Grunau suggests that long-term effects may include an increased incidence of non-specific somatic complaints later in life.

Overall, appropriate treatment of pain can be said to be essential for humanitarian reasons, for attenuation of the stress response with a reduction in incidence of all the autonomic, catabolic, hypermetabolic, endocrine and immunosuppressive sequelae. It is also essential for optimising neurophysiological development, for improvement in outcome by preventing organ failure and to decrease cost by allowing fewer complications, earlier mobilisation and earlier discharge.

In the case of shunt insertion in sick, young neurosurgical patients, intra-operative pain control is essential to provide a stable haemodynamic environment, thus minimising the risks of surges of blood pressure. Such uncontrolled surges in the context of immature cerebral autoregulation predispose to intraventricular haemorrhage with all the associated mortality and morbidity (Mullart, 1994)

The above, coupled with the knowledge that the response can indeed be modified by opioid administration (Anand, Lancet 1987) has caused general and widespread changes in practice and has promoted clinical and pharmaceutical interest and research. Anand and Hickey compared halothane and morphine with high dose sufentanil for anaesthesia and post-operative analgesia in neonatal cardiac surgery. They demonstrated that high dose opioids can virtually eliminate the stress response and may improve post-operative recovery in the critically ill infant.

Anand and McGrath in 1993 wrote the first edition of "Pain in Neonates". They stated that because of the huge improvements in the understanding of the basic sciences, they felt optimistic that "clinical management of pain associated with the care of newborns and young infants is at the threshold of dramatic change".

Huge improvements in understanding and scientific advances in the field of neonatal analgesia have, however, not been matched by changes in practice, which are only really just beginning to occur.

Bush and Harkins discuss the literature that summarises the previously held and inappropriate principles and practice of paediatric pain relief.

Dangers of providing inadequate analgesia in this particular case scenario

Thus the tunnelling phase of shunt insertion, if uncovered by adequate analgesia such as in present practice, may predispose to a sudden uncontrolled rise in blood pressure and because of immature cerebral autoregulation, intra-cranial pressure. This is in the setting of an already compromised cerebral perfusion pressure and can predispose the patient to intraventricular haemorrhage and cerebral ischaemia, as well as to the generalised effects of an unattenuated stress response, such as postoperative catabolism and immunocompromise. Mullart states that fluctuations in cerebral blood flow, cerebral blood volume and cerebral venous pressure appear to play a role in the development of intraventricular haemorrhage with potentially catastrophic consequences.

Measuring Pain and Stress the very young

In general terms, the very young have a different experience of and response to pain. Pain is subjective and young children are unable to communicate their experience of it. Thus methods for measuring both pain and the response to analgesics must be tailored to suit the different age groups. The criteria used for assessing pain in the very young can be classified as behavioural, physiological and biochemical.

In the awake baby, an assessment of behavioural responses can be used both clinically and for research purposes. These behavioural responses include facial expression, crying characteristics, motor responses, body position and sleep patterns. Unfortunately stress of any other origin, such as hunger, can also elicit these signs.

Many different pain measurement tools have been described and all vary in their reliability, validity, feasibility, sensitivity and specificity. The factors influencing the choice of tool used in any given situation include the patient gestational age, behavioural and disease state, the environment, the clinician and the attending nurse and whether it is for research or clinical use. Experienced paediatric nurses are better at using these tools than are trainees (Manne, 1992) and appropriate training is required to optimise their potential. Pain measurement tools and scores assign a numerical value to just one of seven described dimensions and are used with other markers of pain in the overall approach to pain assessment. Behavioural tools are obviously of no use in the unconscious anaesthetized patient, so in this scenario, use is made of physiological or biochemical markers.

Physiological signs of pain and stress include changes in cardiovascular parameters, respiratory rate, intracranial pressure, palmar sweating, oxygenation, vagal tone and skin colour. Researchers disagree, however, about which, if any, markers are the best to study pain and stress.

Lindh used neonatal heart rate and variability of rate to assess pain in a study to assess the efficacy of EMLA (eutectic mixture of local anaesthetic) for venepuncture and found significant changes in the untreated group.

Finke used heart rate, blood pressure and a behavioural analysis to assess post-operative pain. He concluded that post-operatively, at least, not only was it very difficult to attain a reliable and accurate cardiorespiratory assessment, but the parameters also correlated poorly with well-established behavioural scores.

These physiological changes also occur, to confuse the picture further, with other sources of stress, such as hunger or the need for handling.

Biochemical end-points that have been used to assess pain include changes in plasma cortisol, catecholamines, growth hormone, endorphin, insulin and glucose. These markers generally have limited use clinically because of the expense and logistics of such tests but they may be useful research tools to assess the efficacy of new analgesic or sedation regimes.

Duncan used plasma glucose, cortisol and adrenaline to assess the stress response in infants undergoing cardiac surgery and showed changes in these parameters that correlated well with physiological signs of stress. These changes were also shown to be attenuated with the use of high dose fentanyl. He showed that a balanced anaesthetic containing fentanyl twenty-five to fifty micrograms.kg-1 is sufficient to obtund haemodynamic responses to the pre-bypass phase of surgery. Higher doses of fentanyl (one hundred and one hundred and fifty micrograms. kg-1) offered little advantage over fifty micrograms.kg-1, and risked hypotension.

Okur showed that significant changes in plasma cortisol and growth hormone occur in neonates during the first forty-eight hours post-operatively.

Gunnar pointed out, however, that these changes in plasma cortisol are unreliable markers of stress, that marked changes in these levels can occur, without any evidence of stress occurring and in the absence of physiological markers of stress.

Protonotariou published an article suggesting that the inflammatory cytokines are valuable research tools for assessing perinatal stress and early infant immunodevelopment.

Hara suggested that plasma antioxidants and free fatty acids are good markers of neonatal oxidative stress

Quinn used changes in plasma catecholamine levels to assess stress in ventilated preterm infants. He found that certain modes of ventilation were associated with lower adrenaline levels and an improved outcome.
Peters reviewed the literature about the use of adrenocortical axis to assess stress in term and preterm babies. He remarked on the conflicting evidence about the reliability and validity of cortisol levels as an indicator.

Most of these biochemical markers, with the exception of the catecholamines, show a lag in their rise and fall following a painful event. Their time course is hours or days, thus their usefulness in the assessment of response to isolated moments of stress is limited. Catecholamines, however, rise and fall in seconds and have a half-life of about one minute. They may therefore be of more use in the assessment of responses to an acute painful stimulus such as subcutaneous intra-operative tunnelling. Such short half-lives mean, however, that great care is required in the method used to take and test blood samples. Important aspects of sampling and measuring catecholamines include the accurate timing of sample, the choice of an appropriate site for sampling, the immediate spinning down and separation of plasma and the immediate cooling and storage of the sample at -70° Celsius. Subsequent careful thawing and calibration of the liquid chromatogram is required, as is a skilled interpretation of the resulting chromatogram. Any flaw in the sampling, spinning, cooling, storage, thawing and testing of the catecholamines can lead to gross inaccuracies in the final analysis.

Dangers of opioids in small children

Postoperative drowsiness hinders early neurological assessment. In addition, postoperative respiratory depression may raise intra-cranial volume by causing hypercapnia or make artificial ventilation, with all its cerebrovascular sequelae, necessary. This is crucial in this situation where further disturbances in intra-cranial volumes and pressures (in those patients with closed cranial sutures and fontanelles) may cause critical decompensation and cerebral ischaemia.
There has also been an understandable, if excessive, fear of the use of opioids in small children in the past, because of other side effects such as addiction, tolerance, withdrawal and hypotension. Powerful analgesia in the form of an opioid will inevitably increase the risk of post operative respiratory depression as all currently manufactured opioids cause a dose dependant respiratory depression due to their effects on the “mu2” receptors (reclassified and renamed "OP3", since 1997) (Dhawan et al).

The neonate and infant are thought to be at greater risk of side effects for many different physiological and pharmacological reasons that will be discussed in chapter two. Premature babies, i.e. those born before thirty-five weeks of post conceptual age and "x-premies", i.e. babies of less than fifty-six weeks post conceptual age that were born prematurely, are even more at risk than term neonates.

Opiates have even greater potential to cause problems if any pre-operative depression of consciousness exists.

Most paediatric anaesthetists will use alternative means of analgesia wherever possible (local or field blocks), because of the high risk of respiratory depression that small children exhibit to opioid administration, but when opioids are necessary, post operative high care monitoring is provided. This is expensive and labour intensive as well.

Current recommendations for the use of "traditional" opioids in children and small babies vary between institutions, but generally include avoiding the use of fentanyl in infants less than one month of age and morphine in infants less than two months (Kart) unless post operative high care facilities are available for respiratory monitoring and support.

Most authorities have traditionally been more inclined to be guided by the post conceptual age, recommending post operative high care for all ex-preterm infants of up to fifty or even sixty weeks post conceptual age, that receive opioids. This age limit can increase further in the presence of other complicating factors. These postoperative facilities are expensive and in high demand.

All currently available opioid agonists have similar pharmacodynamic profiles, i.e. they cause a dose dependent respiratory depression. This respiratory depression can be minimised by careful consideration of drug, dose, dose interval, mode of administration, etc. given the patient's individual setting.

Remifentanil

Remifentanil is a new opioid with a totally different pharmacokinetic profile that may prove to be of use, during the tunnelling phase, to provide titratable analgesia without causing prolonged respiratory depression.

Remifentanil is a 4-anilidopiperidine derivative and is a selective “mu” receptor agonist with an analgesic potency similar to fentanyl and twenty to thirty times that of alfentanil (Glass). It does not significantly bind to non-opioid receptor groups.

Its pharmacology will be discussed fully in chapter three. The literature suggests that its closest rival, alfentanil, has several kinetic and dynamic differences that make it a less appropriate agent for analgesia of short duration in young children in this setting.

The purpose of the study is to assess the use of remifentanil in this context and to review the relevant literature.

6.OUTCOME of HYDROCEPHALUS

Historically the prognosis has been poor, with mortality rates up to eighty percent (Yashon 1965). Shunts and medical care have improved and today's figures are much better.

The prognosis today depends on the causative lesion rather than the hydrocephalus itself (Dennis 1981). The outlook for any one individual with hydrocephalus is quite variable and depends on a number of factors including the diagnostic category, age, associated abnormalities, complications and treatment (Boynton 1986).

The psychomimetric effects of hydrocephalus are poorly understood. The most commonly reported clinical finding is an uneven development of cognitive function, with verbal intelligence higher than non-verbal.

The "site of alteration" of the cerebrospinal fluid circulation has been reported to influence intellectual outcome and non-verbal intelligence.

Prenatal hydrocephalus has a poorer prognosis. Seventy percent have an Intelligence Quotient lower than eighty (Tardieu 1981).

The thickness of the cortical mantle, assessed pre-operatively, has been reported to correlate with prognosis (Young 1973).

Treatments have resulted in functional recovery, without a real understanding of anatomical correlation. Thus the goal of normalisation of radiological images is probably too simplistic to be accepted (Gruber 1983).

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Chapter 2

Opioids In Premies, Neonates, Infants And Children – Dangers and Differences to Adults

Summary Of This Chapter:

1. INTRODUCTION

During the last few decades it has become apparent that infants and children are very different from adults in their disposition to and response to drugs. Adult studies always precede studies on the young. These studies on children are then often slow or incomplete: ethical considerations and a lack of micromethods for drug analyses hinder detailed trials in small children. Developmental neurophysiological and neuroanatomical studies are only starting to understand basic concepts such as opioid receptor development.

Opioid analgesics are the gold standard for pain relief for neonates, infants and children as well as adults, although much may be achieved by the use of regional analgesic techniques. The young individual, however, appears to be even more at risk from the most serious side effect of opioids, respiratory depression.

2. OPIOID PHYSIOLOGY:

The opioid analgesics act on receptor sites and effector mechanisms usually acted on by a family of neurohormones known as the endogenous opioids. Here is a classification table of these endogenous opioids:

Precursor polypeptides	Endogenous opioids	
1. Proenkephalin A.....	Metenkephalin (Enkephalin group)	
2. Proopimelanocortin (POMC).....	gamma MSH	
	ACTH	
	beta LPH...	beta endorphin
	...	beta MSH
3. Prodynorphin.....	Dynorphin A (1-17).	Dynorphin A
		Dynorphin B
		Neoendorphin

Function of the endogenous opioid peptides:

These opioid peptides are widely distributed in the central nervous system. They are involved in many different, sometimes overlapping control systems including those modulating pain, affective behaviour, motor control, autonomic nervous system modulation and neuroendocrine function. They are also found in the adrenal medulla and in certain exocrine glands. It is now widely believed that in addition to the above peptides, morphine and codeine also occur naturally (Lambert).

Physiology of receptors

Receptors have traditionally been classified into Mu, Kappa and Delta types, all with subclasses, with differing selectivity profiles, pharmacological profiles and distributions in the body. Drugs acting on them may be "receptor- selective" at one dose but may affect additional receptors at higher doses. The receptors have, however, been renamed by the "IUPHAR", the International Union of Pharmacologists, as OP1 (delta), OP2 (kappa) and OP3 (mu) in 1997 (Dhawan).

The mu receptor is the most important receptor clinically. Both beta-endorphin and enkephalin have a very high affinity for the mu receptor and morphine may also be a natural ligand. The receptor can be irreversibly blocked by beta funaltrexamine. 'Mu1' receptors are located supraspinally and modulate analgesia, respiratory depression, mioisis, euphoria, dependence, drowsiness and gastrointestinal effects. 'Mu2' receptors are located spinally and modulate spinal analgesia, respiratory depression and gastrointestinal effects.

Kappa receptors can be subdivided into kappa 1, 2 and 3. Dynorphin A acts on kappa 1 receptors as a natural ligand. Kappa 1 receptor group subdivisions include both spinal (modulating analgesia) and supraspinal (modulating neuroendocrine function). Kappa 2 receptors have been proposed, but as yet remain unidentified and Kappa 3 receptors are supraspinal and modulate analgesia.

Kappa receptor activation may produce analgesia and dysphoria. It also causes less respiratory depression and less mioisis than mu receptor activation.

Encephalins act as the natural ligand of delta receptors, which may be spinal and supraspinal

Sigma receptors have been described. If they do exist, their actions are unclear as yet.

Structurally the receptor walls contain seven trans-membrane spanning regions, with intracellular loops connecting with inhibitory “G” proteins for signal processing. Extracellular loops contain unique ligand binding domains.

The receptor effector mechanism acts by three different intracellular processes. Firstly, activation of membrane or cytosolic enzyme systems including: adenylate cyclase (leading to decreased cyclic adenine monophosphate production), phospholipase A2 (leading to the production of 12

lipoxygenase metabolites) and neuronal nitric oxide synthetase (leading to increased nitric oxide synthesis). Secondly activation of receptor operated potassium channels and thirdly suppression of voltage gated calcium channels

The above cellular processes all then cause an increased depolarisation threshold for the neurone, a shorter duration of action potential and a reduced release of neurotransmitters (especially substance P and glutamate).

Stimulatory effects of opioids may be due to either disinhibition or second messenger release via the release of adenosine and dopamine (these processes involve adenyl cyclase, phosphinositide hydrolysis and calcium increases).

3. OPIOID PHARMACOLOGY

Opioids may be classified by four different classification systems. Firstly by mode of synthesis, i.e. synthetic, semi-synthetic or synthetic. Secondly by their chemical structure, i.e. morphinans, phenypiperidines, methadones, etc. Thirdly, by receptor activity, i.e. mu, delta, kappa. Fourthly by pharmacological action, i.e. agonist, antagonist or mixed actions.

Opioid Pharmacodynamics - (Mainly Mu Effects)

Opioid analgesia is selective in nature (i.e. the other sensory modalities remain intact); it has a psychological component and is best used for dull, visceral pain (it is less effective for bone pain, biliary pain or neuropathic pain).

Mu1 receptors involved in analgesia exist at many sites, i.e. the terminals of primary afferents where they may cause inhibition of neurotransmitter release (including substance P). Mu1 receptors are also involved with postsynaptic inhibition of substance P in interneurones. They exist in the dorsal horn, they cause inhibition of the spinothalamic tract output, they exist in the periaqueductal grey in the medulla, in the nucleus raphe magnus, the locus coeruleus, they can cause enhanced activity of descending bulbospinal pathways and are active in undefined other supraspinal sites.

Opioid euphoria is caused by the activation of dopaminergic neurones in the ventral tegmentum (kappa stimulation, however, inhibits the release of dopamine)

Opioid sedation is caused by the activation of the locus coeruleus.

Opioid respiratory depression (mu2) is due to a direct effect on the brainstem respiratory centre; it occurs early (maximum effect occurs between five to ten minutes post intravenous injection or thirty to ninety minutes post intramuscular injection); it can last up to five hours. It decreases respiratory rate more than tidal volume and is responsible for almost all opiate related deaths. It occurs faster with the more lipid soluble agents and characteristically, patients will breathe if instructed to ("Ondine's curse"). The hypoxic drive remains intact but there is a decreased carbon dioxide responsiveness (this is, however, less profound with kappa agonists or with certain mixed agonist or antagonists).

Opioid effects on the cardiovascular system are multiple. Orthostatic hypotension occurs due to an increase in venous pooling and to a decrease in the systemic vascular resistance and to an inhibition of the baroreceptor reflex with a centrally mediated sympatholysis (via the paraventricular nucleus of the hypothalamus). This effect occurs less with fentanyl and sufentanil. It is also mediated by histamine release. In addition, vagotonia is mediated via opioid receptors in the vagal nucleii. Deceased oxygen consumption, left ventricular end diastolic pressure and cardiac work result from the above. Cerebral circulation is indirectly affected by an increase in arterial carbon dioxide.

Neuroendocrine effects are due to actions on the hypothalamus. These include a resetting of the central thermostat (which may lead to a decreased core temperature) and an inhibition of the release of gonadotrophin releasing hormone, corticotrophin release factor, etc. It also includes an increase in prolactin secretion and finally kappa agonists inhibit antidiuretic hormone.

Ocular effects include miosis. This is caused by both mu and kappa effects, via excitation of the parasympathetic nervous system. It is subject to tolerance and is associated with an increased accommodative power and a decreased intraocular pressure.

Excitatory effects by opioids on the central nervous system effects include convulsions. This may be caused by an inhibition of gamma amino butyric acid, causing excitation of hippocampal pyramidal cells. It may be reversed by naloxone.

Cough suppression is caused by a direct effect on the medullary cough centre and is unrelated to opioid respiratory depressant effects.

Opioids have an effect on the gastrointestinal system. Nausea and vomiting are caused by a direct stimulation of the chemoreceptor trigger zone. It is uncommon in the recumbent patient, but occurs in up to forty percent of ambulatory patients (fifteen percent actually vomit). Other gastrointestinal effects include achlorhydria, decreased gastric motility, increased antral tone, prolonged small bowel transit with decreased small bowel secretions, delayed absorption, increased resting intramural and intraluminal tone, periodic spasms, an increased amplitude of non - propulsive spasms and an increased absorption of water, with drying of faeces. Increased anal

sphincter tone, a decreased reflex relaxation and an inattention to normal sensory stimuli can lead to constipation.

Opioid related contraction of sphincter of Oddi can cause an increased pressure in the common bile duct for between fifteen minutes and two hours. Either trinitrate or naloxone can reverse this.

Opioids may cause tone and amplitude of ureteric contractions to increase. This may be overridden, however, by opioid effects on anti diuretic hormone).

Opioids may cause inhibition of the bladder voiding reflex, an increase of external sphincter tone and an increase in bladder volume.

Opioids may decrease the tone and frequency of contractions of the uterus.

Opioids may cause dilation of cutaneous vessels (especially in the upper body), sweating, pruritus and urticaria.

Opioids may cause inhibition of lymphocyte rosette formation. Beta-endorphin effects may be chemotactic; they may increase precursor cells and may increase the cytotoxic activity of monocytes. Certain immune cells produce "pro-opio melanocortin" and pro-enkephalin. The possibility of a new "epsilon" receptor responsible for these immunological phenomena has been postulated.

Opioid induced muscular rigidity is thought to be due to activation of spinal pathways.

Tolerance to the effects of opioids can be classified as: innate (genetic), pharmacokinetic (changes in distribution or metabolism), pharmacodynamic (receptor density changes) or learned (behavioural). All opioids, it is said, can be discontinued without withdrawal, given an appropriate weaning programme. Proposed mechanisms for the development of tolerance are an increased coupling of opioid receptors to stimulatory G proteins (Gs), an activation of "NMDA" receptors via protein kinase C and calmodulin dependant increases of cytosolic calcium. NMDA agonists and inhibitors prevent development of tolerance to morphine; glutamate, glycine and nitric oxide appear to be involved in this process. Tolerance does not involve the same pathways as pain; thus there is the potential for development of new agents that cause analgesia without inducing tolerance. Tolerance, physical dependence and the potential for withdrawal syndromes are closely linked. Norton wrote that in neonates withdrawal is called the " opioid abstinence syndrome" and is characterised by irritability, restlessness, insomnia, muscle twitches, and movement disorders.

Opioid Pharmacokinetics

Opioids may be readily absorbed through gastrointestinal tract (including the rectum); lipid soluble agents are readily absorbed nasally, buccally and transdermally. First pass metabolism is responsible for a significantly decreased bioavailability of orally administered opioid. Opioids are also absorbed subcutaneously and intramuscularly.

Distribution has been described by a bi-exponential function composed of a rapid initial distribution phase followed by a more slow elimination phase. However some authors suggest a tri-exponential model. Morphine is one-third protein bound. There is a decreased volume of distribution in the elderly. Tissue concentration of morphine is low twenty-four hours post administration. Blood brain barrier passage depends on lipid solubility. Epidural administration may cause twelve to twenty four hours of analgesia (rostral spread of opioid in the cerebrospinal fluid can lead to respiratory depression. This is less of a feature with lipid soluble agents).

The main metabolic product from liver metabolism is morphine 6 glucuronide ("M6G" is twice as potent as morphine systemically and one hundred times as potent spinally). The elimination half-life of morphine is two hours (morphine 6 glucuronide's half-life is longer). Morphine 3 glucuronide is an intermediate, inactive product and sulphation of morphine also occurs to a limited extent, possibly more so in children.

Morphine is excreted by the kidney, as "morphine 6 glucuronide".

4. OTHER RECENT DEVELOPMENTS IN THE LITERATURE:

Opioids have been much discussed in the literature recently. Quite apart from reviews of remifentanil's pharmacology and predictions of its clinical applications, several other issues related to opioids have been published.

In 1992, Evans reported the possible existence of the delta receptor.

The evidence for the existence of mu receptor subtypes mu1 and mu2 has been through pharmacological studies (mu1 modulating analgesia and mu2 respiratory depression). This theory is not as yet supported by any cloning studies. Thus the possibility of a mechanism such as "post receptor translation" of the two sub functions has recently been postulated (Lambert 1998).

Standifer, using antisense oligonucleotide technology, proposed the existence of a morphine 6 glucuronide receptor.

Henderson has identified a new receptor - transmitter system, the "orphan opioid receptor / orpanin fq", which, it is proposed, is bound by the endogenous peptide nociceptin. It is not bound by conventional opioids; nocistatin may reverse its effects. It has a fifty percent homology to other opioid receptors. It is called "ORL1" (opioid receptor like) and it mediates analgesia and other opioid effects (Darland).

Zadina and Hackler discovered the endomorphin peptides 1 and 2 in 1997. It appears that they possess a similar mode of action to the other opioids (calcium entry, cAMP (cyclic adenosine monophosphate) effects) and their clinical significance is presently being investigated.

Research has produced new drugs such as the plasma esterase metabolised remifentanil (see Chapter 3) and the peripherally acting opioid antagonists such as methylnaltrexone (Foss).

Novel routes of opioid administration have been much written about. Intranasal administration can be used for lipid soluble agents, which are well absorbed by this route. It has the advantage of avoiding first pass metabolism First pass metabolism is the metabolism of enterally administered substances by the liver before their release into the systemic circulation and can account for a significantly decreased bioavailability of that substance at it's target site. Formulations include powdered, dissolved and aerosol forms. Uses include premedication, postoperative analgesia and trauma unit analgesia. It is as effective as intravenous administration for severe postoperative pain but side effects include a bitter taste and nasal irritation. It is thought, however, not to be as satisfactory a mode of administration as patient controlled analgesia. Inhalational administration may stimulate opioid receptors in the lung. It is thought to decrease the sense of dyspnoea in chronic obstructive pulmonary disease and is good for palliative care. Side effects include a bitter taste, nasal pruritis and there may be significant individual variability in absorption. The electrical encouragement of transdermal absorption is termed iontophoresis. After deposition of drug at the electrode of the same charge a current then promotes passage to superficial and deep tissues. The passage across the skin depends on drug, the electrode and the current characteristics. Fentanyl has been administered by this route. It is a faster and more controllable mode than transdermal alone but it requires equipment and supervision. Peripheral opioid receptors respond to intra-articularly administered opioid and this may be put to use post-arthroscopy.

5. EFFECTS OF DISEASE STATES ON MORPHINE ACTIONS

The pharmacology of opioids may be influenced by the clinical state of the child; severe illness may influence the pattern of opioid receptors and also their affinity for morphine.

In renal failure, morphine 6 glucuronide accumulates leading to prolonged action.

In head injury, additional increased intracranial pressure due to hypercarbia may exacerbate the problem by causing an increased intracerebral blood volume. Neurological observations may also be misleading due to sedation and miosis.

In asthma, cough reflexes may be inhibited, secretions dried, histamine released and respiratory depression may occur.

In hypovolaemia and shock states, hypotension may occur due to the multiple cardiovascular effects, as outlined above.

Interactions with other drugs may occur, i.e. phenothiazines, monoamine oxidase inhibitors, tricyclics, (additive depressant effect, hypotension, respiratory depression) and amphetamines (euphoria, analgesia).

In liver disease, the effects of the drug may be increased due to underlying changes in liver blood flow, enzyme activity and protein binding. Cirrhosis itself involves cardiovascular changes such as arteriovenous shunts, plasma volume increases, cardiac output increases, peripheral pooling of blood and nutritional changes such as hypoalbuminaemia. Hepatitis by itself causes enzyme activity changes.

6. THERAPEUTIC USES OF OPIOIDS

Opioids main clinical use is for analgesia. It is particularly suited for the relief of moderate to severe, visceral pain

Sub-analgesic doses of opioids can be used for cough suppression.

Opioid effects on gastrointestinal secretions and motility mean that they are useful for the management of diaorrhea, problematic ileostomy drainage and dysentery.

Opioid's effects on the systemic vascular resistance, the venous tone, oxygen consumption and psychological affect make it useful in the management of left ventricular failure

Opioid's dampening of systemic responses to pain, together with the cardiovascular stability associated with their administration makes them a useful agent for anaesthesia.

7. PHARMACOLOGY OF MORPHINE IN THE VERY YOUNG

Kinetics

Studies suggest that a large interindividual variability exists, up to ten-fold (Chay and Duffy) in the kinetics of morphine in neonates.

Oral absorption is dependent on the gastric pH and the gastric emptying time. At birth the gastric pH is neutral because of the presence of alkaline amniotic fluids. At day 1 it falls to a pH of 1-3, but this is poorly maintained, until 3 years of age, when the gastric mucosa and the acid producing mechanisms mature. This means that both acid labile and acidic drugs are absorbed more and alkaline drugs absorbed less in the small infant. Gastric emptying is "slow and linear" in infants less than six months of age, compared to "fast and exponential" in the adult.
Intramuscular absorption of drug is less predictable in neonates due to vasomotor instability, a smaller muscular mass, less subcutaneous fat and a higher proportion of body water than adults.
Transdermal absorption depends on the epidermal stratum corneum thickness and the state of skin hydration. These factors cause transdermal absorption of opioids to be unpredictable in small infants.

The distribution of opioid administered to the newborn varies to that seen in the adult or older child. Protein binding is lower, due to lower albumen and alpha 1 glycoprotein levels, lower affinity of foetal albumen for drugs and competition for binding sites (i.e. by bilirubin). About eighty percent of the drug is unbound to plasma proteins. Body water is seventy five percent of neonatal body weight, versus sixty percent in the adult, with a larger extracellular component (forty versus twenty percent). There is less fat (fifteen versus twenty percent) and less muscle (twenty five percent) than in the adult. Thus drug volumes of distribution tend to be higher in the neonate. Greene suggests that the cerebrospinal fluid morphine concentration is approximately equivalent to the concentration of unbound morphine in plasma. This may cause a significant increase in the "free" morphine that is then able to penetrate the brain. This may explain the observation made by Way of increased brain levels of morphine in the newborn and morphine's more profound respiratory depressant effects. Glare, however, feels that this may be of limited clinical significance, as the percentage protein binding in preterm, term neonates and infants (twenty percent) may not be much different to adults (twenty to thirty five percent) that discrepancies in free morphine plasma concentration is too small, given the individual variation in morphine kinetics. Gulati showed that the cerebrospinal fluid to plasma ratio of morphine is

substantially higher in preterm infants than full term babies. This probably reflects immaturity of the blood brain barrier.

The neonatal brain's blood supply represents approximately thirty four percent of the cardiac output, compared with only fifteen percent for the adult brain, thus a greater proportion of systemically administered opioid will be rapidly delivered to the neonatal brain. There is evidence of an increased choroid plexus relative size and an increased choroidal delivery of and transport of opioids into the fourth ventricle and associated respiratory centre (immature blood brain barrier).

Hepatic metabolism is present but much less developed and slower in the neonate. In addition to the decreased enzymatic activity, the neonatal liver blood flow is reduced, further decreasing metabolism. Phase 1 and phase 2 reactions show differing maturation profiles. Many of the metabolic reactions are catalysed in the liver by microsomal mixed function oxidases that require the cytochrome P450 system, nicotinamide adenine dinucleotide (NADPH) and oxygen. The cytochrome system is very immature at birth and does not reach adult levels until the first month or two of life. However, the P450 system can be induced by various drugs and substrates and matures even in babies of very low gestational age. Pharmacokinetic data from different studies varies somewhat but is consistent in its demonstration of changes with age. Koren found that the half-life of morphine in neonates was fourteen hours and terminal half-life was twenty-five hours. The corresponding values in older children and adults are two hours only for both half-lives. Lynn, however, found morphine elimination half-life values of seven hours in the neonate and four hours in older infants. Clearance values were calculated at six and twenty four ml / min / kg respectively. These findings are consistent with immaturity of hepatic conjugation of morphine in the newborn. Higher plasma and tissue opioid concentrations thus result in the newborn for a given dose or infusion rate, so particular care is required with their clinical use.

Metabolism is even less developed in the premature baby. Kart states that the majority of preterm neonates are capable of glucuronidating morphine and that birth weight, gestational and postnatal ages influence the glucuronidation capability. He states that the volume of distribution is unrelated to age at 2.8 l / kg at all ages, but that half-life and clearance are age-dependant. Bhat et al showed that preterm neonates have longer elimination half-lives than older neonates (ten versus 6.7 hours) and have a delayed clearance of morphine (3.4 vs. 15.5ml / kg / hr). Barret states that half-life is dependent on gestational age; whereas Lynn feels postnatal age is the more relevant and determines how premature and full term infants metabolise drugs. Differing ideas exist on the age at which infant metabolism approaches that of adults, opinions varying from two to six months after birth.

As an additional explanation for this increased half-life, some studies suggest that premature neonates may be able to conjugate morphine to morphine 3 glucuronide more easily than to morphine 6 glucuronide, whereas term babies can do both as readily. The prolonged action of a single dose of morphine in the neonate is probably explained purely on its limited metabolic capacity, rather than the production of high levels of active metabolite (M6G / Morphine ratios are lower in neonates than in older children). This lower metabolic capacity thus leads to a lower elimination rate. Other studies, however, contradict this and state that the ratio of M6G / M3G increases with decreasing birth weight, indicating that the formation of M6G, the active analgesic metabolite, increases with decreasing birth weight (McRorie). Another feature peculiar to premature babies is their use of sulphation as an alternative metabolic pathway. This route subsequently diminishes later in life. A further consideration is that neonates may also perform desulphation and deglucuronidation processes faster than the sulphation and glucuronidation processes themselves. Also, glucuronidation may occur in the neonatal intestine or kidney.

Terminal elimination half-lives may be much longer in all groups (up to twenty five hours in older children) due to both redistribution from the peripheral tissue to the plasma and the enterohepatic circulation. When morphine is continuously infused, plasma concentrations are three times greater and elimination half-lives seven times longer in neonates than older patients. In addition, enterohepatic circulation may cause a further rise in plasma levels even after the infusion has been stopped.

The preterm infant has fewer glomeruli than the term neonate, who has "adult" numbers. At birth, the glomerular filtration rate and the tubular secretion processes are reduced. Maturation processes are complex and take six to twelve months for various renal functions to reach adult values. It seems that renal excretion of unchanged morphine occurs more in neonates than in adults (fifteen versus ten percent). As renal function develops rapidly during the first few days of life, postnatal age may be the important factor determining the excretion of unchanged morphine and metabolites.

It is clear that some neonates even from the age of two weeks have a morphine half-life resembling adult morphine half-life, while others do not reach adult values before the age of two months. Other studies have found that clearance reaches adult values of twenty ml / min / kg also by the age of two months. Hence it seems reasonable, states Kart, to assume that pharmacokinetic data is comparable to adult values by the age of two months post delivery, bearing in mind in some babies this state is achieved after as little as two weeks.

Dynamics

Kart has stated that no dose response curve for morphine analgesia in neonates, infants or children has been established. Various workers including the Cape Town surgical team of Millar, Rode and Cywes have quoted different figures for the minimum effective plasma concentration. This is due not only to different sensitivities towards morphine in neonates, infants and children, but also to variations in pain perceptions as well. Differing sensitivity to morphine may be different because of differing opioid receptor occurrence, distribution, location or affinity for morphine. Another problem with defining an effective plasma concentration is that the measured plasma concentration may not be directly related to the concentration at the receptor site and local concentrations at the receptor site could vary without any detectable variations in plasma. The immature blood brain barrier of neonates and infants might also influence the distribution and effect of morphine.

Morphine depresses the carbon dioxide responsiveness curve more in neonates than in adults. It is more of a respiratory depressant than pethidine due to its greater solubility in the central nervous system. It is thought that the neonatal nervous system has altered numbers and an increased ratio of mu2 to mu1 opioid receptors, both centrally and peripherally, thus favouring respiratory depression over analgesia as a response to a given dose of opioid. Thus higher concentrations of opioids may be required to provide analgesia to neonates. In neonatal rats there is a good correlation between the number of high affinity mu1 receptors and pain relief and the number of low affinity mu2 receptors and respiratory depression. Rats that are two days old have fewer high affinity binding sites than adult rats and are less sensitive to morphine's analgesic effects, despite having higher brain concentrations of the opioid, while showing a similar degree of respiratory depression.

Anand and Hickey (1987), however, are unconvinced by this theory of increased sensitivity to the side effects of opioids and Tyler also disputes the commonly held view that neonates have an increased sensitivity to the respiratory depressant effects of opioids. Kart also feels that neonates are not more susceptible to respiratory depression than older children. Kart concludes that despite shortcomings in our knowledge of the pharmacokinetics of morphine, it can be considered safe to administer it to neonates, infants and children, adjusting the initial regimens according to the analgesic effect and the incidence of side effects. Moorse states that respiratory depression is rarely a clinical problem in term babies taken off the ventilator one hour after stopping a morphine infusion. If it does occur, naloxone can be administered. If it should occur in a preterm baby, respiratory support should be continued rather than risk the use of naloxone, which may cause a massive rebound stress response.

Other effects

Hypotension may occur in dehydrated babies. Histamine release may occur, causing hypotension, bradycardia and flushing. Children with chronic lung disease may be at risk of the effects of airway narrowing.

Gastrointestinal motility is decreased and abdominal distension. Consequently feeding may be compromised.

Neonates who have become tolerant to opioids may need weaning off their regimes gradually to avoid withdrawal syndromes. These syndromes may manifest as irritability, restlessness, muscle twitches and movement disorders. Withdrawal may occur after as little as 48 hours of morphine infusion, but is rarely a clinical problem when managed appropriately.

Neuraxially administered morphine is reported to cause nausea or vomiting in up to 46 percent of children, urinary retention in up to 30 percent, pruritus in up to 57 percent and respiratory depression in up to 25 percent.

Lynn and Nespeca found that a plasma level of 20 nanograms / ml, at steady state, was the threshold above which most children aged 2 - 570 days developed respiratory depression (using strict criteria for the diagnosis of respiratory depression). In this particular study the susceptibility to respiratory depression was found to occur at equal morphine concentrations in neonates, infants and children. Nichols also found, in a concurrent study, that the tendency to respiratory depression following intrathecal administration of morphine was the same for all children, regardless of age, aged four months to fifteen years. He found that respiratory depression was maximum at six hours, but still present at eighteen hours. Attia found similar results for epidurally administered morphine, at a dose of 0.05 mg / kg, with signs of respiratory depression still present at 22 hours.

Kart concludes that respiratory depression can occur hours after administration, by any route, of morphine but severe respiratory depression needing treatment is rarely described (he quotes one case only of fatality- Gourlay- following morphine use). This indicates that awareness of the risk and proper monitoring of respiratory parameters can prevent lethal situations.

Glenski found an increased frequency of side effects but no increase in duration of action if the epidural dose was above 0.1 mg / kg. Other workers have found a decreased duration of action with doses less than this, but with no reduction in incidence of side effects.

What are the acute or long-term effects of the administration of opioids on the developing nervous system? This is especially relevant now with the increasing tendency to use powerful opioids routinely, often for long periods, in the neonatal intensive care unit. Zadina in animal studies on rats showed that administration of beta-endorphin and morphine during the perinatal period results in increased sensitivity to thermal pain that can endure until adulthood. Thus it is not possible to be entirely confident that current empirical practice is without major adverse consequences on

normal neurophysiological development. Anand (1998) has also stressed the clinical and physiological consequences of opiate use on the developing neural system. It is certainly felt that excessive use of opiates sometimes occurs, particularly in the United Kingdom, creating a whole new set of problems.

8. THE PHARMACOLOGY AND USE OF OTHER OPIOIDS IN THE VERY YOUNG

Many compounds are similar pharmacologically to morphine. None are superior in terms of analgesic effect. Patients all have individual responses to individual compounds.

Kinetic studies for pethidine are incomplete but it has been suggested that during the first two days of life more pethidine than norpethidine is excreted; by three days of age, the reverse is true, indicating rapid activation of the enzymes responsible for pethidine metabolism after birth.
Pasternack showed that pethidine causes less respiratory depression than morphine or fentanyl as it penetrates the neonatal blood brain barrier less, but it is rarely used in this age group as it causes greater sedation and it's metabolite norpethidine has the potential to cause delayed respiratory depression. Pethidine does, however, have the ability to prevent or stop post-operative shivering in the older child.

The pharmacokinetics of methadone in children are indistinguishable from adults with an elimination half-life of 19 hours and a clearance of 5.4 ml / min / kg. Methadone has been used as an analgesic only relatively recently. A high plasma level can be achieved from a single intravenous dose. This may prove to be a convenient way of providing prolonged analgesia. Indeed some have recommended it as an alternative to the use of continuous opioid infusions (a "poor mans" patient controlled analgesia).

Little literature exists on codeine's kinetics in children, per se. Codeine is a useful analgesic and antitussive in children. In equipotent doses, codeine's effectiveness as a respiratory depressant and analgesic approaches that of morphine. It also shares a similar side effect profile. Codeine should never be administered intravenously; serious complications such as cardiovascular collapse due to histamine release have been reported.

The fentanyls are highly bound to alpha 1 acid glycoproteins in the plasma, which are reduced in the newborn (Singleton). The kinetics of fentanyl appears to be similar in premature and term babies. In neonates, the plasma fentanyl concentration is lower, the volume of distribution is larger, the elimination half-life is longer, total body clearance greater than in older children and adults, both initially after a bolus and at steady state during an infusion. This T1 / 2 value ranges from 6 to 32 hours (compared to the 2 to 3 hours in the older child). These kinetic values vary between individuals, however, especially in the newborn. Late rebounds in plasma levels may reflect drug release from adipose stores. The prolonged elimination half-life has important clinical implications; i.e. repeated doses will cause accumulation of analgesic and respiratory depressant effects. However the greater clearance may produce lower plasma concentrations and allow tolerance of more drug without respiratory depression. Context-sensitive half-time, the time taken for a drug concentration at it's target site to fall to one half after cessation of it's administration - is dependant on many factors pertaining to both patient and dose administration. More than 90 percent of the drug is metabolised by the liver. Increased intra-abdominal pressure, as commonly occurs in neonates, can triple the elimination half-life, by reducing liver blood flow. Plasma clearance is slower in the first week of life. Clinically its action is short lived so must be administered by frequent intermittent boluses or by continuous infusion.

Fentanyl has a high therapeutic index and is effective at dampening stress responses at low doses. It is also excellent at blocking nociceptive stimuli with concomitant haemodynamic stability (Anand 1987) and is used in high doses for cardiac anaesthesia. Hickey showed that fentanyl blocks increases in pulmonary vascular resistance in stressed normoxic neonates, hence its use by continuous infusion in neonates with pulmonary hypertension requiring extracorporeal membrane oxygenation. It significantly reduces baroreceptor responses of neonates without affecting heart rate or blood pressure. Baroresponse slopes are reduced and shifted to the left, suggesting that fentanyl affects the central nervous system without altering the ratio of parasympathetic to sympathetic tone. It causes significant chest wall rigidity in children. This is due to effects on stimulatory pathways in the spinal cord. It occurs more in the full term than in the premature neonate. This can be overcome by the concomitant use of relaxants, by infusing the drug slowly or by using bolus doses of no more than 3 micrograms / kg. Hypotension may occur in dehydrated babies. Respiratory depression is significant. Tolerance develops after long-term administration, more rapidly than tolerance to morphine. Physical dependence is a risk particularly in newborns given very high dose fentanyl infusions following repair of congenital heart disease (Arnold 1991).

Sufentanil is commonly used for neonatal cardiac surgery. It is ten times as potent as fentanyl. Greeley showed that as with other opioids, sufentanil is more rapidly metabolised and eliminated in 2 to 3 week old neonates than in neonates less than 1 week of age. This metabolism is by O - demethylation and N - dealkylation. The volume of distribution is only half the value in infants as in adults. A shorter elimination half-life shortens the duration of anaesthesia. Henderson states that it can be administered intranasally in doses of 1.5 to 3.0 micrograms / kg and produce effective analgesia and sedation within ten minutes. Sufentanil has a mildly negatively inotropic effect on infant hearts. It reduces serum catecholamine levels. It also decreases lung compliance, limiting its use in spontaneously breathing neonates. Anand and Hickey (1992) showed its great advantage in its ability to maintain superb metabolic and haemodynamic stability.

Alfentanil is very short acting and may be used for short procedures. Alfentanil is a quarter as potent as fentanyl, is more highly protein bound (90 percent) to alpha-1-acid glycoprotein and is less lipid soluble than fentanyl. This causes a more rapid onset and shorter duration of action than fentanyl. Alfentanil has a rapid onset and offset in neonates (Meistelman). Preterm infants have a volume of distribution of 0.5 L / Kg, an elimination half-life of 321 minutes and a clearance of 0.9 ml / kg / min. The prolonged half-life in premies probably reflects the slower clearance at this age. Thus repeated doses are not required as frequently in premies. It is metabolised in the liver by oxidative dealkylation. This enzyme system is likely to be immature in the premature baby, hence the prolonged clearance figures. There is, as with other opioids, great interindividual variability in their pharmacokinetic data. Roure showed that the elimination half-life is 30 percent shorter in neonates than in adults. It reduces lung compliance. Alfentanil may be used for short painful procedures in neonates.

Remifentanil is the newest opioid available for clinical use. It's unique mode of metabolism means that it does not accumulate or have a prolonged action. The time from discontinuation of an infusion to wakefulness and spontaneous ventilation is 8 - 10 minutes. Neonatal data show that it possesses an elimination half-life of 4.4 + / - 1.3 minutes and a clearance of 80 + / - 23 ml / kg / min (Davis 1997). The dose of remifentanil in the neonate has not yet been reported. A summary of the literature available about this new drug is presented in chapter three.

9. CLINICAL GUIDELINES

The variations in the kinetics and dynamics of morphine in neonates, infants and children have contributed to the historical opinion that morphine is unsafe to use in children due to the risk of severe side effects. However, even though there is significant variation in morphine handling among children and within the same child, the meta - analysis performed by Kart et al of the kinetic values for morphine reveal that it is possible to establish an overall course for the development of morphine pharmacokinetics and based on this knowledge recommended regimens for morphine administration have been established. Thus guidelines based on kinetic data are useful, but they must be used carefully and doses titrated according to dynamic effect.

Kart's paper sets out to describe age appropriate dosage regimes. He believes that opioid administration to a neonate or infant of less than two months of age needs to be done in a monitored setting. This is in line with Yaster and Maxwell's conclusions in Schecter's grand review of childhood pain. Remifentanil's unique kinetic profile may now, however, mean that an opioid can possibly be administered to even a small baby without necessitating the expense and extra workload of postoperative admission to a high care unit.

Present practice is that young babies receiving opioids need to be carefully monitored. In South Africa this means a high care area. Nursing care on general wards is not sufficient.
At the Red Cross Children's Hospital, any child of less than 50 weeks post conceptual age receiving an opioid goes to a high care unit. In the case of other postnatal problems, this limit may increase to 60 weeks. Premature babies or neonates may require ventilation.
Other units may recommend high care monitoring for any child receiving an opioid up to the age of six months, or even older if there are additional problems.
Lynn, however, states that high care is required only for babies up to 48 weeks of post conceptual age, providing they are otherwise healthy
Yaster, in 1993, recommended that the use of any opioid in children less than 2 months old must be limited to a monitored setting, while those children older than 2 months may safely be monitored as older children or adults, on a general ward. Guidelines will also depend on the child, the illness, the agent used, and the route of administration and general logistics.
Perhaps with increasing experience of the intra-operative use of remifentanil in the very young, the requirement for such labour intensive and expensive post-operative care facilities will not as definite.

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Masters Dissertation - University Of Cape Town

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Chapter Three - "Remifentanil" a review

Summary Of This Chapter

1. THE SEARCH FOR THE IDEAL ANALGESIC

Lynn states that the search for the ideal analgesic to use in children and infants remains an elusive goal. The properties of an ideal compound would include potent analgesia capable of blunting the hormonal and catabolic responses to the stress of surgery or painful procedures and a rapid onset with minimal effects on haemodynamic and other variables.
This ideal agent would have minimal undesired effects on ventilation, gastrointestinal motility, and bladder function and would not induce pruritus. Any metabolic by-products should be inert, with metabolism unaffected by renal or hepatic impairment or immaturity. No tolerance or dependence would occur.
This ideal is far from being achieved, thus the search for the ideal pharmaceutical product continues and meanwhile we optimise our use of available agents, using our knowledge of their kinetics and dynamics, by modifying dosage, mode and timing of administration, etc., in the different patient groups.
Side effects may, however, be unavoidable with the opioid analgesics, since the same family of receptors that mediate analgesia also mediate ventilatory depression, nausea, constipation and urinary retention. So an opioid whose dose, plasma level and site effect can be titrated to maximum therapeutic effect with minimal undesirable effects becomes the best we can achieve.

Fentanyl has historically been regarded as being more cardiovascularly stable than morphine and pethidine; the more recent alfentanil is faster and more titratable than fentanyl and the even more recent sufentanil's faster offset time and cardiovascular stability after a large bolus dose makes it suitable for use in "fast-tracking" post cardiac surgery.
However all of these undergo accumulation in peripheral compartments after repeated or continuous dosing leading to a protracted decline in drug concentration on termination of the administration. Remifentanil appears, according to initial evaluations, to be most modifiable of all.
It has been registered in Europe and the USA for a few years and has recently been registered here in South Africa in 1999.

2. REMIFENTANIL KINETICS - A COMPARISON WITH OTHER OPIOIDS

Remifentanil is a novel member in the family of the 4-anilidopiperidine opioid analgesics, a group that also includes the traditional agents fentanyl, alfentanil and sufentanil. Remifentanil is the first in a newly developed class of synthetic, selective, mu-opioid agonists whose unique metabolism by blood and tissue esterases yields an ultrashort elimination half-life in adults (Glass). This imparts brevity of action, precise and rapidly titratable effects, non-cumulative effects and rapid recovery after cessation of administration. Its pharmacological effects otherwise essentially parallel other opioids in this class. It is a hydrochloric salt, a methyl ester derivative of a 4-anilidopiperidine propanoic acid. It contains the same basic structure as fentanyl, sufentanil and alfentanil but with the addition of a propanoic acid methyl ester group at position 1 of the piperidine ring. It does not significantly bind to non-opioid receptor groups.

It exhibits a linear and dose independent pharmacokinetic profile; its distribution can be described by either a 2 or 3-compartment model, although the third compartment is small (less than five percent) and only relevant after infusions lasting more than one hour. Seventy per cent of a dose of remifentanil is bound to plasma proteins of which two-thirds is alpha 1 acid glycoprotein. Traditional opioids show a higher degree of binding (> 90 percent). The lipid solubility of remifentanil is lower than that of sufentanil or fentanyl, but is similar to that of alfentanil. Intravenous remifentanil, 1 to 2 μg per kg, shows a bi-exponential or tri-exponential decline in plasma concentrations (alfentanil shows a tri-exponential decline). Continuous remifentanil infusions lasting more than one hour conform more to a three-compartment model. Although the distribution of remifentanil into the second compartment is very rapid, distribution into the third compartment is quite limited and accounts for less than 5 percent of the total exposure. This is in marked contrast with the kinetic profile of traditional opioids, particularly when they are administered for prolonged periods when significant accumulation can occur in the third compartment. Subsequent problems with toxicity following discontinuation of these older drugs may then occur because of redistribution from these tissues. The volume of distribution (Vd) in the steady state in adults is 24 - 40 Litres (0.39L / Kg) and is dose independent. The Vd of alfentanil is 0.52 L / Kg and is dose dependent. This low Vd also sets remifentanil apart from other opioids and together with its' esterase metabolism is responsible for the rapid,

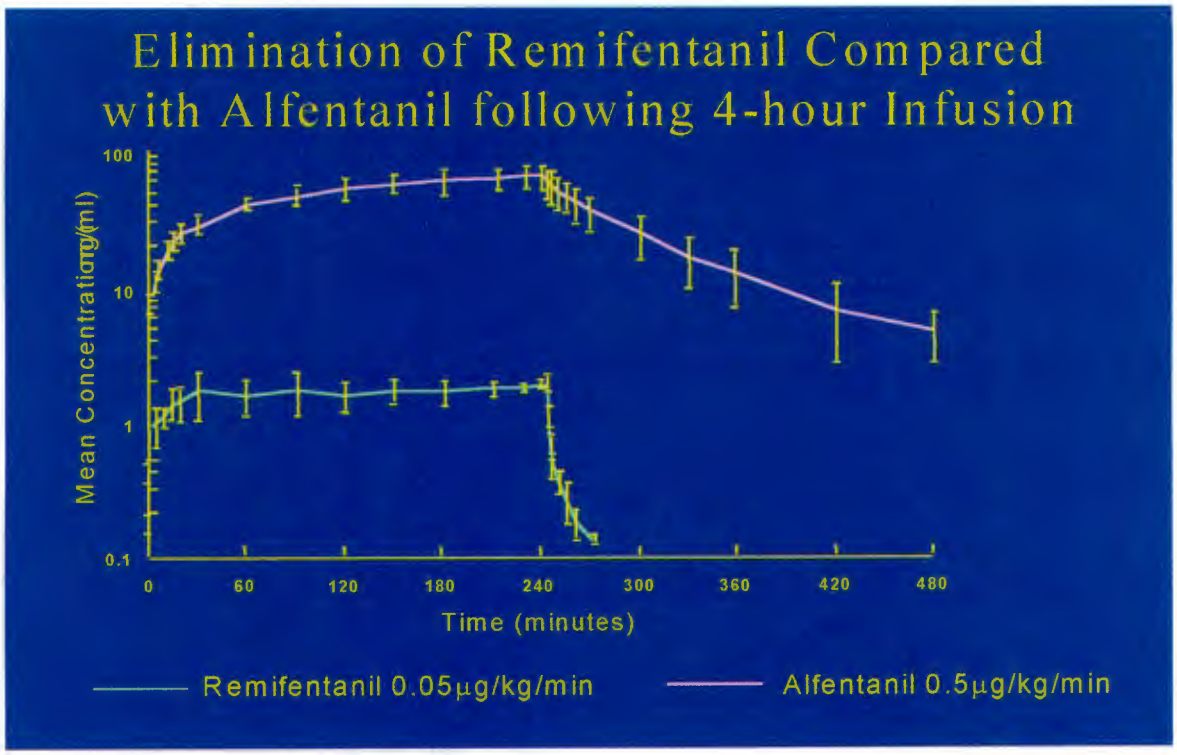
titratable offset that is remifentanil's hallmark. It is significantly faster and more titratable than all other opioids, including alfentanil. This difference is, however, less marked when purely a bolus dose is used. The central compartment Vd is 5.7 - 8.0 L, with a mean residence time of between 5.7 - 7.7 minutes.

The time required for equilibration of peak blood concentration and peak effect (T1 / 2 keo) is similar for both remifentanil and alfentanil (1.6 vs. 0.96 min) (Egan and Minto) thus accounting for its rapid onset and rapid pharmacodynamic response to changes in plasma concentration. Egan based this on the effect site concentration / EEG (electroencephalogram) relationship and Glass found similar figures (1.3 minutes for remifentanil), based on analgesic measurements. This is due to remifentanil's relatively low lipid solubility. Sufentanil and fentanyl both show slower equilibration between plasma and effect compartment.

Remifentanil is metabolised to effectively inactive products, which are excreted mainly by the kidney. Metabolism is independent of plasma cholinesterase activity (Stiller). Remifentanil is de-esterified by non-specific plasma and tissue esterases, with consequent liberation of a carboxylic acid metabolite, which is 4600-fold less potent than the parent drug. Remifentanil is also N-dealkylated, albeit negligibly.

Metabolism of remifentanil is temperature dependent, thus infusion rates need adjusting during hypothermic cardiopulmonary bypass, this causing a 20 percent decrease in clearance (Russell and Royston). Bodyweight, age or gender does not influence total clearance of remifentanil, however obese patients have less central clearance. Thus ideal body weights should be used for dose calculations in obese patients, rather than actual weight.

Terminal half-lives do not adequately reflect the overall concentration decay curves for drugs with complex three-compartment kinetics. Hence the use of the term: "context sensitive half time". The "Context Sensitive Half Time" of a compound with three-compartment distribution is initially very short, as the drug is removed from the central compartment by both distribution and metabolism. There may be little difference in this value between traditional opioids and remifentanil. However the context sensitive half time of the traditional opioids, including alfentanil, increases with duration of infusion, whereas this does not occur with remifentanil. Alfentanil has a CSHT of 55 minutes after a 3-hour infusion (Egan) compared with 4 minutes for remifentanil, whatever the duration of infusion.



The ester linkage is cleaved by tissue and blood esterases, giving a very short elimination half-life (Egan). This occurs at its propionic methyl ester group to yield the carboxylic acid metabolite (88 percent of the dose is recovered in the urine in this form). It is not metabolised by the liver. Remifentanil has an elimination half-life of 8 - 10 minutes. Alfentanil also has a short elimination half-life but accumulates after prolonged infusions.

Computer simulations based on pharmacokinetic parameters allow us to graphically show how blood concentrations of a drug decline after infusions of variable duration. Here is such a table with the values of the context sensitive half times:

INFUSION DURATION	100 MIN	200 MIN	300 MIN
Remifentanil	3	3	3
Alfentanil	45	55	58
Sufentanil	20	25	35
Fentanyl	220	262	-

(Egan 1996)

This data has been obtained from adults and shows that the offset of remifentanil is independent of duration of infusion and that it is unique in this. It has a distribution phase half-life of 0.94 minutes and a rapid onset of action (1.3 min half time for equilibration between plasma and effect compartment). It has a clearance from the central compartment of 2.9 L / min (41.2 ml / min / kg), compared to 9.0 ml / min / kg for alfentanil. It has a mean terminal elimination half-life of 10 minutes, compared to the 57.8 minutes of alfentanil. This high clearance and low steady state volume of distribution results in a faster decline in blood concentration of remifentanil compared to alfentanil.
After discontinuation of a three-hour infusion, time to spontaneous ventilation is 4 minutes, time to extubation is 4.2 - 7 minutes, time to respond to verbal commands is 3 - 4.6 minutes and time to the requirement for an analgesic is 21 minutes.
It is said, however, that for infusions of short duration, i.e. < 10 minutes, the kinetic differences between remifentanil and alfentanil are not that readily apparent.

Remifentanil's kinetics appear to be consistent between individuals of different ages and pathophysiological states. Kharash suggested there was a large individual variation in alfentanil's pharmacokinetics due to individual variability in cytochrome P450 A34 enzyme activity.

3. REMIFENTANIL DYNAMICS, a comparison with other opioids

With the exception of remifentanil's nearly 20 fold greater potency, the dynamics of remifentanil and alfentanil are quite similar. Higher potency has several dynamic implications including the potential for a longer onset time, by the "law of mass action" (bombardment of target receptor with fewer drug molecules) and the potential for a shorter duration of action, due to the presence of fewer molecules to eliminate. This definitely appears to be true for duration of action, but although statistically significant, the difference in onset time is probably clinically unimportant.

Remifentanil, like alfentanil, produces a dose dependent increase in analgesia. The onset of action of analgesia is similar to that of alfentanil and Glass' early studies suggested a peak analgesic effect at 1 - 3 minutes after intravenous administration, with a maximum PaCO2 seen at 5 minutes (return to baseline at 20 minutes versus 30 minutes with alfentanil), using twice the recommended bolus dose. It has a potency similar to fentanyl and 20 - 30 times that of alfentanil based on various clinical end points, including analgesic effects (Glass). Its offset is 10 times as rapid as alfentanil following a 3-hour infusion in Kapilas' study on 30 healthy volunteers. Remifentanil facilitates better control of intraoperative haemodynamic responses than alfentanil (Monk) and is approximately 15 times as potent as alfentanil in blunting the catecholamine response to surgical stimuli. Herreods showed that patients with poor left ventricular function undergoing coronary artery bypass graft surgery receiving remifentanil showed superior attenuation of stress response to maximum sternal spread than patients receiving fentanyl.

Cerebrovacular responsiveness to increasing PaCO2 levels is maintained during a remifentanil infusion, with cerebral blood flow increasing with increasing PaCO2 levels (Baker). In addition, reduction in cerebral blood flow in response to hypocapnia is not affected by remifentanil. Forde agreed with these findings in 1998.

Thus there is no evidence of remifentanil causing raised intracranial pressure (Guy). Equally Hindman found that single doses of remifentanil or alfentanil did not produce any clinically significant changes in intracranial pressure. He did, however, show that at higher doses cerebral perfusion pressure decreases in parallel with a decrease in mean arterial pressure. He found that mean arterial pressures do not decrease more than 20 percent from the baseline.

Remifentanil, used as a sole induction agent induces and maintains a stable electro encephalographic state (> 50 percent reduction in spectral edge frequency) without evidence of seizure activity. A dose of 4 - 6 μg / kg without premedication, produces a loss of consciousness in 60 percent of patients. However, because of a high incidence of apnoea and muscle rigidity it is not recommended for use as a sole induction agent. The EEG effects closely parallel its arterial concentration. Its' rapid recovery profile makes it useful for neuroanaesthesia, i.e. for early assessment post operatively. Patients can be extubated and then coma scales and the neurological picture can be assessed very early.

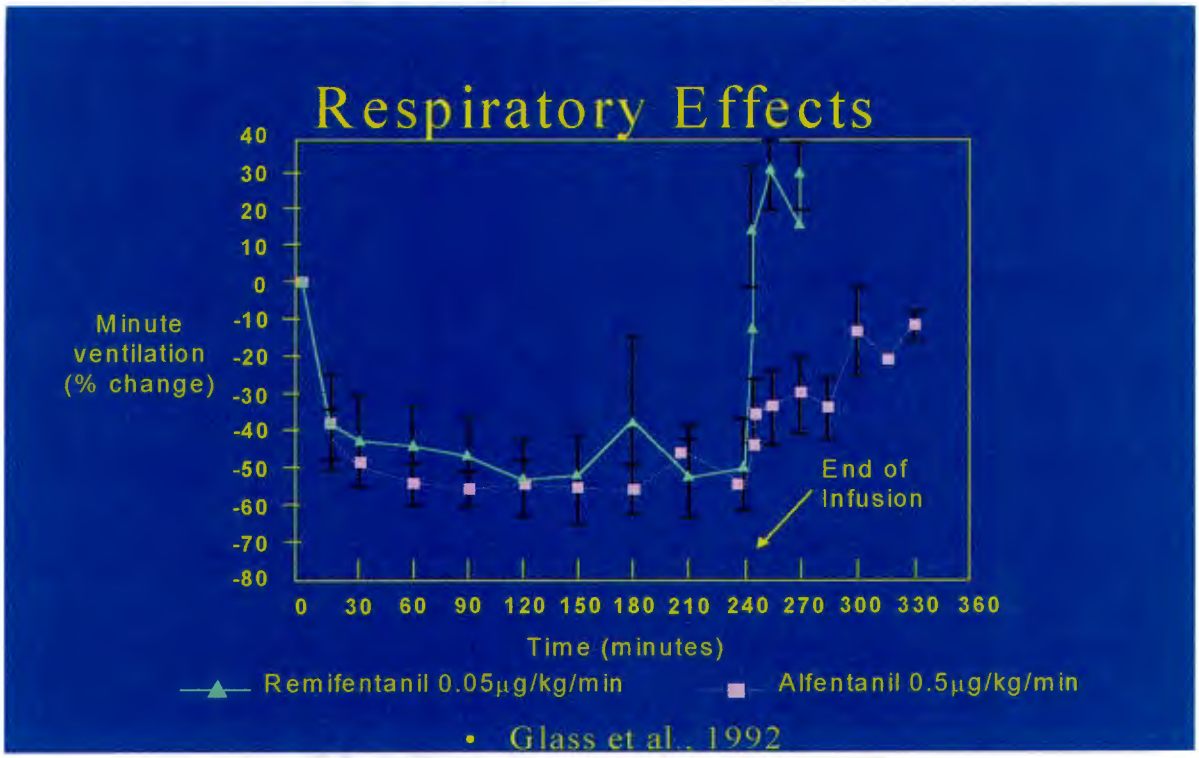
It causes a reduction in the minimum alveolar concentration value of anaesthetic volatile agents when used in combination. It has a sparing effect on hypnotics and sedatives and its' unique kinetic profile facilitates 'real time' management of intraoperative stress. Schraag was keen to point out his findings that when he used middle latency auditory evoked potentials, remifentanil appeared to give no quantitative contribution to the suppression of the potentials during propofol anaesthesia. Thus, he concluded, remifentanil might in fact contribute to a misleading clinical suggestion of adequate anaesthesia. Remifentanil does produce, however, a dose dependent reduction in auditory and somatosensory evoked responses during isoflurane anaesthesia.

Remifentanil does not cause histamine release, but does cause a significant decline in heart rate and blood pressure over time. Glass quoted a 15 – 20 percent fall in blood pressure and a moderate degree of bradycardia. These changes are readily attenuated by intravenous anticholinergic premedication and are easily reversed by adrenergic agents (Pitts). This fall in blood pressure and heart rate is exaggerated when remifentanil is combined with propofol. The hypotension is exaggerated even more in the presence of hypovolaemia. Berghmanns demonstrated, by using transoesophageal echocardiographic analyses, that the pathophysiological mechanism underlying the hypotension associated with the use of remifentanil was related to a reduction in left ventricular preload and afterload without a change in contractile state.
Alfentanil is said to have unpredictable effects on the cardiovascular system and may cause changes in the pulmonary vascular resistance. Alfentanil may cause a rise in pulmonary vascular resistance that may result in a reversal of the transitional circulation back to the foetal state in neonates.

Like alfentanil, remifentanil produces a dose dependent respiratory depression with the peak effect on PaCO2 and PaO2 occurring 5 minutes after a single intravenous bolus dose (Glass and Hardmann). Complete recovery from the respiratory depressant effects appears to occur in 15 minutes (Schlugman) and Amins' study showed that spontaneous recovery of ventilatory function is faster after cessation of a remifentanil infusion than an alfentanil infusion (20 minutes vs. 30 minutes). Infusions of remifentanil of < 0.5 microgram/kg/min do appear to permit spontaneous ventilation during isoflurane or propofol anaesthesia.

Its' rapid elimination from the central compartment, coupled with its' limited distribution into peripheral compartments, means that recurrent respiratory depression does not occur. This is in marked comparison to the traditional opioids. Mahla reported this unpredictable and significant problem with the use of alfentanil.

Recovery of respiratory function is rapid on cessation of the infusion, in line with its' overall recovery profile.



Glass, in 1992, showed that following a 4-hour infusion, recovery of respiratory function occurred in 8 minutes in patients receiving a remifentanil infusion and 61 minutes in patients receiving an alfentanil infusion.

Dershwitz reported his use of remifentanil in total intravenous anaesthesia, with propofol, for procedures of varying duration. He found the recovery profile (time to spontaneous ventilation / time to response to voice / time to extubation) very rapid. He also found that analgesia was required soon after the infusion was stopped. He also noted the bradycardia and the hypotension that has been widely acknowledged.

A relatively high incidence of rigidity has been reported when remifentanil is used alone at high doses to induce anaesthesia. The mechanism is thought to involve opioid receptors in the brainstem and basal ganglia. The rigidity is reversed by naloxone. Remifentanil in

lower doses, particularly in combination with hypnotic agents, does not usually produce clinically significant muscle rigidity (1 percent incidence) and even then, did not interfere with ventilatory support.

Remifentanil causes other typical 'mu' side effects of nausea, vomiting, pruritus, etc. Its brevity of action not only ensures a rapid resolution of these adverse effects, but also necessitates early establishment of postoperative analgesia.

Big Studies comparing remifentanil to alfentanil

Cartwright et al published a big study comparing the two agents in patients undergoing day case surgery, with the agent being discontinued just prior to the end of surgery. They found that the remifentanil group experienced significantly fewer stress responses and required less rescue analgesia intraoperatively, in adults. Psychometric functioning and mental agility showed better recovery in the remifentanil group. They did, however, find that general recovery profiles were faster in the alfentanil group: times to spontaneous ventilation, response to verbal commands, adequate respiratory rate, extubation were all faster in the alfentanil group. However the times were all low (i.e. time to spontaneous ventilation, five minutes versus eight minutes). Intra-operative hypotension and postoperative shivering were higher in the remifentanil group.

Davis and Lermann found that fewer remifentanil recipients required naloxone for respiratory depression and that recovery occurred at a comparable time to children receiving alfentanil infusions (they looked at orientation, extubation, discharge to the ward and ambulation) in children undergoing elective strabismus surgery. The remifentanil patients had greater postoperative pain and showed a lower incidence of postoperative hypoxaemia. Nausea and vomiting and haemodynamic parameters were similar in the two groups. Davis states in this paper that the quoted infusion rate of 1 micrograms / kg / minute may, in fact, be too much in this age group.

Other studies confirm these findings and add that postoperative analgesia is required earlier in the patients who received remifentanil.

Shuttler, however, found little difference in the recovery profile between the two groups, in a large double blind study on patients undergoing major abdominal surgery. He did find

that time to extubation was more predictable and less variable in the remifentanil group. His large study also found that remifentanil was better than alfentanil at blunting haemodynamic responses intra-operatively. He found a similar overall incidence of side effects in both groups, with more hypotension and bradycardia in the remifentanil group. This was easily controlled by dose titration.

4. EFFECTS OF ORGAN DISEASE

Dershwitz and Hoke found that kinetics are not altered significantly by liver disease and Shlugman showed the same for renal impairment, although patients with either disease did appear to show an increased sensitivity to the respiratory depressant effects of the opioid. The significance of this is unclear given the brevity of action of the drug.
Steady state concentrations of the metabolite are much higher in-patients with renal impairment. This, however, has very little clinical significance because of its low potency. The metabolite is 30% extracted by the dialysis process.

Both "ageing" and " obesity", however, do alter the kinetics of the drug. Patients over 65 years of age are sufficiently sensitive to warrant a 50% reduction in the dose recommendations. There is a small decrease in both clearance and volume of distribution with increasing age. Dosages for obese patients should be based on their " ideal body weight" and not their " actual total body weight".

5. ADMINISTRATION

Recommended regimes include a bolus dose of 1 microgram per kilogram slowly over at least 30 seconds, followed by an infusion rate of 0.2 - 0.5 μg / kg / min. Kinetic data suggests that on commencing or changing the rate of infusion, 80 percent of the steady state blood concentration is reached within 5 - 8 minutes.
Intubation responses are only effectively prevented at an infusion rate of 1μg / kg / min. Woods recently tried doses of 2 μg / kg to ablate responses to intubation but found that the subsequent duration of apnoea was significantly longer than in those receiving only 1μg /

kg. Haemodynamic stability can be achieved intraoperatively with a background infusion rate of 0.2μg / kg / min, with increases of up to 0.5μg / kg / min during periods of stimulation.

Paventi suggested that infusion rates of at least 0.5 μg / kg / min are required to completely dampen the catecholamine response to laparoscopic cholecystectomy.

Postoperative analgesia appears to be achieved at an infusion rate of 0.1 μg / kg / min (with 0.025μg increments as required), higher rates causing respiratory depression. This regime has been found to provide better post operative analgesia than 0.15 mg / kg of morphine given 20 minutes prior to the end of surgery followed by intermittent bolus doses.

Recovery profiles are independent of the infusion rate.

6. CLINICAL USES AND FINDINGS

The following have been approved by Control Councils in Europe and North America as appropriate indications for use:

1. Analgesia during induction and maintenance of general anaesthesia
2. Postoperative analgesia under close supervision in post-anaesthesia or intensive care setting
3. Analgesia during monitored anaesthesia care.

Remifentanil decreases the Minimum Alveolar Concentration (MAC) of isoflurane, but demonstrates a ceiling effect; i.e. very high plasma levels do not decrease the MAC further. It also decreases the amount of propofol required for a given stimulus.

Much work has and is being done to define the place of this drug in modern anaesthesia. McAtamney et al have shown that it is effective in dampening the stress response to endotracheal intubation. Valenti has suggested its' usefulness for conscious sedation, but acknowledged its' poor amnesic effects. Boccara has highlighted its' potential as an adjunct "patient controlled analgesic" in conjunction with local field block for hernia surgery. Stuart also tested it and found it to be effective for "patient maintained analgesia" for day case gynaecological laparoscopy. Gustorff has recently suggested that it may have a place in the testing of chronic neuropathic pain for opioid responsiveness.

7. COMPARISON WITH OTHER SEDATIVES

It has also been used and recommended for sedation and analgesia during local and regional blocks. Greater patient comfort, less sedation and therefore more co-operation have been found but the risk of respiratory depression has been emphasised (Lauwers).

8. TOLERABILITY

Typical mu opioid side effects occur. At recommended doses common events (i.e. with greater than a 1 percent incidence) include bradycardia, hypotension and skeletal muscle rigidity. Muscle rigidity is reduced when remifentanil is administered concurrently with a hypnotic induction agent.

Respiratory depression occurs more commonly (7 percent incidence) when remifentanil is administered for postoperative analgesia than when given during induction or maintenance of general anaesthesia (less than 1percent incidence).

During monitored anaesthesia at recommended dose common adverse events include (greater than 18 percent incidence) nausea, vomiting, pruritus and headache. These events can be decreased by the concomitant administration of midazolam 2 mg (higher doses of midazolam increase the incidence of respiratory depression- GlaxoWellcome Inc).

Postoperative shivering, nausea, vomiting and fever have also been reported (greater than 5 percent incidence).

Other side effects (1-5 percent incidence) after discontinuation of remifentanil have included respiratory depression, dizziness, visual disturbance, hypotension, headache, shivering and pruritus.

Excessive doses of remifentanil increase the incidence of these adverse events, especially muscle rigidity and bradycardia. Tachycardia and hypertension have, however, been reported at these higher doses.

Tolerance to the effects of remifentanil has been shown, by Vinik, to occur rapidly in humans not undergoing constant painful stimuli. He found that a constant-rate infusion resulted in a 75 percent reduction of analgesic effect after a three-hour period. Thus, he concludes, tolerance is profound, of rapid onset and needs considering when setting up target-controlled infusions.

9. REMIFENTANIL IN NEUROSURGERY

There are negligible direct cerebrovascular effects following remifentanil administration. This is particularly desirable in neuroanaesthesia, as neurosurgical patients may be susceptible to changes in cerebral blood volume, cerebrovascular tone and intracranial pressure, resulting from an increased cerebral blood flow. Neurosurgical patients are particularly vulnerable to damage from increased cerebral blood flow due to their diminished intra-cranial compliance. This can lead to brain herniation or decreased perfusion and ischaemia.

Guy also suggested that remifentanil was a good analgesic agent for use during elective craniotomy (1997).

Coles showed that total intravenous anaesthesia using a propofol infusion together with a remifentanil infusion allowed good haemodynamic conditions for craniotomy and this regime showed faster recovery than propofol and either alfentanil or fentanyl infusions. Maintenance requirements of propofol were less in the remifentanil group.

Summors has suggested that the use of remifentanil during acoustic neuroma surgery decreases propofol requirements and therefore speeds recovery from anaesthesia.

It is vital that there is no postoperative delay in recovery or respiratory depression leading to hypercarbia and increased intracranial blood volume.

10. REMIFENTANIL IN PAEDIATRICS

Little work has, as yet, been done on the use of remifentanil in paediatrics. This is the first big study including neonates and preterm babies.

In early studies Davis suggested that in a child over age of two years of age the pharmacology of remifentanil is comparable to that of an adult. He found clearances of 58.7 ml / kg / min, volumes of distribution of 0.2 L / Kg and elimination half lives of 5 min in 10 children aged 2 – 12 years, but further work is needed to assess the kinetics and dynamics of the drug and to assess the activity of esterases in infants. He and Lermann used remifentanil in children undergoing squint surgery. Davis subsequently wrote, in an abstract based on a study of six neonates, that the pharmacokinetic parameters appeared similar in neonates and older children.

Robinson recently published a paper stating that remifentanil was a good alternative to suxamethonium or alfentanil for providing good intubating conditions in children aged two to twelve and showed that both remifentanil and alfentanil caused a similar degree of attenuation of the stress response to intubation, with a similar recovery time to spontaneous ventilation.

Wee wrote a case report on the successful use of a combined remifentanil intravenous infusion and an epidural ropivacaine infusion in a term neonate at risk of transient myasthenia gravis, for repair of bladder extrophy. He noted the hypotension and bradycardia that he feels is marked in neonates, particularly on bolus administration.

More recently Eck published a case report about its' use in three infants with complex medical problems and suggested that although it is known that the pharmacological profile of remifentanil has not been published in infants, and that other opioid kinetics have generally been found to be different in neonates and young infants compared with older children, it seems that it does have a short duration of action in this age group, even after a prolonged infusion, and therefore may prove to be particularly useful in certain patients of this age group.

Grundmann compared haemodynamic and recovery profiles between children receiving propofol and remifentanil "total intravenous anaesthesia" (TIVA) and children receiving desflurane and nitrous oxide. He found a significantly lower perioperative heart rate and less postoperative agitation in the "TIVA" group. All but one of the recovery landmarks (i.e. extubation, eye opening, Aldrete score > 9) were similar, but the "TIVA" group showed a delayed return to spontaneous ventilation of 11 compared to 7 minutes post termination of anaesthesia.

Kan gave a remifentanil infusion, at a rate of 0.1 microgram / kg / minute, to nineteen mothers during caesarean section under epidural anaesthesia. He found a sedative and respiratory depressant effect on the mothers but no adverse effects on the babies.

Jones reported the successful use of patient-controlled analgesia using remifentanil in a labouring woman with thrombocytopenia and concluded that good analgesia without maternal or foetal side effects was possible, provided that the woman could anticipate the contraction and that bolus doses were of appropriate size (0.5 μg / kg).

Thus, little work has, as yet, been done on the use of remifentanil in paediatrics. This is the first big study including neonates and preterm babies. Further work is required. The studies

to date suggest that remifentanil is safe and effective in children, including term and preterm babies, but that the usual side effects of hypotension and respiratory depression are of concern due to the babies limited physiological reserve.

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Masters Dissertation - University Of Cape Town

Dr. Neil Chambers

Chapter 4 - "The Trial: Remifentanil And The Tunnelling Phase Of Paediatric Ventriculoperitoneal Shunt Insertion"

Dr. Neil Chambers, Red Cross Children's Hospital, 1998-99.
Co-Workers For The Trial: Professor MFM. James, Dr. Tessa Lopez And Dr. Jenny Thomas.

Contents Of This Chapter:

1. THE AIM OF THE STUDY

The tunnelling phase of ventriculoperitoneal shunt insertion has traditionally not received optimal analgesic cover, for fear of the predictable dose-dependant side effects of opioids in small children (Kart, Bhat) with an already compromised cerebral perfusion. Known side effects of opioids include hypotension, delayed recovery and post-operative respiratory depression. There is a high risk of post-operative respiratory depression and a delayed recovery is likely in sick neonates with poorly developed respiratory drive, especially when there is a depressed level of consciousness preoperatively due to intracranial pathology. The resultant hypercarbia may compromise cerebral perfusion further by increasing intracranial volume or pressure.

Inadequate analgesia in this setting, however, may predispose to multiple complications, including intraventricular haemorrhage (Mullart).

The aim of the study is to see if remifentanil could usefully attenuate the signs of pain and stress caused by tunnelling without causing any dangerous side effects.

It is not the intention of the study to assess remifentanil as the "ideal opioid", as it is considered to be in some of the work quoted in chapter 3. It is difficult, as discussed in chapter 1, to assess the stress response in the very young. It is even harder to assess what constitutes a clinically significant attenuation of that stress response, where statistical and clinical significance are not the same. Much work has been published on the value or otherwise of the stress response and it's attenuation. Little hard evidence exists in the literature, but perceived wisdom is that an uncontrolled stress response is damaging and that careful attenuation can improve outcome (Anand). Each individual clinical situation, however, is multi-factorial and outcome studies on one group cannot be assumed to be relevant to another. I have therefore set out to assess whether a statistically significant attenuation of the degree of stress response is demonstrable with the use of remifentanil, when compared to placebo. Further work is then required to assess the relevance of the findings in terms of outcome. It has been assumed for the purposes of this study that an increase from baseline of 15 – 20% or more in the parameters that mark stress can be taken to represent clinically significant stress, and an equal degree of attenuation in these parameters can be taken to represent clinically relevant suppression of the response. I have also set out to examine if any evidence exists that the use of remifentanil in this scenario causes a statistically significant increase in the degree and duration of the well documented side effects of opioids, in particular hypotension, delayed recovery and post-operative respiratory depression.

Thus we set out to compare remifentanil with placebo in order to see whether remifentanil's unique kinetic profile makes it suitable for use in this group of patients. We chose not to include an additional opioid, such as alfentanil, as a third group because remifentanil appears to have significant advantages over the other opioids and because having three different treatment options would have decreased the sample sizes and therefore decreased the likelihood of achieving valuable statistical results.

2. SUMMARY

We have studied 62 children (13 neonates (8 "x-premies"), 24 infants and 25 older children), undergoing the insertion of a cerebrospinal fluid drainage shunt under general anaesthesia for the relief of hydrocephalus. Patients were allocated randomly to one of two groups: group R (n=33) received remifentanil 1 microgram per kilogram and group S (n=29) who received saline just prior to the tunnelling phase of shunt insertion, in a double blind, prospective study. We compared the cardiovascular responses to the agent, the stress response to tunnelling, the recovery profiles, the post-operative respiratory depression and the side effects in the two groups.

Patient characteristics such as ASA status, age, sex, height, weight and baseline cardiovascular parameters were similar in both groups within each age category. Surgical characteristics such as technique and associated procedures were similar and anaesthesia characteristics, such as total duration and the duration from drug administration to the end of anaesthesia were generally similar in both groups. A standardised anaesthetic protocol was followed for each patient, details of which are given below.

Group S (control) demonstrated a significantly greater stress response to the stimulus of tunnelling, with a greater degree and duration of rise in heart rate and blood pressure, and a significant rise in plasma catecholamines compared to group R (remifentanil). Some group S patients, in fact, showed a reduction in stress levels in spite of tunnelling. The differences were generally consistent across the different age groups.

There was no evidence that remifentanil causes a delayed recovery, there being no prolongation, in the remifentanil group, in the time required from the end of surgery to fulfilling the criteria for extubation, discharge to recovery and discharge to the ward, in all age groups. In fact, the remifentanil group appeared to recover slightly faster than the control group.

There was some evidence of post-operative respiratory depression and increased oxygen requirements in both groups, but with no difference between the two groups, at all ages.

There was some evidence of cardiovascular depression in the remifentanil group, with some children exhibiting a degree of bradycardia and hypotension, either before or even during the tunnelling.

There was no difference between term babies and ex-premies of similar post conceptual age in their overall response to remifentanil.

There was no difference between groups in post-operative analgesic requirements, in blood loss and there were no other significant side effects in either group.

We conclude that remifentanil is an appropriate and safe analgesic to provide balanced anaesthesia to cover the tunnelling phase of cerebrospinal fluid shunt insertion and patients show a good recovery profile. There was no evidence of additional postoperative respiratory depression or of major complications, in children of all ages, including ex-premature babies.

3. STUDY PROTOCOL - PATIENTS AND METHODS

The Research Ethics Committee of the University of Cape Town approved the study. At the time of the trial the drug was unregistered in South Africa. The Medicines Control Council thus granted permission for the trial. Full explanation was given to and written consent was obtained from the parents or guardians.

Of the 91 patients presenting during the trial period, we studied 62 patients: 8 x-premies, 13 neonates, 24 infants and 25 children over the age of one year. These groups were identified at the start of the trial. Power analysis, based on the assumption that a 20% increase in heart rate or blood pressure would represent clinically important stress responses, and with an assumed standard deviation of such an increase of approximately 15 mmHg or beats per minute indicated that a minimum of 8 subjects in each age group and drug group should be included to establish reasonable statistical power, with a beta error of 0.1. The "x-premies" group was made up of patients from both the neonate and infant groups, who were born before 35 weeks of post conceptual age and were still less than 56 weeks of post conceptual age. All patients were ASA 2 or 3 and were undergoing the insertion or revision of a cerebrospinal fluid shunt. Exclusion criteria included severe cardiorespiratory disease, guardian refusal, logistical problems (i.e. time constraints) or protocol violations.

Patients were allocated randomly to one of two groups by the opening of a sealed envelope by a non-participating clinician. Inside each envelope was either the letter "A" or "B", the random sequence having been generated by a "random number generation computer programme". Remifentanil or saline were then prepared and handed to the trial worker (myself, the author, only) who remained blinded until completion of the trial, when the codes were broken and the results analysed.

Standard pre-operative fasting intervals were applied. If required, premedication was with midazolam, 0.5 mg/kg. In fact, no patient received premedication. Caffeine (10 mg/kg) was given as a respiratory stimulant to premies and ex- premies (up to 60 weeks of post conceptual age), as is our usual practise according to the Red Cross Hospital protocol.

On arrival in theatre a full set of observations were performed as a pre-induction baseline. These were: heart rate, non invasive blood pressure, respiratory rate, oxygen saturation on room air and

transcutaneous carbon dioxide partial pressure. These measurements were to be compared to post-operative parameters to assess post-operative respiratory depression and analgesic requirements.
Inhalational induction was then performed with nitrous oxide, oxygen and either sevoflurane or halothane. Only halothane was actually used for the inhalational induction, although sevoflurane was also allowable by protocol, should it have been indicated clinically (i.e. for a difficult airway). It was felt that the differing rates of elimination of the two agents were immaterial, considering that the overall duration of anaesthesia is about 2 hours.
Isoflurane, at 1-% end tidal concentration using a calibrated agent monitor, was then immediately substituted to maintain anaesthesia with nitrous oxide and 30 % O2. The vocal cords were sprayed with lignocaine and oral endotracheal intubation performed (minimal apparatus dead space ensured). Intermittent positive pressure ventilation to an end tidal carbon dioxide partial pressure of 3.5 to 4.5 kPa was achieved.

Intravenous access was obtained by the femoral vein. Atracurium (0.5 mg/kg), cloxacillin (25 mg/kg) plus further antibiotics were administered at the surgeon's request.
The intravenous fluid regime was modified Ringers Lactate with 2 % added glucose, giving an initial rehydration bolus of 8 ml/kg and then maintenance at a rate of 4 ml/kg/hr, with challenges of 4 ml/kg if indicated clinically.

Temperature was maintained above 35.5°C by both active and passive manoeuvres, to exclude temperature changes as a source of post-operative respiratory depression or delayed recovery.

The patient was then turned, positioned, cleaned, draped and given. Bupivacaine and por 8 to scalp and abdominal sites was given (bupivacaine 3 mg/kg and por 8, 5IU in 50 ml, max 4 ml/kg). Skin incision and surgery followed.

"Steady state" observations were then recorded and serum catecholamine levels were taken just prior to remifentanil/placebo administration. These observations were heart rate, blood pressure, oxygen saturation, transcutaneous carbon dioxide partial pressure and rectal temperature. The remifentanil or control was then given as a bolus over 1 minute, with full sets of the above measurements being recorded during this minute and for one further minute, to detect adverse cardiovascular responses to the drug, immediately prior to tunnelling.

Tunnelling was then performed and full sets of the same measurements were taken mid - tunnelling and then at one minute intervals for ten minutes and then at five minute intervals until the end of surgery. From these readings, the maximal deviations from the "steady state" cardiovascular parameters were subsequently compared, as were the durations of time for a return to within 5 % of these "steady state" cardiovascular parameters. The degree of these cardiovascular deviations from "steady state" and the duration of these deviations were taken as markers of the stress response to tunnelling. The tunnelling stage generally lasted about four minutes.

A second venous blood sample for serum catecholamines was taken just after tunnelling, for comparison with the "steady state" serum catecholamine levels.

The catecholamine samples were immediately placed into cooled (4 degrees Celcius), heparinised tubes and spun down, the plasma separated and frozen at –70°C. The samples were then analysed at the University of Cape Town Anaesthetics Laboratory by electrochemical detection after separation with reverse phase high-performance liquid chromatography using dihydrobenzylamine as the internal standard. The coefficient of variation of the method is 7.9% for noradrenaline and 8.7% for adrenaline; the lower limit of sensitivity was 20 pg.ml-1.

On application of the wound dressing, reversal was given. This was subject to adequate spontaneous reversal of neuromuscular blockade as assessed by a peripheral nerve stimulator and therefore incomplete reversal of neuromuscular blockade as a factor in post-operative respiratory depression was excluded. Anaesthetic gases were turned off and weaning from the ventilator commenced.

The time intervals from the end of surgery to extubation, to moving to recovery, to readiness for discharge were compared between the two groups. Specific criteria had to be achieved for each stage. A Red Cross Hospital modification of Steward's criteria was used (see table attached table).

Table of criteria used to assess post-operative recovery

RED X MODIFIED STEWARDS' CRITERIA:
Criteria for extubation: Spontaneous breathing, Sats >95% on FiO2 40 %, normothermic, cardiovascularly uncompromised.
Criteria for moving to Recovery: Maintaining airway, Sats >95% with added FiO2

Criteria for Discharge to ward:

Respiratory: can breath deeply or cough, Sats >95% on room air, normal respiratory pattern

Cardiovascular: HR and SBP within 10% of pre-op value, warm peripherally.

Neurological: pain free, moving all 4 limbs, opening eyes, responding to commands or painful stimulus

Temperature: >35. 5 axillary

Adverse events, blood loss, and additional comments were recorded and the patients were kept in recovery for two hours post administration of the drug for full monitoring including respiratory rate, transcutaneous carbon dioxide partial pressure, oxygen requirements (added oxygen was given if peripheral oxygen saturation < 95% on room air) and analgesic requirements (see table).

Table of criteria used to assess post-operative analgesia requirements

Criteria for administration of analgesia:

Restless, crying, heart rate or blood pressure > 10% above pre-induction baseline (having first been given "Tender Loving Care" including comforting and handling by the recovery room nursing staff and / or ½ Darrows Dextrose or feed to babies to exclude hunger).

The degree and duration of changes in the respiratory parameters from pre-operative baseline were recorded. In addition, the time in minutes until transcutaneous CO2 levels decreased to (1) a steady state and (2) 6.0 kPa and then to (3) 5.3 kPa, was recorded, along with (4) any rebound respiratory depression.

To assess evidence of intra-operative cardiovascular depression due to remifentanil, we looked at heart rate and blood pressure, just before and just after administration of the "drug" and looked at the percentage changes in these parameters. No other variable was involved during this period. Thus if at p =0.05 the cardiovascular changes in the two groups were different, a statistically significant degree of cardiovascular depression could be implied.

To assess the signs of pain and stress we looked at the changes in heart rate, blood pressure and plasma catecholamine levels with tunnelling. Measurements were made just before, during and after

tunnelling and percentage changes from the "before" readings in control and remifentanil groups were compared. These findings were compared within different age groups and with all ages grouped together. Statistical analysis was performed to assess possible differences existed between the remifentanil and the control group. Thus if at p =0.05 the two groups were different, a statistically significant attenuation of the stress response could be concluded.

To assess whether any delay in recovery was caused, we measured the time in minutes from the end of surgery until specific criteria were fulfilled. These criteria assessed whether the patient was ready to be extubated, to be taken to recovery and to be discharged to the ward. Thus if at p = 0.05 the times taken to achieve these criteria two groups were different, a statistically significant delay in recovery could be implied.

To assess post-operative respiratory depression we looked at post-operative respiratory rate, post-operative oxygen requirements (added oxygen was given until the peripheral saturation stayed above 95%) and transcutaneous carbon dioxide measurements. Transcutaneous carbon dioxide readings and measurements of respiratory rate were taken pre-induction and post-operative recordings were then compared. These comparisons included the maximum percentage deviation from the pre-operative baseline, the time in minutes taken to descend to 6.0 kPa, the time in minutes taken to descend to 5.3kPa and the time taken in minutes until the readings became steady. Thus if at p = 0.05 the two groups differ, a statistically significant degree of post-operative respiratory depression could be implied.

Transcutaneous carbon dioxide (CO2) partial pressure was measured using a Novametrix CO2 meter manufactured by Medtronics. The sensor consists basically of a modified pH electrode bathed in an electrolyte solution covered by a thin membrane across which CO2 can diffuse.

Changes in CO2 concentration cause pH changes according to the Henderson-Hasselbalch equation, leading to the generation of a voltage. The sensor incorporates a warming device that heats skin to 45 degrees Celsius, causing superficial tissue vasodilatation and a decreased distance for tissue CO2 to diffuse towards the sensor. A digital graphical display of tissue CO2 level then monitors changes with a lag time of approximately one minute.

Transcutaneous carbon dioxide measurement is often used as a research tool to monitor tissue levels both in adults and in children. However, there have been problems with the use of transcutaneous measurement in the past and the literature over the last two decades has reflected this.

McLellan in 1981 compared arterial and transcutaneous carbon dioxide levels in healthy volunteers given varying concentrations of inspired gas. He found that the cutaneous capnograph accurately and consistently reflected the arterial levels with only a small time lag in these healthy adults.

Kost in 1983 monitored transcutaneous levels of carbon dioxide in premature babies with respiratory distress syndrome. While he found that although there was good correlation with arterial levels, he found there to be a significant calibration drift and thus recommended that it calibration be repeated at three hourly intervals.

Rome in 1984 demonstrated the relative inaccuracy of the earlier models and advised caution in the interpretation of their data. He found that in nine ex-premature infants with bronchopulmonary dysplasia the transcutaneous partial pressure consistently overestimated the arterial pressure by 9 kPa.

Wimberley in 1985 also pointed out the problem of electrode drift, stating that although a valuable tool, transcutaneous monitoring should not be regarded as a replacement for arterial sampling. In addition, Wimberley pointed out that with increasing electrode temperature, transcutaneous readings increase by a factor similar to the anaerobic temperature coefficient of PCO2 in blood. He found that transcutaneous measurements of carbon dioxide to be more accurate that measurements of oxygen.

Geven in 1987 concluded that the transcutaneous meter gives reasonably good correlation with arterial levels in sick newborns. He felt that the meter could not replace arterial sampling, but may decrease the frequency of arterial samples required.

Kavanagh in 1992, however, found that the transcutaneous carbon dioxide readings correlated poorly with arterial levels in 30 post-operative, spontaneously breathing adults.

Binder in 1994 tested transcutaneous carbon dioxide readings in very low birth weight infants at different sensor temperatures (43 and 40 degrees Celsius) and found good correlation with umbilical arterial measurements. Thus he recommended the use of the lower temperature sensor. This work was done in the light of the decreasing use of transcutaneous blood gas monitoring following the advent of pulse oximetry. Thus he found that transcutaneous carbon dioxide levels do in fact give accurate readings and he suggested that this mode of monitoring should continue to have a place.

Tobias in 1997 demonstrated that transcutaneous carbon dioxide measurements were a more accurate reflection of arterial partial pressures than were end tidal measurements in infants and toddlers under 48 months of age being ventilated for respiratory failure. He found that the transcutaneous level correlated well with the arterial reading. He compared end-tidal, transcutaneous and arterial levels. The ETCO2 to PaCO2 difference was 6.8 +/- 5.1 mm Hg, while the TC-CO2 to PaCO2 difference was 2.3 +/- 1.3 mm Hg ($P < 0.0001$). The absolute difference of the TC-CO2 and PaCO2 was 4 mm

Hg or less in 96 of the 100 values, while the ETCO2 to PaCO2 difference was 4 mm Hg or less in 38 of the 100 values ($P < 0.0001$).

Arsowa in 1997 pointed out the problems of using end-tidal carbon dioxide readings in 61 ventilated neonates to assess the adequacy of ventilation and suggested the use of transcutaneous monitoring. He found a good correlation ($r=0.72$) between end-tidal and transcutaneous readings but a significant discrepancy between the two. Thus he concluded that transcutaneous measurement is more accurate in this age group due to ventilation-perfusion mismatch causing inaccuracy in the end-tidal readings (12mmHg difference). In addition, there is the problem of apparatus dead space further decreasing the accuracy of end-tidal assessments.

Drummond also in 1997 reported his use of the transcutaneous meter to assess post-operative hypercarbia in 64 adults, post-craniotomy patients following extubation. He compared the levels recorded with arterial samples and found them to correlate well. He also found that post operative transcutaneous hypercarbia is a good predictor of post operative seizures, lower post-operative Glasgow coma scale, re-intubation and correlates well with the degree of intra-operative brain disturbance.

Lang in 1998 used continuous transcutaneous monitoring to assess tissue carbon dioxide levels in patients undergoing brain stem death apnoea tests. He showed a good correlation with arterial levels.

O'connor in 1998 recommended the use of the transcutaneous monitor for the long distance transport (greater than 30 miles) of ventilated neonates. He found in his prospective trial that monitored neonates were more likely to arrive with normal blood gases and experience lower peak airway pressures than non-monitored neonates. He also found that pre-transport stabilization times were not different between the two groups.

There were reports of burns being caused by the early transcutaneous gas monitors in addition to the reports of inaccuracy. The risk of burns has now been eradicated through design changes. The advent of pulse oximetry, with its ease of use, also caused a decrease in the use of the transcutaneous meter. There are areas of the world where its use is reduced or not available because of economic reasons, but it is considered a standard of care in many leading centres. However, most level three intensive care units in North America today use transcutaneous monitoring on their critical neonates. In the ICUs in the Children's Hospital at the University College of Los Angeles, very few blood gases are taken, almost all gas partial pressures being monitored transcutaneous.

The accuracy and clinical applicability of the transcutaneous monitor have been questioned but more recent studies generally agree that it has a place both for research and clinical purposes. Rauch showed that in a paediatric intensive care unit there was significant correlation between the intermittently taken arterial and transcutaneous carbon dioxide levels in neonates and infants with a

variety of underlying pathologies. There was, however, a consistent difference between the arterial and transcutaneous readings. He recommended further refinement of the technology to produce greater accuracy.

Transcutaneous readings depend not only on blood gases, but also local perfusion, site preparation and skin density. Skill is required in its application and interpretation. Transcutaneous readings are thus reflections of blood gas values. Blood gas values hopefully reflect organ values.

During the time that studies on the usefulness or otherwise of the transcutaneous meter have been reported, the companies making them have created newer, improved versions as a response to the problems and criticisms. Thus the early problems of user unfriendliness with problematic sensors, inaccuracy, poor repeatability, baseline sensor electrode drift, lack of compensation for temperature or atmospheric pressure, heat related skin injuries etc. have been largely attended to. In addition smaller, lighter sensors are more easily and safely applied to the neonatal chest wall, where larger, heavier sensors may cause compression, twisting or even ischaemia of the relatively less perfused neonatal tissue. It should be noted that it is important to change measurement sites on a regular basis.

In this study we used the Novametrix 860 meter. The Novametrix 860 transcutaneous carbon dioxide meter is the most recent model manufactured by Novametrix. Its advantages over older versions include more reliable and durable sensors. The sensor is a Stow-Severinghaus pH / Clark-type polargraphic variety. It is small and light and has a fast response time and can be easily re-membraned when required.

The monitor demonstrates real time analysis with a 45 second response time, rapid automatic two-point calibration procedures against known gases with built-in barometric pressure compensation for increased accuracy. Stability is quoted at "better than 2mmHg/hr".

An automatic skin timer enhances patient safety and comfort.

Technically, the displayed carbon dioxide partial pressure is compensated for metabolic factors related to the temperature effect and carbon dioxide production. It has limit alerts that are adjustable and retainable. It has the facility to select different sensor temperatures to accommodate differing diffusion distances due to differing skin and subcutaneous tissue thickness, i.e. for neonates or adults. There is an automatic power shutdown to the sensor heater to prevent burns if temperature limit is reached. Also the duration of sensor activity at one given site is monitored and limited to prevent injury.

Local power is the amount of energy required to heat the tissue to the appropriate temperature. This is also monitored and displayed.

To monitor trends this monitor has a digital, continuous display with a memory.

We also looked for other side effects or differences such as chest wall rigidity, post-operative analgesic requirements and bleeding.

During this study, within patient changes, represented as a percentage of the baseline readings are compared between control and remifentanil groups. Absolute values have not been used because of the huge variation of baselines and changes with age.

Thus the control group represents the "usual" levels of stress response, the "usual" recovery profile and the "usual" post-operative respiratory patterns. Against this standard the remifentanil group can be compared, using standard statistical analysis. Any significant differences found between the two groups thus demonstrate a significant difference in stress level, recovery profile or post-operative respiratory profile.

It is the intention of this trial to compare the response to remifentanil versus control within each separate age group as well as looking at all ages combined. It is beyond the scope of this study to compare age groups with each other, although the data and mode of statistical analysis does allow inter-age group comparisons to be made. This is an area for further study.

4. RESULTS:

This section consists of a classification of the parameters analysed, a description of the modes of statistical analyses used and then the individual results sections.

Classification of the parameters analysed

There were 33 patients in group R (remifentanil) and 29 patients in group S (control). Within each treatment group, the patients were then divided into "x-premies", neonates, infants, over 1 year olds and all ages combined. The following parameters are assessed statistically:

Patient Characteristics:

An analysis is performed to compare the patient profiles (age, weight, height, baseline cardiovascular parameters) in the remifentanil and control groups, both overall and within each age bracket, to ensure statistical comparability.

Anaesthesia Characteristics:

An analysis is performed to ensure that a comparable duration of anaesthesia was received by the remifentanil and the control groups, both overall and within each age bracket.

Response To Drug:

An analysis is performed to compare the haemodynamic response to administration of remifentanil and control, both overall and within each age bracket.

Response To Tunnelling:

An analysis is performed to compare the degree and duration of changes in autonomic and endocrine markers of stress, in the remifentanil and control groups, both overall and within each age bracket.

Recovery Profile:

An analysis is performed to compare the rates of recovery from anaesthesia in the remifentanil and control groups, both overall and within each age bracket.

Respiratory Depression:

An analysis is performed to compare the degree of post-operative respiratory depression in the remifentanil and control groups, both overall and within each age bracket.

Explanation of statistical analyses used, including definitions of patient groups:

Age categories

The age groups that have been looked at are x-premies, neonates, infants, older children and all ages combined.

X-premies are babies born before 35 weeks of post conceptual age and who are still less than 56 weeks of post conceptual age. This group is made up of patients from both the neonate and infant age brackets. They have been analysed separately because premature babies may represent a group that is distinct from term babies.

Neonates are babies during their first 28 days of extra-uterine life.

Infants are babies between the ages of one month and one year.

Older children are children over the age of one year.

Treatment Groups

The patients have all been allocated randomly to receive either remifentanil (R) or saline (S) as control

Abbreviations

ANOVA = Analysis of Variance

Statistical Tests

The modes of analysis were chosen by an independent body at the Medicines Research Council and were part of the original design protocol. Tests were used for parametric data and for non-parametric data.

Tests for parametric data

For the parametric data, tables include basic statistical data, using number of patients in sample, mean and standard deviation.

Several different types of statistical analysis have then been applied to this data. The use of different types of analysis can increase the amount of statistical evidence available from which to make final conclusions.

The tests applied to this parametric data include analysis of variance, which uses pooled data to test each age group. This increases the power of the result when all ages together are considered, because

of the increased numbers involved, but it decreases the accuracy of result within each specific age category.

The ANOVA tables suggest the statistical likelihoods of the following:

In the first column, first row "Code" refers to remifentanil or control grouping. The p value in this row suggests the statistical likelihood that the means in the remifentanil and control groups are the same, when all age groups are combined.

In the second row "agecode" refers to age groupings. The p value in this row suggests the statistical likelihood that the means in each age category are the same (this is unrelated to remifentanil or control groupings).

In the third row "code#agecod" refers to the effect of age on the response to remifentanil or control. The p value in this row suggests whether the conclusion reached by the p value in row one is also applicable to each individual age group as well. A "p" value of < 0.05 is regarded as significant.

95% confidence intervals for the means are given. If one interval overlaps with the other, there is considered to be no statistically significant difference between the means of the remifentanil and control groups.

95% confidence intervals for the difference between the means. This assesses the difference between remifentanil and control group means and gives the 95% confidence limits of this difference. If one limit is a positive figure and the other limit is negative, the difference includes the number zero, i.e. the means are considered not statistically different.

T tests between the means. This is a standard 2 sample T test that gives a p value which if < 0.05 suggests that the means are statistically different and if > 0.05 suggests that they are not significantly different.

Box and whisker charts. These are reader friendly charts that give an easy visual representation of the means or medians and their 95% confidence intervals. If the intervals overlap with each other, there is no statistically significant difference.

The conclusions that can be drawn from each individual test have been stated in bold, immediately underneath the test.

Tests for non-parametric data

For the non parametric data, ie where "censored" data (arbitrary cut off values) have been used, the tables include medians and 95% confidence intervals.

The tests applied to this data include cox regression tests, which is comparable to the analysis of variance test for parametric data. As with analysis of variance tables the p value in the first row suggests the statistical difference between the remifentanil and control groups when all age groups are combined. The p value in the second row suggests age differences, unrelated to remifentanil or control groupings. The p value in the third row suggests whether the conclusions reached by the p value in row one are applicable equally to all age groups.

Log rank tests give a p value for each individual age category that suggests the statistical likelihood that the medians are the same.

Wilcox and –2LR test results are also included, although no conclusions have been drawn from them due to the decreased accuracy of these tests.

Box and whisker charts are presented as either the mean and the 95% confidence interval of the mean for parametric data, or as the median and the 95% confidence interval of the median for non-parametric data.

Generally speaking there should be good correlation between the results of the various tests. This is not always the case, however, because of differences between the tests, i.e. analysis of variance testing uses pooled variances using data from all age groups together and thus conclusions are not as accurate for individual age categories as a conclusions made from a two sample T test or a 95% confidence interval. On occasions the box and whisker confidence interval graphs are at odds with the comparable confidence interval figures; this is due to the use of slightly different statistical computer programmes. Usually there is good agreement between these different types of statistical analysis, but in borderline cases, results may differ slightly.

Final conclusions are given at the end of each section, using all the data from all the tests. Again, conclusions are written in bold.

Individual Results for each parameter

Patient Characteristics

Age, weight, height and baseline cardiovascular parameters are compared in the remifentanil and control groups, within each age group, using box and whisker charts, analysis of variance, T tests and 95% confidence intervals, at p = 0.05. They are found to be similar. Thus differences found during the trial between the groups can be interpreted as being related purely to the effect of remifentanil or control.

This "All ages " table shows the means, standard errors of the mean and p values testing the null hypothesis that the remifentanil and control groups have the same characteristics and are thus comparable:

	Age (months)	Weight (Kg)	Height (cm)	Heart rate Beats/min	Systolic Pressure mm Hg	Mean Pressure mm Hg	Diastolic Pressure mm Hg
Control	34.8 (8.9)	10.5 (1.9)	76.3 (6.2)	106.7 (4.0)	85.6 (3.7)	60.1 (3.3)	50.4 (3.2)
Remifent	23.6 (5.8)	8.65 (1.2)	71.8 (4.7)	113.2 (4.0)	83.4 (3.9)	60.4 (3.0)	48.2 (2.6)
P value	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

On the following pages numbered A to AA are the detailed statistics for each variable within each age category

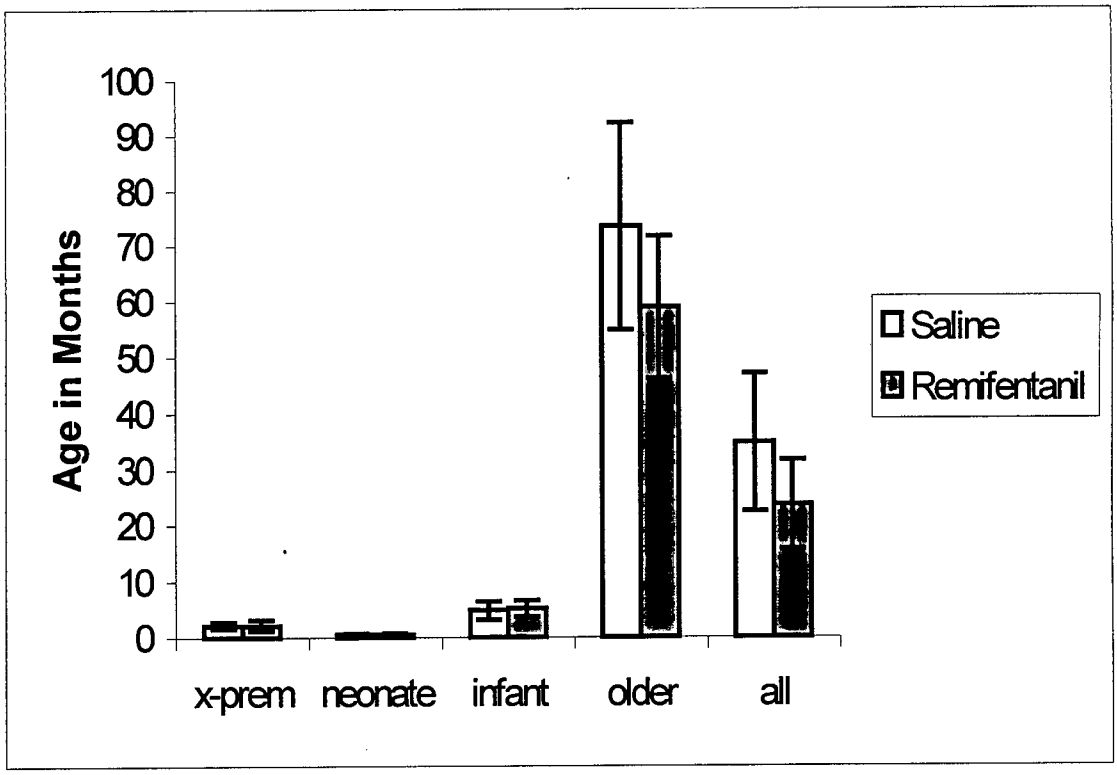
Table to show the sex distribution within remifentanil and control groups

The first column shows the number of females
The second column shows the number of males
The third column shows both sexes combined
The rows show the remifentanil numbers (R) and the control numbers (S)

	f	m	all
S	14	15	29
R	15	18	33
All	29	33	62

This shows that both remifentanil and control groups have a similar proportions of male and female.

Mean age, in months & 95% confidence intervals, remifentanil versus control



Confidence intervals and two sample T test to compare the mean ages, in months, between remifentanil and control groups, in each age group:

X-premie

	N	Mean	StDev	SE Mean	95% CI
S	4	2.112	0.895	0.45	1.48 - 2.74
R	4	2.12	1.33	0.67	1.18 - 3.06

Confidence intervals overlap, therefore the mean ages are not significantly different

95% Confidence interval for the difference between the means -2.07 to 2.05

The difference between the means is therefore not significant

T test for null hypothesis that the means are the same:
T= -0.02 P=0.99 DF= 5

The null hypothesis is proven, thus the mean ages are not significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	0.520	0.236	0.11	0.4 - 0.7
R	8	0.587	0.243	0.086	0.5 - 0.7

Confidence intervals overlap, therefore the mean ages are not significantly different

95% Confidence interval for the difference between the means -0.38 to 0.247

The difference between the means is therefore not significant

T test for null hypothesis that the means are the same:
T= -0.50 P=0.63 DF= 8

The null hypothesis is proven, thus the mean ages are not significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	4.77	3.78	1.1	3.2 - 6.4
R	13	5.15	3.68	1.0	3.7 - 6.6

Confidence intervals overlap, therefore the mean ages are not significantly different

95% Confidence interval for the difference between the means -3.6 to 2.8

The difference between the means is therefore not significant

T test for null hypothesis that the means are the same :
T= -0.25 P=0.80 DF= 21

The null hypothesis is proven, thus the mean ages are not significantly different

Older Child

	N	Mean	StDev	SE Mean	95% CI
S	13	73.5	48.7	14	54.7 - 92.2
R	12	59.0	31.9	9.2	46.3 - 71.8

Confidence intervals overlap, therefore the mean ages are not significantly different

95% Confidence interval for the difference between the means -48.5 to 20

The difference between the means is therefore not significant

T test for null hypothesis that the means are the same
T= -0.88 P=0.39 DF= 20

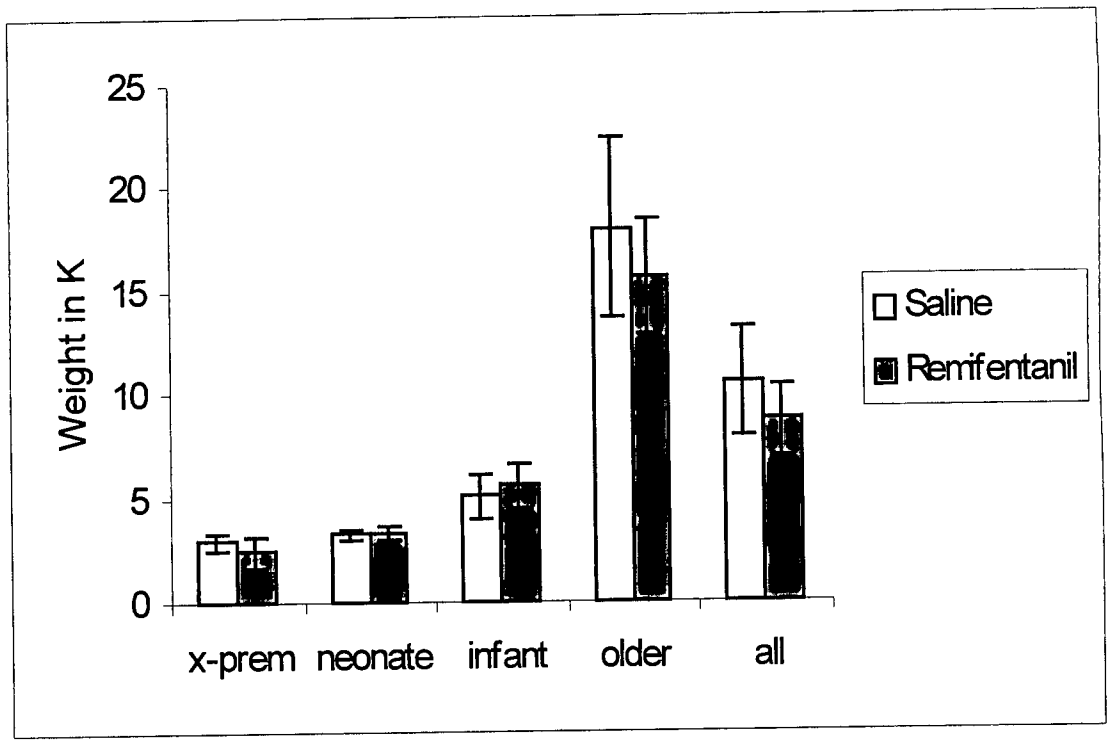
The null hypothesis is proven, thus the mean ages are not significantly different

CONCLUSION

Notwithstanding the quite large, but not statistically significant, mean age difference of the two groups, the distributions into the five age categories of the remifentanil and control groups are quite similar. A chi-square test of homogeneity of the distributions gives result: observed chi-square = 0.644 on 2 degrees of freedom, which is not significant.

There was also no statistical difference, at p= 0.05, between the mean ages in the remifentanil and control groups, within each age group, using, 95% confidence intervals for the means, 95% confidence intervals for the difference between the means , T tests and box and whisker confidence interval charts.

Mean weight in kg & 95% confidence intervals, remifentanil versus control



Two sample T test and 95% confidence intervals to compare weights, in kilograms, between remifentanil and control groups, in each age group:

X-premies

	N	Mean	StDev	SE Mean	95% CI
S	4	2.875	0.690	0.34	2.4 - 3.35
R	4	2.42	1.00	0.50	1.72 - 3.12

Confidence intervals overlap, therefore the mean weights are not significantly different

95% Confidence interval for the difference between the mean weights -1.12 to 2.02

The difference between the mean weights is therefore not significant

T test for null hypothesis that the mean weights are the same
T= 0.74 P=0.49 DF= 5

The null hypothesis is proven, thus the mean weights are not significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	3.220	0.449	0.20	2.94 - 3.50
R	8	3.283	0.642	0.23	2.97 - 3.60

Confidence intervals overlap, therefore the mean weights are not significantly different

95% Confidence interval for the difference between the mean weights -0.74 to 0.61

The difference between the mean weights is therefore not significant

T test for null hypothesis that the mean weights are the same
T= -0.21 P=0.84 DF= 10

The null hypothesis is proven, thus the mean weights are not significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	5.06	2.49	0.75	4.02 - 6.11
R	13	5.54	2.76	0.77	4.48 - 6.61

Confidence intervals overlap, therefore the mean weights are not significantly different

95% Confidence interval for the difference between the mean weights is -2.71 to 1.75

The difference between the mean weights is therefore not significant

T test for null hypothesis that the mean weights are the same
T= -0.45 P=0.66 DF= 21

The null hypothesis is proven, thus the mean weights are not significantly different

Older Child

	N	Mean	StDev	SE Mean	95% CI
S	13	18.0	11.2	3.1	13.69 - 22.34
R	12	15.59	6.86	2.0	12.84 - 18.34

Confidence intervals overlap, therefore the mean weights are not significantly different

95% Confidence interval for the difference between the mean weights is -10.1 to 5.3

The difference between the mean weights is therefore not significant

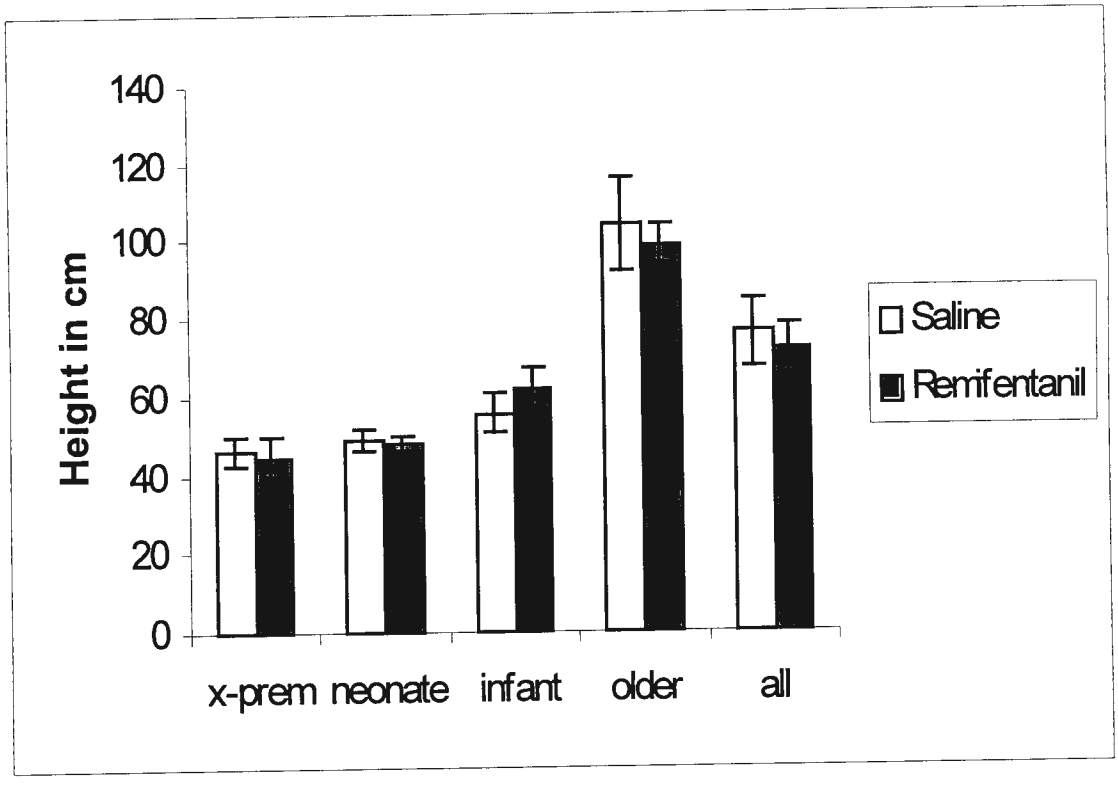
T test for null hypothesis that the mean weights are the same
T= -0.66 P=0.52 DF= 20

The null hypothesis is proven, thus the mean weights are not significantly different

CONCLUSION

There was no difference between weights in the remifentanil and control groups , within each age group, at p=0.05, using 95% confidence intervals of the means, 95% confidence intervals of the difference between the means, T tests and box and whisker charts

Mean height, in cm & 95% confidence interval, remifentanil versus control



Two sample T test and confidence interval to compare height in centimetres between remifentanil and control groups, in each age group:

X-Premies

	N	Mean	StDev	SE Mean	95% CI
S	4	45.75	4.92	2.5	42.3 - 49.3
R	4	44.25	7.14	3.6	39.3 - 49.3

Confidence intervals overlap, therefore the mean heights are not significantly different

95% Confidence interval for the difference between the mean heights is -9.6 to 12.6

The difference between the mean heights is therefore not significant

T test for null hypothesis that the mean heights are the same

T= 0.35 P=0.74 DF= 5

The null hypothesis is proven, thus the mean heights are not significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	49.00	4.64	2.1	46.1 - 51.9
R	8	47.75	4.30	1.5	45.6 - 49.9

Confidence intervals overlap, therefore the mean heights are not significantly different

95% Confidence interval for the difference between the mean heights is -4.7 to 7.2

The difference between the mean heights is therefore not significant

T test for null hypothesis that the mean heights are the same
T= 0.49 P=0.64 DF= 8

The null hypothesis is proven, thus the mean heights are not significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	55.6	12.1	3.7	50.5 - 60.7
R	13	61.8	16.1	4.5	55.6 - 68.1

Confidence intervals overlap, therefore the mean heights are not significantly different

95% Confidence interval for the difference between the mean heights is -18.2 to 5.8

The difference between the mean heights is therefore not significant

T test for null hypothesis that the mean heights are the same
T= -1.07 P=0.29 DF= 21

The null hypothesis is proven, thus the mean heights are not significantly different

Older Child

	N	Mean	StDev	SE Mean	95% CI
S	13	104.3	30.8	8.6	92.4 - 116.2
R	12	98.7	22.0	6.3	89.9 - 107.6

Confidence intervals overlap, therefore the mean heights are not significantly different

95% Confidence interval for the difference between the mean heights is -27.7 to 16.6

The difference between the mean heights is therefore not significant

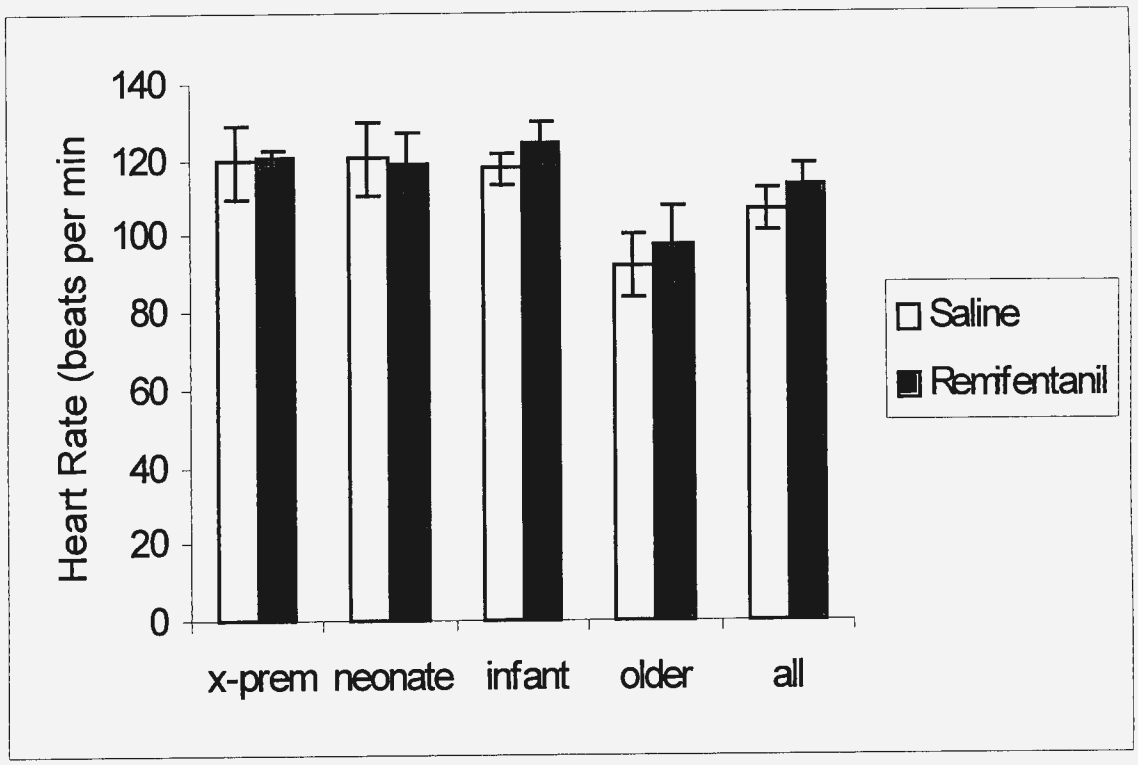
T test for null hypothesis that the mean heights are the same
T= -0.52 P=0.61 DF= 21

The null hypothesis is proven, thus the mean heights are not significantly different

CONCLUSION

There was no difference, at p=0.05, between heights in the remifentanil and control groups, within each age group, using 95% confidence intervals for the mean, 95% confidence intervals for the difference between the means,Ttests and box and whisker charts.

Mean baseline heart rate , in beats per minute & 95% confidence interval, remifentanil versus control



Basic statistics

Rows contain the number, mean and standard deviation of baseline heart rate in control (S) or remifentanil (R)
Columns contain the age categories: neonate, infant, >1yr old, all ages

	neonate	infant	> 1yr	all ages
S number	5	11	13	29
mean	120.20	117.82	92.00	106.66
sd	15.53	10.08	22.16	21.51
R number	8	13	12	33
mean	118.87	124.00	97.58	113.15
sd	17.48	15.01	26.36	23.17
all number	13	24	25	62
mean	119.38	121.17	94.68	110.11
sd	16.10	13.10	23.92	22.47

Analysis of variance for differences between the baseline heart rate in the remifentanil and control groups

The p values in the final column test the null hypothesis that comparative groups are the same. The first row (marked "code") compares the remifentanil group baseline heart rate against the control. The second row (agecod) compares baseline heart rates in different age groups. The third row (code*agecod) assesses whether the comparability of remifentanil and control group baseline heart rates, as suggested by row one, are consistent amongst the differing age groups.

Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	651.4	166.9	166.9	0.46	**0.501**
agecod	2	9652.1	9728.9	4864.5	13.38	**0.000**
code* agecod	2	128.5	128.5	64.2	0.18	**0.838**
Error	56	20358.2	20358.2	363.5		
Total	61	30790.2				

Thus the anova table shows that baseline heart rates are different from one age group to the next, as would be expected (p = 0.000).
It also concludes that there is no statistical difference between the baseline heart rates in the remifentanil and control groups (p = 0.501) and that this is consistent in the different age groups (p = 0.838).

95 % confidence intervals and T tests to compare the baseline heart rates in beats per minutes between remifentanil and control groups, in each age group:

X-Premies

	N	Mean	StDev	SE Mean	95% CI
S	4	119.5	14.0	7.0	109.7 - 129.3
R	4	120.25	3.30	1.7	117.9 -122.6

Confidence intervals overlap, therefore the mean heart rates are not significantly different

95% confidence interval for the difference between the mean heart rates is -23.6 to 22.1

The difference between the mean heart rates is therefore not significant

T test for null hypothesis that the mean heart rates are the same
T= -0.10 P=0.92 DF= 3

The null hypothesis is proven, thus the mean heart rates are not significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	120.2	15.5	6.9	110.5 - 129.9
R	8	118.9	17.5	6.2	110.3 - 127.5

Confidence intervals overlap, therefore the mean heart rates are not significantly different

95% confidence interval for the difference between the mean heart rates is -19.7 to 22.4

The difference between the mean heart rates is therefore not significant

T test for null hypothesis that the mean heart rates are the same
T= 0.14 P=0.89 DF= 9

The null hypothesis is proven, thus the mean heart rates are not significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	117.8	10.1	3.0	113.6 - 122.0
R	13	124.0	15.0	4.2	118.2 - 129..8

Confidence intervals overlap, therefore the mean heart rates are not significantly different

95% confidence interval for the difference between the mean heart rates is -16.9 to 4.5

The difference between the mean heart rates is therefore not significant

T test for null hypothesis that the mean heart rates are the same
T= -1.20 P=0.24 DF= 21

The null hypothesis is proven, thus the mean heart rates are not significantly different

Older Child

	N	Mean	StDev	SE Mean	95% CI
S	13	92.0	22.2	6.1	83.5 - 100.5
R	12	97.6	26.4	7.6	87.0 - 108.2

Confidence intervals overlap, therefore the mean heart rates are not significantly different

95% confidence interval for the difference between the mean heart rates is -14.8 to 25.9

The difference between the mean heart rates is therefore not significant

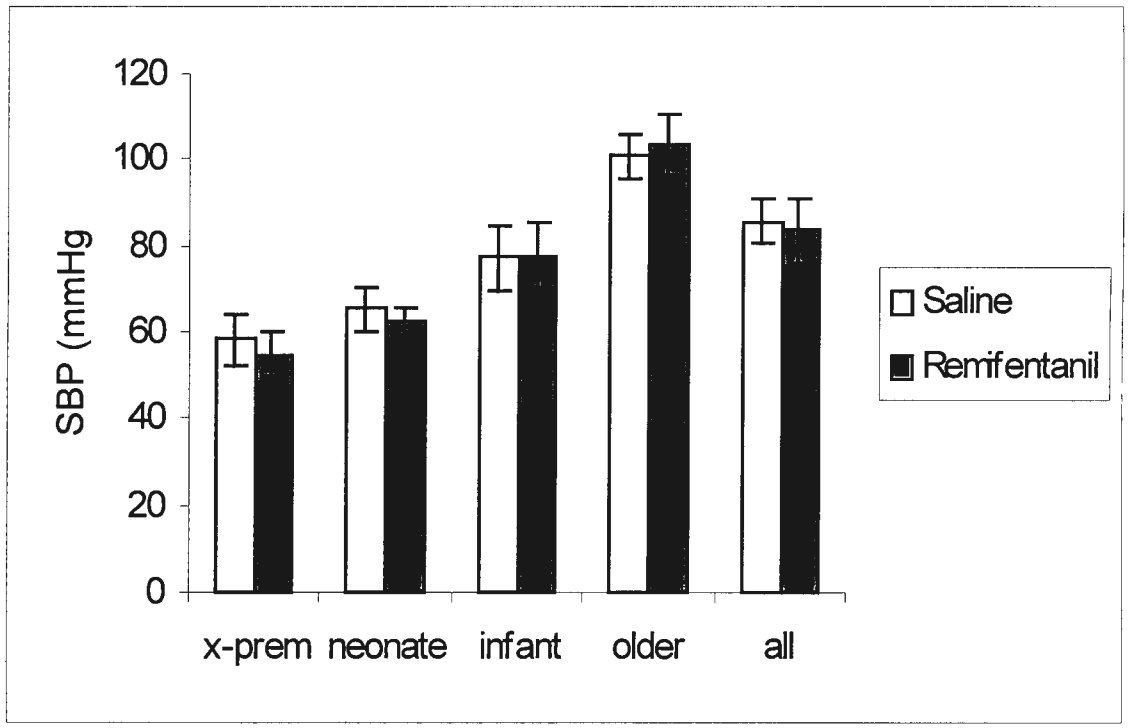
T test for null hypothesis that the mean heart rates are the same
T= 0.57 P=0.57 DF= 21

The null hypothesis is proven, thus the mean heart rates are not significantly different

CONCLUSION:

There was no statistical difference, at p=0.05, between the baseline heart rates in the remifentanil and control groups , using analysis of variance, 95% confidence intervals of the means, 95% confidence intervals of the difference between the means, T tests and box and whisker charts, in all age groups.
There was obviously a significant difference in heart rate from one age group to the next.

Mean baseline systolic blood pressure, in mm Hg, 95% confidence intervals, remifentanil versus control



Basic statistics

Rows contain the number, mean and standard deviation of baseline systolic pressure in control (S) or remifentanil (R)
Columns contain the age categories: neonate, infant, >1yr old, all ages

		neonate	infant	> 1 yr	all
S	number	5	11	13	29
	mean	65.20	77.00	100.77	85.62
	sd	8.56	17.25	13.13	20.02
R	number	8	13	12	33
	mean	62.50	77.69	103.42	83.36
	sd	6.37	20.12	13.30	22.23
all	number	13	24	25	62
	mean	63.54	77.38	102.04	84.42
	sd	7.07	18.46	13.01	21.08

Analysis of variance for baseline systolic blood pressure in mm Hg, a comparison between remifentanil and control groups

Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	78.6	0.6	0.6	0.00	**0.958**
agecod	2	14552.6	14190.0	7095.0	31.97	**0.000**
code* agecod	2	59.1	59.1	29.5	0.13	**0.876**
Error	56	12426.8	12426.8	221.9		
Total	61	27117.1				

Thus the anova table shows that baseline systolic pressures are different from one age group to the next, as would be expected (p = 0.000).
It also concludes that there is no statistical difference between the baseline systolic pressures in the remifentanil and control groups (p = 0.958) and that this is consistent amongst the different age groups (p = 0.876).

Confidence intervals and T tests to compare baseline systolic blood pressures in mm Hg between remifentanil and control groups, in each age group:

X-Premies

	N	Mean	StDev	SE Mean	95% CI
S	4	58.25	8.54	4.3	52.2 - 64.3
R	4	54.75	6.99	3.5	49.9 - 59.7

Confidence intervals overlap, therefore the mean systolic pressures are not significantly different

95% confidence interval for the difference between the mean systolic pressures is -10.7 to 17.7

The difference between the mean systolic pressures is therefore not significant

T test for null hypothesis that the mean systolic pressures are the same
T= 0.63 P=0.55 DF= 5

The null hypothesis is proven, thus the mean systolic pressures are not significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	65.20	8.56	3.8	59.9 - 70.5
R	8	62.50	6.37	2.3	59.4 - 65.6

Confidence intervals overlap, therefore the mean systolic pressures are not significantly different

95% confidence interval for the difference between the mean systolic pressures is -8.2 to 13.6

The difference between the mean systolic pressures is therefore not significant

T test for null hypothesis that the mean systolic pressures are the same
T= 0.61 P=0.57 DF= 6

The null hypothesis is proven, thus the mean systolic pressures are not significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	77.0	17.3	5.2	69.8 - 84.2
R	13	77.7	20.1	5.6	69.9 - 85.4

Confidence intervals overlap, therefore the mean systolic pressures are not significantly different

95% confidence interval for the difference between the mean systolic pressures is -16.6 to 15.2

The difference between the mean systolic pressures is therefore not significant

T test for null hypothesis that the mean systolic pressures are the same
T= -0.09 P=0.93 DF= 21

The null hypothesis is proven, thus the mean systolic pressures are not significantly different

Older Child

	N	Mean	StDev	SE Mean	95% CI
S	13	100.8	13.1	3.6	95.7 - 105.8
R	12	103.4	13.3	3.8	98.1 - 108.8

Confidence intervals overlap, therefore the mean systolic pressures are not significantly different

95% confidence interval for the difference between the mean systolic pressures is -8.3 to 13.6

The difference between the mean systolic pressures is therefore not significant

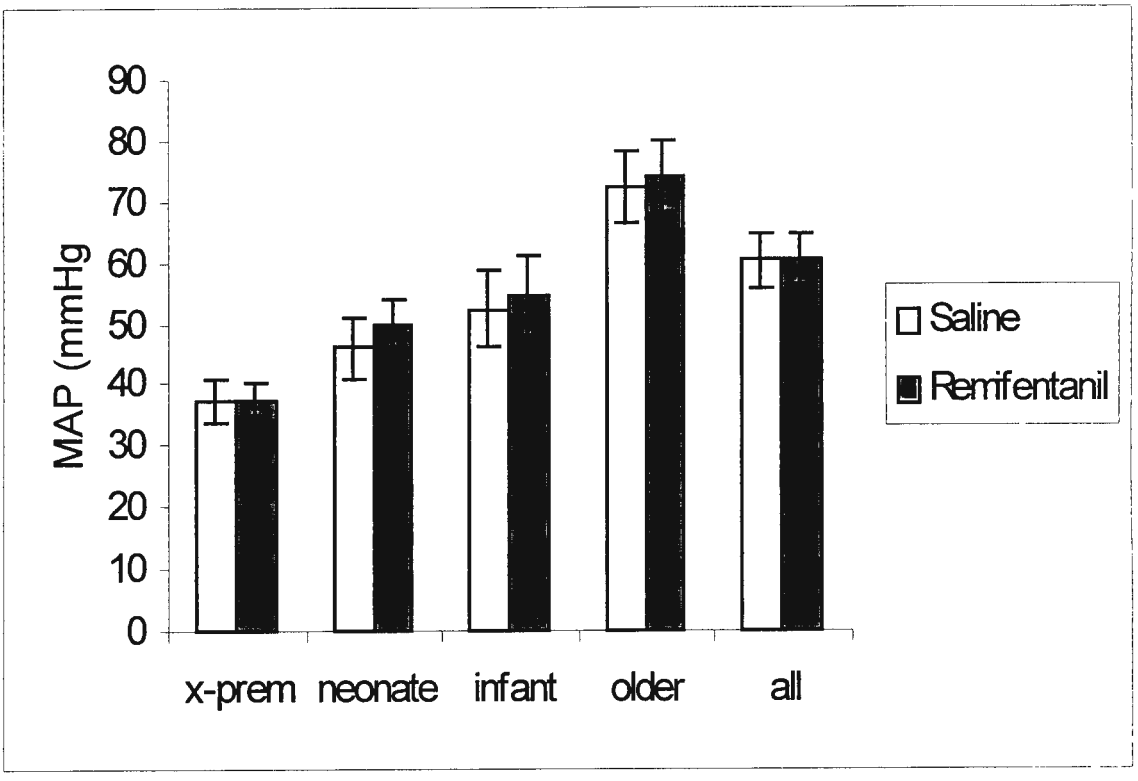
T test for null hypothesis that the mean systolic pressures are the same
T= 0.50 P=0.62 DF= 22

The null hypothesis is proven, thus the mean systolic pressures are not significantly different

CONCLUSION:

There was no statistical difference, at p=0.05, between the baseline systolic blood pressure in the remifentanil and control groups, in each age group, using analysis of variance, 95% confidence intervals of the mean, 95% confidence intervals of the difference of the means, Ttests and box and whisker charts. There was obviously a significant difference in systolic blood pressure from one age group to the next.

Mean baseline mean arterial pressure, in mm Hg, & 95% confidence intervals, remifentanil versus control



Basic statistics

Rows contain the number, mean and standard deviation of baseline mean arterial pressure in control (S) or remifentanil (R)
Columns contain the age categories: neonate, infant, >1yr old, all ages

		neonate	infant	> 1 yr	all ages
S	number	5	11	13	29
	mean	46.000	52.273	72.154	60.103
	sd	7.810	15.389	15.421	17.951
R	number	8	13	12	33
	mean	50.000	54.538	73.917	60.485
	sd	7.728	16.313	14.884	17.277
all	number	13	24	25	62
	mean	48.462	53.500	73.000	60.306
	sd	7.699	15.593	14.874	17.451

Analysis of variance for baseline mean arterial pressure in mmHg, a comparison between remifentanil and control groups :

Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	2.2	98.7	98.7	0.48	**0.491**
agecod	2	7050.4	7043.0	3521.5	17.13	**0.000**
code*agecod	2	10.5	10.5	5.3	0.03	**0.975**
Error	56	11514.0	11514.0	205.6		
Total	61	18577.2				

Thus the anova table shows that baseline mean arterial pressures are different from one age group to the next, as would be expected (p = 0.000).
It also concludes that there is no statistical difference between the baseline mean arterial pressures in the remifentanil and control groups (p = 0.491) and that this is consistent amongst the different age groups (p = 0.975)

Confidence intervals and two sample T test and to compare baseline mean arterial pressures in mm Hg between the remifentanil and control groups, in each age group.

X-Premies

	N	Mean	StDev	SE Mean	95% CI
S	4	37.25	4.99	2.5	33.75 - 40.8
R	4	37.50	4.04	2.0	34.7 - 40.3

Confidence intervals overlap, therefore the baseline mean arterial pressures are not significantly different

95% confidence interval for the difference between the baseline mean pressures is -8.5 to 8.0

The difference between the baseline mean pressures is therefore not significant

T test for null hypothesis that the baseline mean pressures are the same
T= -0.08 P=0.94 DF= 5

The null hypothesis is proven, thus the baseline mean pressures are not significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	46.00	7.81	3.5	41.1 - 50.9
R	8	50.00	7.73	2.7	46.2 - 53.8

Confidence intervals overlap, therefore the baseline mean arterial pressures are not significantly different

95% confidence interval for the difference between the baseline mean pressures is -14.2 to 6.2

The difference between the baseline mean pressures is therefore not significant

T test for null hypothesis that the baseline mean pressures are the same
T= -0.90 P=0.39 DF= 8

The null hypothesis is proven, thus the baseline mean pressures are not significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	52.3	15.4	4.6	45.8 - 58.7
R	13	54.5	16.3	4.5	48.2 - 60.8

Confidence intervals overlap, therefore the baseline mean arterial pressures are not significantly different

95% confidence interval for the difference between the baseline mean pressures is -15.7 to 11.2

The difference between the baseline mean pressures is therefore not significant

T test for null hypothesis that the baseline mean pressures are the same
T= -0.35 P=0.73 DF= 21

The null hypothesis is proven, thus the baseline mean pressures are not significantly different

Older Child

	N	Mean	StDev	SE Mean	95% CI
S	13	72.2	15.4	4.3	66.2 - 78.1
R	12	73.9	14.9	4.3	67.9 - 79.9

Confidence intervals overlap, therefore the baseline mean arterial pressures are not significantly different

95% confidence interval for the difference between the baseline mean pressures is -10.8 to 14.3

The difference between the baseline mean pressures is therefore not significant

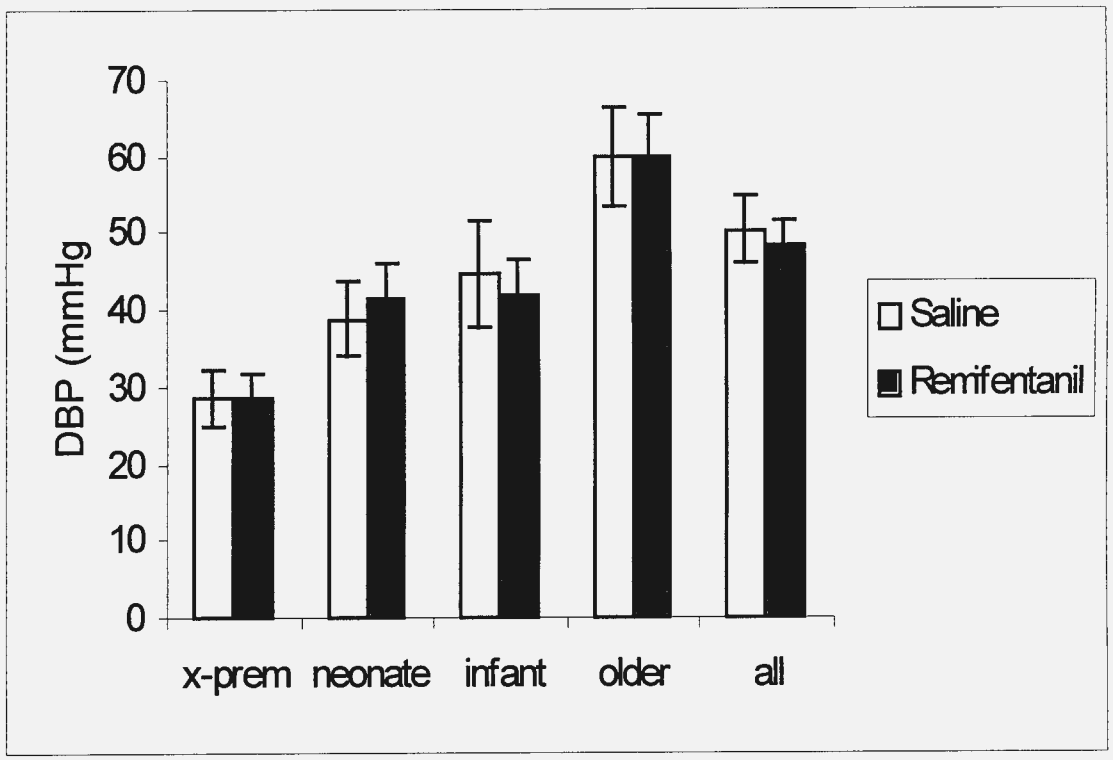
T test for null hypothesis that the baseline mean pressures are the same
T= 0.29 P=0.77 DF= 22

The null hypothesis is proven, thus the baseline mean pressures are not significantly different

CONCLUSION:

There was no statistical difference, at p=0.05, between the baseline mean arterial blood pressure in the remifentanil and control groups, in each age group, using analysis of variance, 95%confidence intervals of the means, 95% confidence intervals of the difference of the means, Ttests and box and whisker charts. There was obviously a significant difference in mean arterial pressure from one age group to the next.

Mean baseline diastolic pressure, in mm Hg, & 95% confidence intervals, remifentanil versus control



Basic statistics

Rows contain the number, mean and stand deviation of baseline diastolic pressure in control (S) or remifentanil (R)
Columns contain the age categories: neonate, infant, >1yr old, all ages

		neonate	infant	> 1 yr	all ages
S	number	5	11	13	29
	mean	38.800	44.545	59.846	50.414
	sd	7.855	16.464	16.370	17.303
R	number	8	13	12	33
	mean	41.250	41.846	59.667	48.182
	sd	10.110	12.314	13.970	14.970
all	number	13	24	25	62
	mean	40.308	43.083	59.760	49.226
	sd	9.041	14.102	14.948	16.008

Analysis of variance for baseline diastolic blood pressure in mm Hg, a comparison between remifentanil and control groups:

Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	76.9	0.3	0.3	0.00	**0.970**
agecod	2	4642.9	4675.8	2337.9	12.06	**0.000**
code*agecod	2	56.0	56.0	28.0	0.14	**0.866**
Error	56	10855.1	10855.1	193.8		
Total	61	15630.8				

Thus the anova table shows that baseline diastolic pressures are different from one age group to the next, as would be expected (p = 0.000).
It also concludes that there is no statistical difference between the baseline diastolic pressures in the remifentanil and control groups (p = 0.970) and that this is consistent amongst the different age groups (p = 0.866)

Confidence intervals and two sample T tests to compare baseline diastolic blood pressures in mm Hg between remifentanil and control groups, in each age group

X-Premies

	N	Mean	StDev	SE Mean	95% CI
S	4	28.50	5.45	2.7	24.7 - 32.3
R	4	28.75	4.27	2.1	25.8 - 31.69

Confidence intervals overlap, therefore the baseline diastolic pressures are not significantly different

95% confidence interval for the difference between the baseline diastolic pressures is -9.1 to 8.6

The difference between the baseline diastolic pressures is therefore not significant

T test for null hypothesis that the baseline diastolic pressures are the same
T= -0.07 P=0.95 DF= 5

The null hypothesis is proven, thus the baseline diastolic pressures are not significantly different

Neonates

	N	Mean	StDev	SE Mean	95% CI
S	5	38.80	7.85	3.5	33.9 - 43.7
R	8	41.3	10.1	3.6	36.3 - 46.2

Confidence intervals overlap, therefore the baseline diastolic pressures are not significantly different

95% confidence interval for the difference between the baseline diastolic pressures is -13.6 to 8.7

The difference between the baseline diastolic pressures is therefore not significant

T test for null hypothesis that the baseline diastolic pressures are the same
T= -0.49 P=0.64 DF= 10

The null hypothesis is proven, thus the baseline diastolic pressures are not significantly different

Infants

	N	Mean	StDev	SE Mean	95% CI
S	11	44.5	16.5	5.0	37.6 - 51.4
R	13	41.8	12.3	3.4	37.1 - 46.6

Confidence intervals overlap, therefore the baseline diastolic pressures are not significantly different

95% confidence interval for the difference between the baseline diastolic pressures is -10.0 to 15.4

The difference between the baseline diastolic pressures is therefore not significant

T test for null hypothesis that the baseline diastolic pressures are the same
T= 0.45 P=0.66 DF= 18

The null hypothesis is proven, thus the baseline diastolic pressures are not significantly different

Older Child

	N	Mean	StDev	SE Mean	95% CI
S	13	59.8	16.4	4.5	53.5 - 66.2
R	12	59.7	14.0	4.0	54.1 - 65.3

Confidence intervals overlap, therefore the baseline diastolic pressures are not significantly different

95% confidence interval for the difference between the baseline diastolic pressures is -12.8 to 12.4

The difference between the baseline diastolic pressures is therefore not significant

T test for null hypothesis that the baseline diastolic pressures are the same
T= -0.03 P=0.98 DF= 22

The null hypothesis is proven, thus the baseline diastolic pressures are not significantly different

CONCLUSION:

There was no statistical difference, at p=0.05, between the baseline diastolic blood pressure in the remifentanil and control groups, within in each age group, using analysis of variance, 95% confidence intervals of the means, 95% confidence intervals of the difference of the means, T tests and box and whisker charts.

There was obviously a significant difference in diastolic pressure from one age group to the next.

OVERALL CONCLUSION:

The remifentanil and control groups are comparable, within each age group, in terms of age, weight, height and baseline cardiovascular parameters, using several different forms of statistical analysis.
Thus differences found between the remifentanil or control groups can be interpreted as being related solely to the effect of remifentanil or control.

Anaesthetics Characteristics -

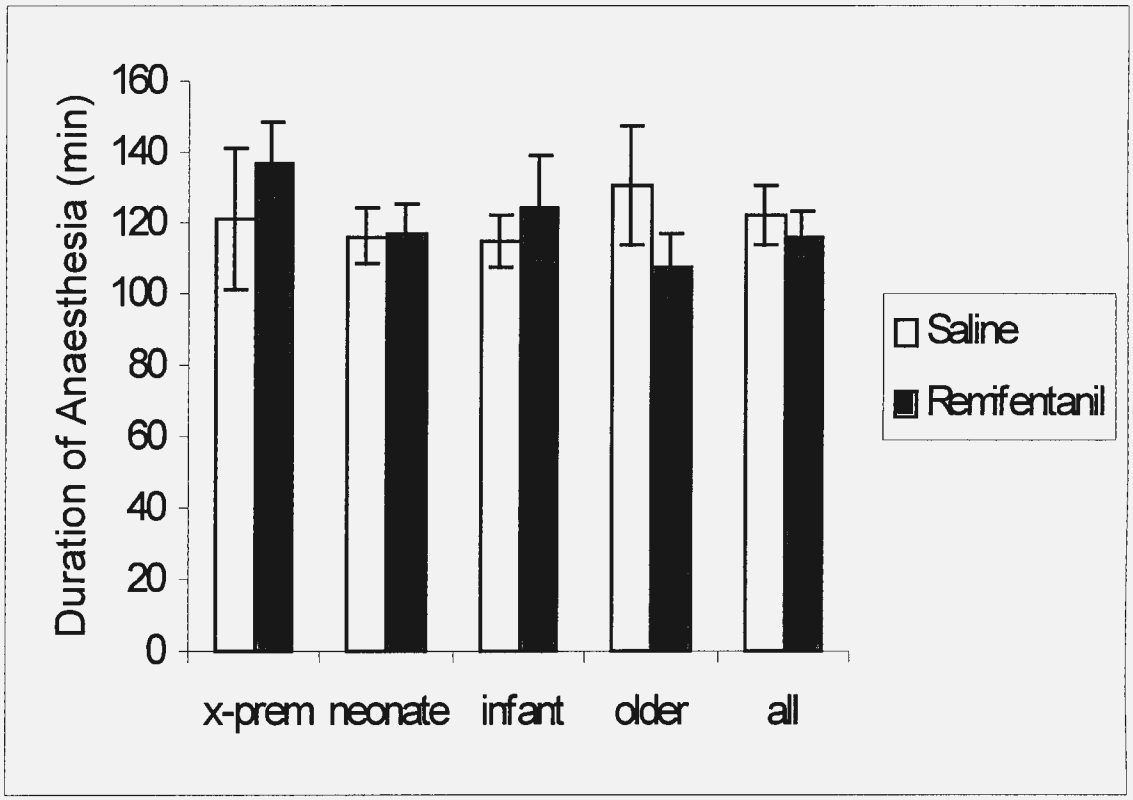
The duration of anaesthesia, in minutes, is compared in remifentanil and control groups, within each age group, as is the duration of time from administration of the drug until the end of surgery using box and whisker charts, analysis of variance, T tests and 95% confidence intervals, at p = 0.05.
The duration of anaesthesia is found to be similar in remifentanil and control groups.
The duration of time between administration of the "drug" and the end of surgery was found to be similar in the remifentanil and control groups, except in the older child where the control group had a longer time interval. (The control group took 57 and the remifentanil group 35 minutes). This, presumably, was just a chance occurrence and is discussed later.

This "All ages combined" table shows the means, standard errors of the mean and p values confirming the null hypothesis that the remifentanil and control groups had the same duration of anaesthesia:

	Duration of anaesthesia, in minutes	Duration from drug administration to the end of Surgery, in minutes
Control	122.1 (5.9)	48.1 (4.4)
Remifent	116.2 (5.1)	39.7 (4.3)
P value	> 0.05	> 0.05

On the following pages numbered A to I are the detailed statistics for each variable in each age category

Mean durations of anaesthesia, in minutes & 95% confidence intervals



Basic statistics

Rows contain the number, mean and standard deviation of mean duration of anaesthesia, in minutes, in control (S) or remifentanil (R)

Columns contain the age categories: neonate, infant, >1yr old, all ages

		neonate	infant	> 1 yr old	all ages
S	number	5	11	13	29
	mean	116.20	115.09	130.38	122.14
	sd	13.29	17.99	43.42	31.72
R	number	8	13	12	33
	mean	116.50	124.23	107.42	116.24
	sd	17.00	39.15	22.46	29.44
all	number	13	24	25	62
	mean	116.38	120.04	119.36	119.00
	sd	15.08	31.02	36.21	30.42

Analysis of variance for duration of anaesthesia, in minutes: a comparison between remifentanil and control groups

Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	536.5	280.2	280.2	0.30	**0.587**
agecod	2	88.0	91.0	45.5	0.05	**0.953**
code*agecod	2	3283.5	3283.5	1641.8	1.75	**0.183**
Error	56	52526.0	52526.0	938.0		
Total	61	56434.0				

The anova table shows that there is no statistical difference between the durations of anaesthesia in the remifentanil and control groups (p = 0.587) and that this is consistent amongst the different age groups (p = 0.838).

Confidence intervals and two sample T tests to compare the durations of anaesthesia in minutes in remifentanil and control groups, in each age group:

X-Premie

	N	Mean	StDev	SE Mean	95% CI
S	4	121.0	28.2	14	101.4 - 140.6
R	4	137.2	15.3	7.7	126.4 - 148.0

Confidence intervals overlap, therefore the mean durations of anaesthesia are not significantly different

95% confidence interval for the difference between the mean durations of anaesthesia is -61 to 28.3

The difference between the mean durations of anaesthesia is therefore not significant

T test for null hypothesis that the mean durations of anaesthesia are the same
T= -1.01 P=0.37 DF= 4

The null hypothesis is proven, thus the mean durations of anaesthesia are not significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	116.2	13.3	5.9	107.9 - 124.5
R	8	116.5	17.0	6.0	108.1 - 124.9

Confidence intervals overlap, therefore the mean durations of anaesthesia are not significantly different

95% confidence interval for the difference between the mean durations of anaesthesia is -19.1 to 18.5

The difference between the mean durations of anaesthesia is therefore not significant

T test for null hypothesis that the mean durations of anaesthesia are the same
T= -0.04 P=0.97 DF= 10

The null hypothesis is proven, thus the mean durations of anaesthesia are not significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	115.1	18.0	5.4	107.6 - 122.6
R	13	124.2	39.1	11	109.1 - 139.3

Confidence intervals overlap, therefore the mean durations of anaesthesia are not significantly different

95% confidence interval for the difference between the mean durations of anaesthesia is -34.8 to 16

The difference between the mean durations of anaesthesia is therefore not significant

T test for null hypothesis that the mean durations of anaesthesia are the same
T= -0.75 P=0.46 DF= 17

The null hypothesis is proven, thus the mean durations of anaesthesia are not significantly different

Older Child

	N	Mean	StDev	SE Mean	95% CI
S	13	130.4	43.4	12	113.3 - 147.1
R	12	107.4	22.5	6.5	98.4 - 116.4

Confidence intervals overlap, therefore the mean durations of anaesthesia are not significantly different

95% confidence interval for the difference between the mean durations of anaesthesia is -51.7 to 6

The difference between the mean durations of anaesthesia is therefore not significant

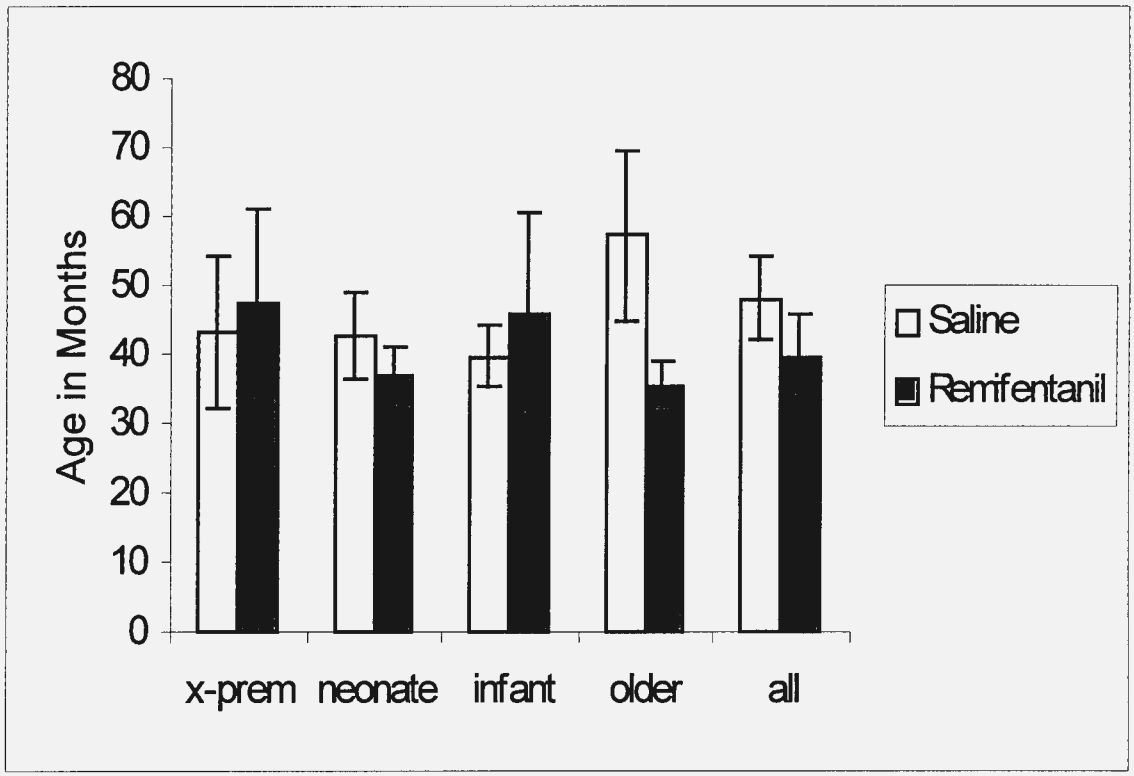
T test for null hypothesis that the mean durations of anaesthesia are the same
T= -1.68 P=0.11 DF= 18

The null hypothesis is proven, thus the mean durations of anaesthesia are not significantly different

CONCLUSION:

There is no statistical difference, at p=0.05, between the durations of anaesthesia in the remifentanil and control groups, in all age groups, using analysis of variance, 95% confidence limits of the means, 95% confidence limits of the difference between the means, two sample T tests and box and whisker charts.

Mean duration of time in minutes from drug administration until the end of surgery, in minutes & 95% confidence intervals



Basic statistics

Rows contain the number, mean and standard deviation of time from drug administration, in minutes, until end of surgery in control (S) or remifentanil (R)

Columns contain the age categories: neonate, infant, >1yr old, all ages

		neonate	infant	> 1 yr old	all ages
S	number	5	11	13	29
	mean	42.800	39.636	57.308	48.103
	sd	10.183	10.308	32.053	23.782
R	number	8	13	12	33
	mean	36.625	45.769	35.167	39.697
	sd	9.117	38.027	9.408	24.817
all	number	13	24	25	62
	mean	39.000	42.958	46.680	43.629
	sd	9.635	28.467	26.110	24.507

Analysis of variance for the duration of time, in minutes, from drug administration until the end of surgery: a comparison of remifentanil and control groups

Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	1090.8	753.5	753.5	1.29	**0.261**
agecod	2	383.7	378.6	189.3	0.32	**0.725**
code*agecod	2	2448.0	2448.0	1224.0	2.10	**0.133**
Error	56	32714.0	32714.0	584.2		
Total	61	36636.5				

The anova table shows that there is no statistical difference between the durations of time in minutes from drug administration until the end of surgery in the remifentanil and control groups (p = 0.261) and that this is consistent amongst the different age groups (p = 0.133).

95% confidence intervals and two sample T tests to compare the duration, in minutes, in remifentanil and control groups from administration of the drug to the end of surgery:

X-Premie

	N	Mean	StDev	SE Mean	95% CI
S	4	43.0	15.9	7.9	31.9 - 54.1
R	4	47.2	19.9	10	33.2 - 61.2

Confidence intervals overlap, therefore the mean durations from drug administration to end are not significantly different

95% confidence interval for the difference between the mean durations from drug administration until the end of surgery is -37.0 to 28

The difference between the mean durations from drug administration until the end of surgery is therefore not significant

T test for null hypothesis that the mean durations from drug administration until the end of surgery are the same

T= -0.33 P=0.75 DF= 5

The null hypothesis is proven, thus the mean durations from drug administration until the end of anaesthesia are not significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	42.8	10.2	4.6	36.5 - 49.1
R	8	36.63	9.12	3.2	32.3 - 41.1

Confidence intervals overlap, therefore the mean durations from drug administration to end of surgery are not significantly different

95% confidence interval for the difference between the mean durations from drug administration until the end of surgery is -7.0 to 19.4

The difference between the mean durations from drug administration until the end of surgery is therefore not significant

T test for null hypothesis that the mean durations from drug administration until the end of surgery are the same

T= 1.11 P=0.31 DF= 7

The null hypothesis is proven, thus the mean durations from drug administration until the end of surgery are not significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	39.6	10.3	3.1	35.3 - 44.0
R	13	45.8	38.0	11	31.1 - 60.4

Confidence intervals overlap, therefore the mean durations from drug administration to end are not significantly different

95% confidence interval for the difference between the mean durations from drug administration until the end of surgery is -29.7 to 17

The difference between the mean durations from drug administration until the end of surgery is therefore not significant

T test for null hypothesis that the mean durations from drug administration until the end of surgery are the same
T= -0.56 P=0.59 DF= 14

The null hypothesis is proven, thus the mean durations from drug administration until the end of surgery are not significantly different

Older child

	N	Mean	StDev	SE Mean	95% CI
S	13	57.3	32.1	8.9	45.0 - 69.7
R	12	35.17	9.41	2.7	31.4 - 38.9

Confidence intervals DO NOT overlap, therefore the mean durations from drug administration to end are significantly different. This is probably a chance finding in this age group and is at odds with the findings in all other age groups and with all ages combined

95% confidence interval for the difference between the mean durations from drug administration until the end of surgery is -42.1 to -2.2

The difference between the mean durations from drug administration until the end of surgery IS THEREFORE significant. As with the above confidence interval, it is probably a chance finding and is at odds with the results in all other age groups

T test for null hypothesis that the mean durations from drug administration until the end of surgery are the same
T= -2.38 P=0.032 DF= 14

The ALTERNATIVE hypothesis is proven, thus the mean durations from drug administration until the end of surgery are significantly different. Again, this a probably a chance finding, as stated for the above two tests.

CONCLUSION:

Except in the case of the > 1 year olds, there is no difference between remifentanil and control groups, at p=0.05, in **the duration of time between administration of the "drug" until the end of surgery, in all age groups. This conclusion is reached by using 95% confidence intervals for the mean, 95% confidence intervals for the differences between the means, analysis of variance, T tests and box and whisker charts**

In the over 1 year old child, the control group result was 57 minutes and the remifentanil group 35 minutes. This was probably a chance occurrence, given that this age group overall had a mean duration of 46 minutes compared to 43 minutes in infants and 39 minutes in neonates (no statistical difference)

Cardiovascular response to drug

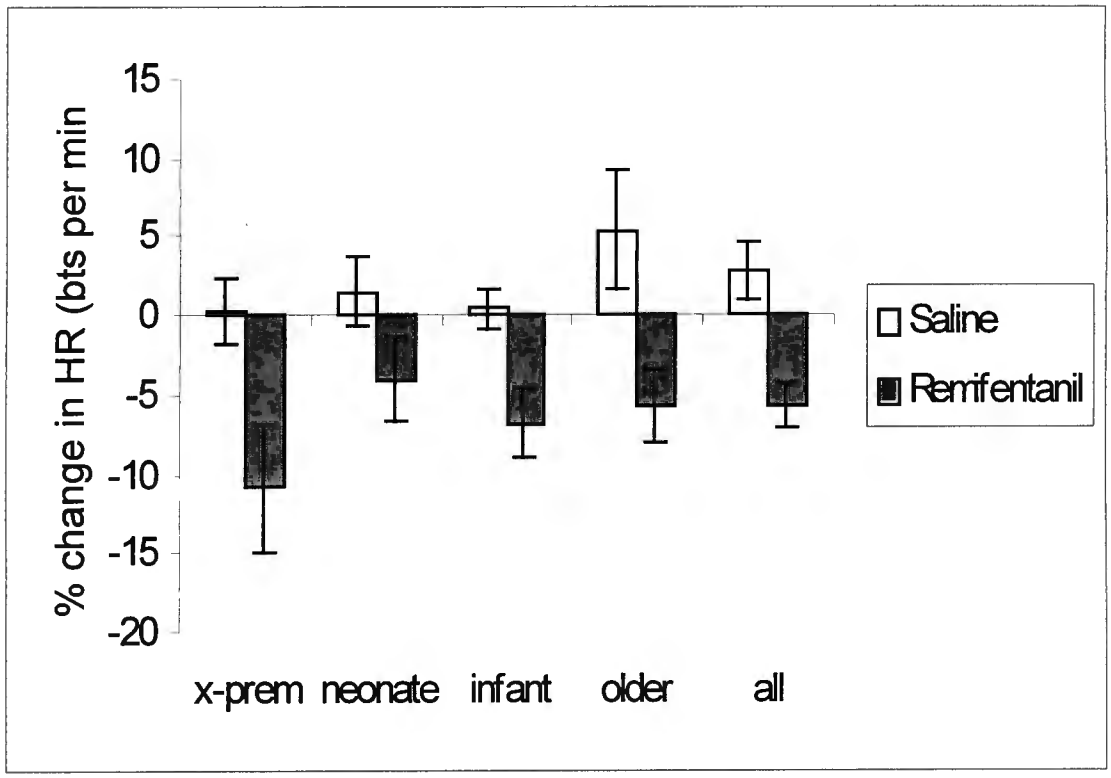
Cardiovascular responses to the administration of remifentanil and control are compared, using box and whisker charts, 95% confidence intervals, T tests and analysis of variance, in each age group. There was a decrease in heart rate and blood pressure post remifentanil administration, compared to control, which, generally speaking, was statistically significant, across the age groups, at $p = 0.05$. These findings seemed to be even more significant the older the child.

This "All ages combined" table shows the means, standard errors of the mean and p values testing the null hypothesis that the remifentanil and control groups had the same cardiovascular response to the drug:

	Percentage Heart Rate Change	Percentage Systolic Pressure Change	Percentage Mean Pressure Change	Percentage Diastolic Pressure Change
Control	2.8 (1.4)	5.8 (2.2)	8.2 (3.0)	4.6 (3.9)
Remifentanil	-5.8 (1.0)	-2.1 (2.5)	-7.9 (2.9)	-8.8 (3.6)
P value	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$

On the following pages numbered A to S are the detailed statistics for each variable in each age category

Mean percentage change in heart rate, in beats per minute, from baseline, & 95% confidence intervals, remifentanil versus control



Basic statistics

Rows contain the number, mean and standard deviation of maximum percentage change in heart rate post drug administration in control (S) or remifentanil (R)

Columns contain the age categories: neonate, infant, >1yr old, all ages

		neonate	infant	> 1 year	all ages
S	number	5	11	13	29
	mean	1.4400	0.3818	5.3538	2.7931
	sd	3.5225	3.0649	10.0095	7.3295
R	number	8	13	12	33
	mean	-4.0375	-6.8154	-5.7417	-5.7515
	sd	5.3976	5.7798	5.5028	5.5230
all	number	13	24	25	62
	mean	-1.9308	-3.5167	0.0280	-1.7548
	sd	5.3688	5.9104	9.7971	7.6900

Analysis of variance for the percentage change in heart rate post drug administration, a comparison of remifentanil and control groups

Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	1126.95	865.16	865.16	21.21	**0.000**
agecod	2	116.37	112.76	56.38	1.38	**0.259**
code*agecod	2	80.21	80.21	40.10	0.98	**0.380**
Error	56	2283.77	2283.77	40.78		
Total	61	3607.29				

Thus the anova table shows that percentage change in heart rate from baseline post drug administation is statistically different between remifentanil and control groups (p=0.000). Remifentanil causing a significant bradycardia when compared to control. This finding is consistent amongst the different age groups (p = 0.380).

Confidence intervals and two sample T tests to compare the percentage change in heart rate post drug administration, a comparison of remifentanil and control

X-Premie

	N	Mean	StDev	SE Mean	95% CI
S	4	0.25	3.03	1.5	(-1.85) - 2.35
R	4	(-10.90)	5.70	2.9	(-15.0) - (-6.9)

Confidence intervals DO NOT overlap, therefore the mean percentage changes in heart rate after drug administration are significantly different

95% confidence interval for the difference between the mean percentage changes in heart rate post drug administration is 2.2 to 20.1

The difference between the mean percentage change in heart rate after drug administration IS THEREFORE significant

T test for null hypothesis that the mean percentage changes in heart rate post drug administration are the same.
T= 3.45 P=0.026 DF= 4

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in heart rate are significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	1.44	3.52	1.6	(-0.75) - 3.63
R	8	(-4.04)	5.40	1.9	(-6.69 - (-1.38)

Confidence intervals DO NOT overlap, therefore the mean percentage changes in heart rate after drug administration are significantly different

95% confidence interval for the difference between the mean percentage changes in heart rate post drug administration is 0.0 to 11.0

The difference between the mean percentage change in heart rate after drug administration IS THEREFORE significant

T test for null hypothesis that the mean percentage changes in heart rate post drug administration are the same.
T= 2.21 P=0.05 DF= 10

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in heart rate are significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	0.38	3.06	0.92	(-0.90) - 1.67
R	13	-6.82	5.78	1.6	(-9.04) - (-4.59)

Confidence intervals DO NOT overlap, therefore the mean percentage changes in heart rate after drug administration are significantly different

95% confidence interval for the difference between the mean percentage changes in heart rate post drug administration is 3.31 to 11.1

The difference between the mean percentage change in heart rate after drug administration IS THEREFORE significant

T test for null hypothesis that the mean percentage changes in heart rate post drug administration are the same.
T= 3.89 P=0.0011 DF= 18

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in heart rate are significantly different

Older child

	N	Mean	StDev	SE Mean	95% CI
S	13	5.4	10.0	2.8	1.49 - 9.21
R	12	-5.74	5.50	1.6	(-7.95) - (-3.53)

Confidence intervals DO NOT overlap, therefore the mean percentage changes in heart rate after drug administration are significantly different

95% confidence interval for the difference between the mean percentage changes in heart rate post drug administration is -17.8 to -4.4

The difference between the mean percentage change in heart rate after drug administration IS THEREFORE significant

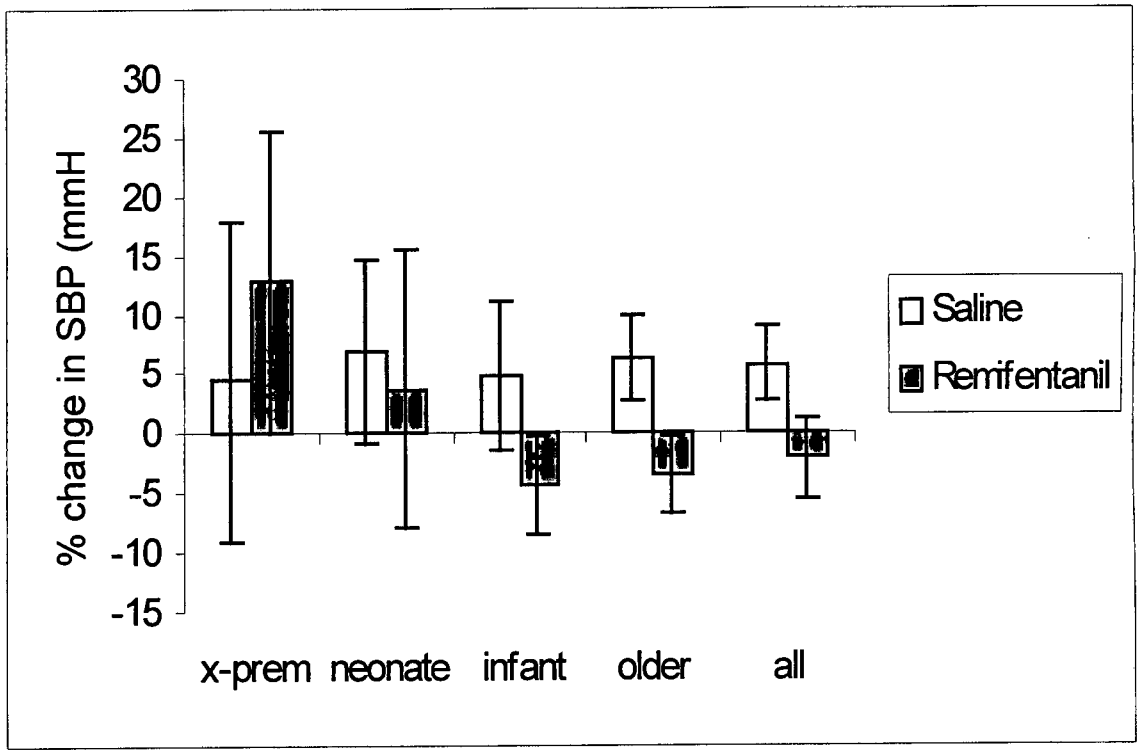
T test for null hypothesis that the mean percentage changes in heart rate post drug administration are the same.
T= -3.47 P=0.0027 DF= 18

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in heart rate are significantly different

CONCLUSION:

There is a statistically significant fall, at p=0.05, in the heart rate post remifentanil administration, compared to the control group, in all age groups, using 95% confidence intervals of the mean, 95% confidence intervals of the difference of the means, analysis of variance tables, T tests and box and whisker charts. The mean percentage change in heart rate after remifentanil administration was -5.8 (sd= 5.5) and after control was +2.8 (sd=7.3) when all ages are considered.

Mean percentage change in systolic pressure post drug administration, in mm Hg, & 95% confidence intervals, remifentanil versus control:



Basic statistics

Rows contain the number, mean and standard deviation of maximum percentage change in systolic blood pressure post drug administration in control (S) or remifentanil (R)

Columns contain the age categories: neonate, infant, >1yr old, all ages

		neonate	infant	> 1 year old	all ages
S	number	5	11	13	29
	mean	6.860	4.755	6.323	5.821
	sd	12.526	14.933	9.140	11.774
R	number	8	13	12	33
	mean	3.700	-4.369	-3.400	-2.061
	sd	23.778	10.717	8.299	14.197
all	number	13	24	25	62
	mean	4.915	-0.188	1.656	1.626
	sd	19.613	13.358	9.895	13.604

Analysis of variance for the percentage change in systolic blood pressure post drug administration, remifentanil versus control

Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	958.8	741.6	741.6	4.17	**0.046**
agecod	2	279.8	213.2	106.6	0.60	**0.552**
code*agecod	2	97.7	97.7	48.9	0.27	**0.761**
Error	56	9953.7	9953.7	177.7		
Total	61	11289.9				

Thus the anova table shows that percentage change in systolic blood pressure from baseline post drug administration is statistically different in the remifentanil and control groups (p=0.046). Remifentanil causes a statistically significant degree of hypotension (-2.06%) when compared to control (5.8%). This finding is consistent amongst the different age groups (p = 0.761).

Confidence intervals and two sample T test to compare percentage change in systolic pressure post drug administration, remifentanil versus control

X-Premie

	N	Mean	StDev	SE Mean	95% CI
S	4	4.4	19.4	9.7	(-9.2) - 18.0
R	4	12.9	18.2	9.1	0.2 - 25.6

Confidence intervals overlap, therefore the mean percentage changes in systolic pressure post drug administration are not significantly different

95% Confidence interval for the difference between the mean percentage changes in systolic pressure post drug administration is -42.8 to 25.8

The difference between the mean percentage changes in systolic pressure post drug administration is therefore not significant

T test for null hypothesis that the mean percentage changes in systolic pressure post drug administration are the same
T= -0.64 P=0.55 DF= 5

The null hypothesis is proven, thus the mean percentage changes in systolic pressure post drug administration are not significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	6.9	12.5	5.6	(-0.93) - 14.65
R	8	3.7	23.8	8.4	(-7.99) - 15.39

Confidence intervals overlap, therefore the mean percentage changes in systolic pressure post drug administration are not significantly different

95% Confidence interval for the difference between the mean percentage changes in systolic pressure post drug administration is -19.4 to 25.7

The difference between the mean percentage changes in systolic pressure post drug administration is therefore not significant

T test for null hypothesis that the mean percentage changes in systolic pressure post drug administration are the same
T= 0.31 P=0.76 DF= 10

The null hypothesis is proven, thus the mean percentage changes in systolic pressure post drug administration are not significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	4.8	14.9	4.5	(-1.5) - 11.01
R	13	-4.4	10.7	3.0	(-8.5) - (-0.24)

Confidence intervals overlap, therefore the mean percentage changes in systolic pressure post drug administration are not significantly different

95% Confidence interval for the difference between the mean percentage changes in systolic pressure post drug administration is -2.3 to 20.5

The difference between the mean percentage changes in systolic pressure post drug administration is therefore not significant

T test for null hypothesis that the mean percentage changes in systolic pressure post drug administration are the same
T= 1.69 P=0.11 DF= 17

The null hypothesis is proven, thus the mean percentage changes in systolic pressure post drug administration are not significantly different

Older Child

	N	Mean	StDev	SE Mean	95% CI
S	13	6.32	9.14	2.5	2.80 - 9.85
R	12	-3.40	8.30	2.4	(-6.73) - (-0.07)

Confidence intervals DO NOT overlap, therefore the mean percentage changes in systolic pressure post drug administration are significantly different

95% Confidence interval for the difference between the mean percentage changes in systolic pressure post drug administration is -17.0 to -2.5

The difference between the mean percentage changes in systolic pressure post drug administration IS THEREFORE significant

T test for null hypothesis that the mean percentage changes in systolic pressure post drug administration are the same
P=0.011 DF= 22

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in systolic pressure post drug administration are significantly different

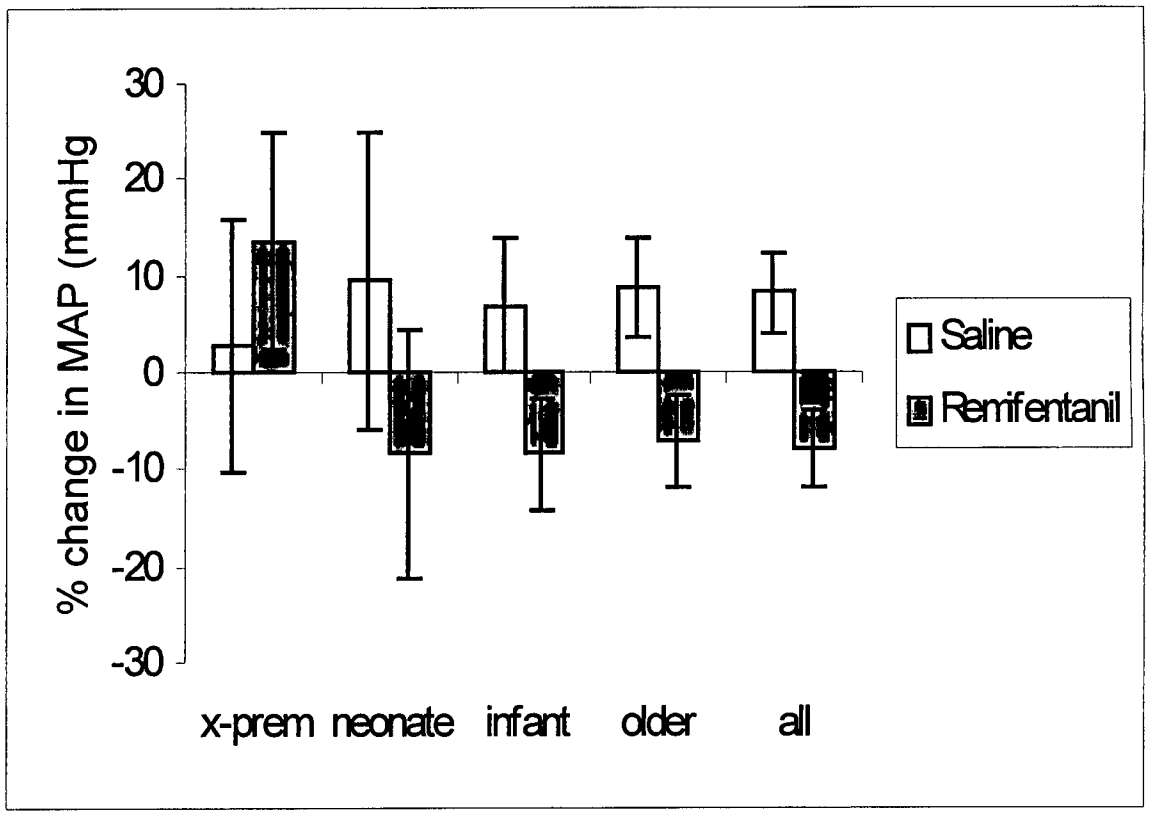
CONCLUSION:

Analysis of variance tables suggest that there is a statistically significant fall, at p = 0.05, in systolic blood pressure, all age groups, post remifentanil administration when compared to control and this is consistent amongst all age groups.

T tests, 95% confidence intervals of the mean, 95% confidence intervals for the difference between the means and box and whisker charts confirms this finding in older children and all ages together but show no significant differences, at p=0.05, in neonate, infant and x-premie groups.

The mean percentage systolic blood pressure change after control was + 5.8 (sd=11.8) and after remifentanil -2.1 (sd= 14.2), when all ages are considered.

Mean percentage change of mean arterial pressure post drug administration, in mm Hg, & 95% confidence interval, remifentanil versus control:



Basic statistics

Rows contain the number, mean and standard deviation of maximum percentage change in systolic blood pressure post drug administration in control (S) or remifentanil (R)
Columns contain the age categories: neonate, infant, >1yr old, all ages

		neonate	infant	> 1 year old	all ages
S	number	5	11	13	29
	mean	9.520	6.873	8.762	8.176
	sd	24.648	16.403	13.239	16.098
R	number	8	13	12	33
	mean	-8.400	-8.385	-7.092	-7.918
	sd	25.884	14.650	12.165	16.683
all	number	13	24	25	62
	mean	-1.508	-1.392	1.152	-0.390
	sd	25.994	17.008	14.860	18.179

Analysis of variance for the percentage change from baseline in mean arterial pressure post drug administration, remifentanil versus control:

Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	3998.1	3681.0	3681.0	12.79	**0.001**
agecod	2	30.3	33.3	16.7	0.06	**0.944**
code*agecod	2	14.7	14.7	7.4	0.03	**0.975**
Error	56	16116.	16116.9	287.8		
Total	61	20160.1				

Thus the anova table shows that percentage change in mean blood pressure from baseline post drug administration is statistically different between remifentanil and control groups (p=0.001). Remifentanil causes a statistically significant degree of hypotension (-7.9%) when compared to control (8.2%). This finding is consistent amongst the different age groups (p = 0.975).

Confidence intervals and two sample T test for the percentage change from baseline in mean arterial pressure post drug administration, remifentanil versus control

X-Premie

	N	Mean	StDev	SE Mean	95% CI
S	4	2.8	18.6	9.3	(-10.2) - 15.8
R	4	13.6	16.0	8.0	2.4 - 24.8

Confidence intervals overlap, therefore the mean percentage changes in mean arterial pressure post drug administration are not significantly different

95% Confidence interval for the difference between the mean percentage changes in mean arterial pressure post drug administration is -42.2 to 20.7

The difference between the mean percentage changes in mean arterial pressure post drug administration is therefore not significant

T test for null hypothesis that the mean percentage changes in mean arterial pressure post drug administration are the same

T= -0.88 P=0.42 DF= 5

The null hypothesis is proven, thus the mean percentage changes in mean arterial pressure post drug administration are not significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	9.5	24.6	11	(-5.80) - 24.84
R	8	-8.4	25.9	9.2	(-21.12) - 4.32

Confidence intervals overlap, therefore the mean percentage changes in mean arterial pressure post drug administration are not significantly different

95% Confidence interval for the difference between the mean percentage changes in mean arterial pressure post drug administration is -15 to 51.0

The difference between the mean percentage changes in mean arterial pressure post drug administration is therefore not significant

T test for null hypothesis that the mean percentage changes in mean arterial pressure post drug administration are the same

T= 1.25 P=0.25 DF= 8

The null hypothesis is proven, thus the mean percentage changes in mean arterial pressure post drug administration are not significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	6.9	16.4	4.9	0.00 - 13.75
R	13	-8.4	14.6	4.1	(-14.03) - (-2.74)

Confidence intervals DO NOT overlap, therefore the mean percentage changes in mean arterial pressure post drug administration are significantly different

95% Confidence interval for the difference between the mean percentage changes in mean arterial pressure post drug administration is 1.9 to 28.6

The difference between the mean percentage changes in mean arterial pressure post drug administration IS THEREFORE significant

T test for null hypothesis that the mean percentage changes in mean arterial pressure post drug administration are the same
T= 2.38 P=0.027 DF= 20

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in mean arterial pressure post drug administration are significantly different

Older Child

	N	Mean	StDev	SE Mean	95% CI
S	13	8.8	13.2	3.7	3.66 - 13.87
R	12	-7.1	12.2	3.5	(-11.97) - (-2.21)

Confidence intervals DO NOT overlap, therefore the mean percentage changes in mean arterial pressure post drug administration are significantly different

95% Confidence interval for the difference between the mean percentage changes in mean arterial pressure post drug administration is -26.4 to -5.3

The difference between the mean percentage changes in mean arterial pressure post drug administration IS THEREFORE significant

T test for null hypothesis that the mean percentage changes in mean arterial pressure post drug administration are the same
T= -3.12 P=0.0050 DF= 22

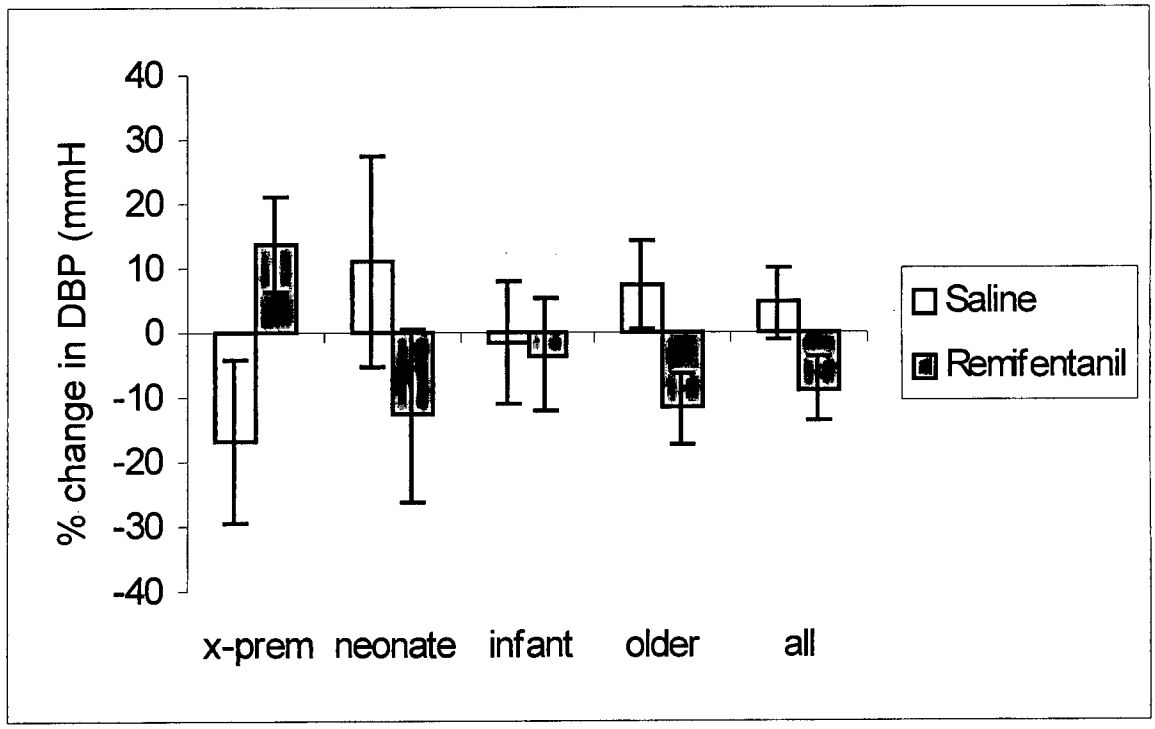
The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in mean arterial pressure post drug administration are significantly different

CONCLUSION:

Anova tables suggest that there is a statistically significant fall, at p = 0.05, in the mean blood pressure, all age groups, post remifentanil administration, compared to control.
95% confidence intervals of the means, 95% confidence intervals of the difference between the means, T tests and box and whisker charts confirm this for infants, older children and all ages together and show no significant differences in neonates and x-premies, at p = 0.05

The mean percentage change in mean arterial pressure after control was + 8.2 (sd=16.1) and after remifentanil - 7.9 (sd=16.7) when all ages are included.

Maximum percentage change of diastolic pressure post drug administration, in mm Hg, & 95% confidence intervals, remifentanil versus control:



Basic statistics

Rows contain the number, mean and standard deviation of maximum percentage change in diastolic blood pressure post drug administration in control (S) or remifentanil (R)

Columns contain the age categories: neonate, infant, >1yr old, all ages

		neonate	infant	> 1 year old	all ages
S	number	5	11	13	29
	mean	11.040	-1.555	7.262	4.569
	sd	26.305	23.037	17.593	21.133
R	number	8	13	12	33
	mean	-12.750	-3.469	-11.833	-8.761
	sd	27.012	22.556	13.605	20.807
all	number	13	24	25	62
	mean	-3.600	-2.592	-1.904	-2.526
	sd	28.309	22.296	18.286	21.842

Analysis of variance for the percentage change in diastolic blood pressure post drug administration, remifentanil versus control

Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	2742.5	3073.1	3073.1	6.87	**0.011**
agecod	2	0.2	24.0	12.0	0.03	**0.974**
code*agecod	2	1320.5	1320.5	660.2	1.48	**0.237**
Error	56	25037.5	25037.5	447.1		
Total	61	29100.7				

Thus the anova table shows that percentage change in diastolic blood pressure from baseline post drug administration is statistically different between remifentanil and control groups (p=0.011). Remifentanil causing statistically significant degree of hypotension(-8.8%) when compared to control (+4.6%). This finding is consistent amongst the different age groups (p = 0.237).

Confidence intervals two sample T tests for the percentage change in diastolic pressure post drug administration, remifentanil versus control

X-Premie

	N	Mean	StDev	SE Mean	95% CI
S	4	(-17.0)	17.9	9.0	(-29.6) - (-4.4)
R	4	13.5	10.3	5.2	6.2 - 20.8

Confidence intervals DO NOT overlap, therefore the mean percentage changes in diastolic pressure post drug administration are significantly different. In fact, the remifentanil group show a paradoxical increase in diastolic pressure when compared to control. The numbers involved are small and this is probably a chance finding.

95% Confidence interval for the difference between the mean percentage changes in diastolic pressure post drug administration is -59.2 to -1.7

The difference between the mean percentage changes in diastolic pressure post drug administration IS THEREFORE significant. Again, the remifentanil group show a paradoxical increase, presumably due to the small numbers involved and chance.

T test for null hypothesis that the mean percentage changes in diastolic pressure post drug administration are the same
T= -2.94 P=0.042 DF= 4

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in diastolic pressure post drug administration are significantly different, again with a paradoxical increase in pressure in the remifentanil group

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	11.0	26.3	12	(-5.31) - 27.39
R	8	-12.8	27.0	9.6	(-26.02) - 0.52

Confidence intervals overlap, therefore the mean percentage changes in diastolic arterial pressure post drug administration are not significantly different

95% Confidence interval for the difference between the mean percentage changes in diastolic pressure post drug administration is -11 to 58.7

The difference between the mean percentage changes in diastolic pressure post drug administration is not significant.

T test for null hypothesis that the mean percentage changes in mean arterial pressure post drug administration are the same
T= 1.57 P=0.16 DF= 8

The null hypothesis is proven, thus the mean percentage changes in diastolic pressure post drug administration are not significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	-1.6	23.0	6.9	(-11.21) - 8.1
R	13	-3.5	22.6	6.3	(-12.16) - 5.23

Confidence intervals overlap, therefore the mean percentage changes in diastolic arterial pressure post drug administration are not significantly different

95% Confidence interval for the difference between the mean percentage changes in diastolic pressure post drug administration is -17.5 to 21.4

The difference between the mean percentage changes in diastolic pressure post drug administration is not significant.

T test for null hypothesis that the mean percentage changes in mean arterial pressure post drug administration are the same
T= 0.20 P=0.84 DF= 21

The null hypothesis is proven, thus the mean percentage changes in diastolic pressure post drug administration are not significantly different

Older Child

	N	Mean	StDev	SE Mean	95% CI
S	13	7.3	17.6	4.9	0.48 - 14.04
R	12	-11.8	13.6	3.9	(-17.29) - (-6.37)

Confidence intervals DO NOT overlap, therefore the mean percentage changes in diastolic pressure post drug administration are significantly different.

95% Confidence interval for the difference between the mean percentage changes in diastolic pressure post drug administration is -32.1 to -6.1

The difference between the mean percentage changes in diastolic pressure post drug administration IS THEREFORE significant, with the remifentanil group showing a fall in pressure when compared to control

T test for null hypothesis that the mean percentage changes in mean arterial pressure post drug administration are the same
T= -3.05 P=0.0059 DF= 22

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in diastolic pressure post drug administration are significantly different, with the remifentanil group showing a fall in pressure when compared to the control group

CONCLUSION:

Analysis of variance tables suggest that there is a statistically significant fall, at p = 0.05, in diastolic blood pressure, all age groups, post remifentanil administration.

95% confidence intervals of the means, 95% confidence interval of the difference between the means, T tests and box and whisker charts confirm this for older children and all ages together, but show a non significant fall in diastolic pressure post remifentanil in neonates and infants.

Paradoxically, probably by chance and because of small numbers, all forms of statistical analysis showed that diastolic blood pressure rises post remifentanil in the x-premie group

The mean percentage change in diastolic blood pressure after control was + 4.6 (sd=21.1) and after remifentanil - 8.8 (sd=20.8) (all ages included).

OVERALL CONCLUSION:
There was a decrease in heart rate post remifentanil administration, compared to control, which was statistically significant, by all modes of analysis across the age groups. These findings seemed to be even more significant the older the child.

There was a decrease in blood pressure in the remifentanil group, when compared to control, when all ages are combined and for the older child. The infant and neonate showed a non-significant decrease in blood pressure post remifentanil, when compared to control. Greater numbers are required to make further conclusions.

The clinical significance of these findings is probably very limited. Normal peri-operative changes in haemodynamics are usually far greater than the changes, as demonstrated here, that are related to remifentanil administration. Due care, however, must be taken, therefore careful pre-loading and timing of administration to coincide with the stimulus is advised.

Paradoxically the x-premie group was found to show an increase in pressure with remifentanil, probably due to the small numbers involved and because of chance. Thus real conclusions cannot be drawn about the response by very young babies and this is an area that merits further investigation in the future.

Stress response to tunnelling

Heart rate, blood pressure and plasma catecholamine level changes following tunnelling are compared in remifentanil and control groups, in each age group, using box and whisker charts, analysis of variance, T tests and 95% confidence intervals. The control group generally showed a statistically greater increase and duration of increase of all these markers of pain and stress post tunnelling, when compared to the remifentanil group, in all age groups. Some of the remifentanil patients even showed a reduction from baseline in these parameters. These differences were again even greater the older the child.

Plasma adrenaline levels were also measured but quantities assayed were too low to be of clinical significance. It should be noted that noradrenaline is primarily a neurotransmitter and plasma concentrations reflect the activation of the sympathetic nervous system in general. Adrenaline is primarily a hormone, and the concentrations found in anaesthetized subjects are frequently too low for detection using the HPLC method. However, the lower limit of sensitivity of the method is below the level at which adrenaline becomes active (around 40pg/ml). It is therefore entirely valid to exclude the adrenaline data where the majority of the values are below clinically relevant concentrations.

These 3 "All ages combined" tables show the means, standard errors of the mean and p values testing the null hypothesis that the remifentanil and control groups had the same response to tunnelling (bold, underlined figures are medians, as they used "censored", non-parametric results):

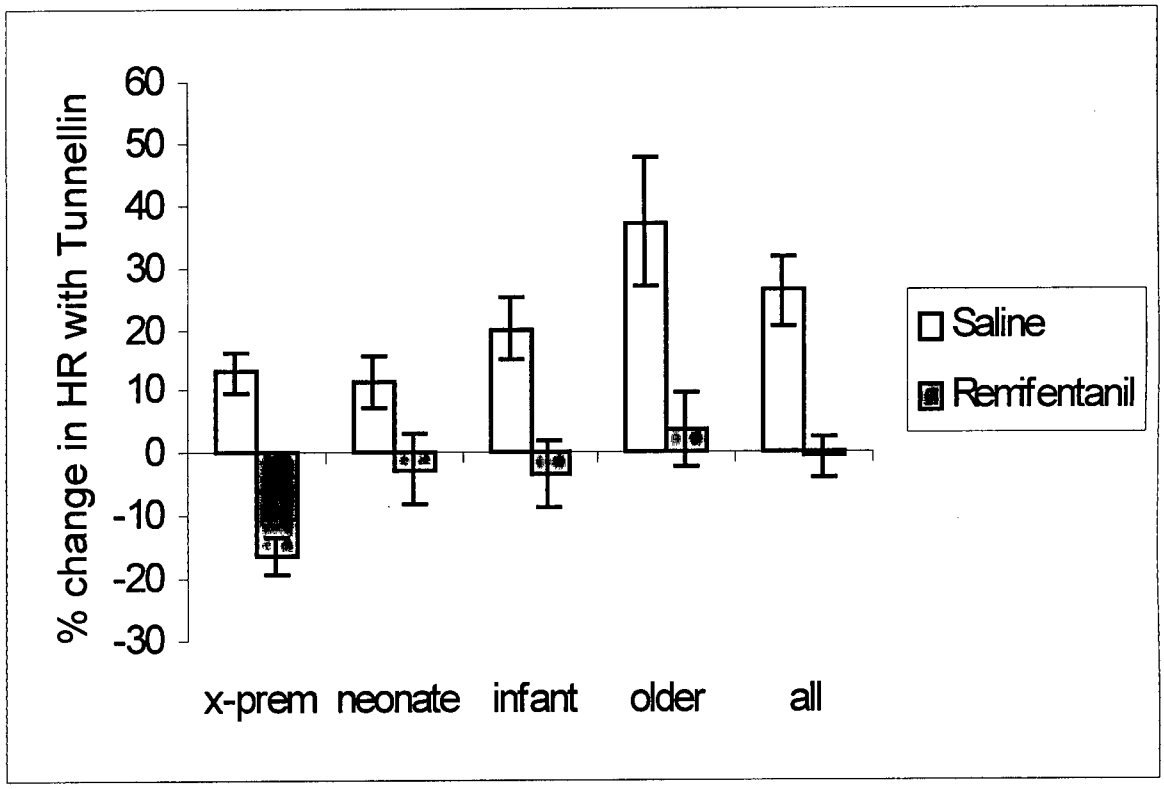
	Percentage Heart Rate change	Percentage Systolic Blood Pressure change	Percentage Mean Arterial Pressure change	Percentage Diastolic Blood Pressure change
Control	26.2 (4.9)	33.9 (3.1)	41.4 (3.6)	46.3 (5.2)
Remif	-0.7 (2.4)	1.1 (2.9)	-1.4 (3.6)	-2.8 (4.7)
P value	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$

	Duration of Heart Rate change in minutes	Duration of Systolic Blood Pressure change in minutes	Duration of Mean Pressure change in minutes	Duration of Diastolic Pressure change in minutes
Control	**5**	**10**	**8**	**6**
Remif	**0**	**0**	**0**	**0**
P value	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$

	Percentage change from baseline in plasma noradrenaline
Control	32.8 (14.5)
Remif	-8.4 (7.5)
P value	$p < 0.05$

On the following pages numbered A to FF are the detailed statistics for each variable in each age category

Maximum percentage change in heart rate in response to tunnelling, in beats per minute, & 95% confidence intervals



Basic statistics

Rows contain the number, mean and standard deviation of maximum percentage change in heart rate post tunnelling in control (S) or remifentanil (R)

Columns contain the age categories: neonate, infant, >1yr old, all ages

		neonate	infant	> 1 year old	all ages
S	number	5	11	13	29
	mean	11.380	19.964	36.992	26.117
	sd	6.918	12.334	26.775	21.840
R	number	8	13	12	33
	mean	-2.625	-3.454	3.583	-0.694
	sd	11.727	13.978	14.709	13.734
all	number	13	24	25	62
	mean	2.762	7.279	20.956	11.847
	sd	12.102	17.611	27.346	22.356

Analysis of variance for the maximum percentage change from baseline in heart rate post tunnelling, remifentanil versus control

Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	11095.6	7682.1	7682.1	26.88	**0.000**
agecod	2	2565.8	2754.6	1377.3	4.82	**0.012**
code*agecod	2	822.6	822.6	411.3	1.44	**0.246**
Error	56	16003.1	16003.1	285.8		
Total	61	30487.1				

Thus the anova table shows that percentage change in heart rate from baseline post tunnelling is statistically different between remifentanil and control groups (p=0.000). The control group shows a statistically significant rise in heart rate (+26%) when compared to the remifentanil group (-0.7%). This finding is consistent amongst the different age groups (p = 0.246).

Confidence intervals and two sample T tests for the maximum perentage change from baseline in heart rate post tunneling, remifentanil versus control

X-Premie

	N	Mean	StDev	SE Mean	95% CI
S	4	12.98	4.76	2.4	9.6 - 16.3
R	4	(-16.17)	4.12	2.1	(-19.1) - (-13.2)

Confidence intervals DO NOT overlap, therefore the mean percentage changes in heart rate post tunnelling are significantly different

95% confidence interval for the difference between the mean percentage changes in heart rate post tunnelling is 21.1 to 37.2

The difference between the mean percentage changes in heart rate post tunnelling IS THEREFORE significant

T test for null hypothesis that the mean percentage changes in heart rate post tunnelling are the same
T= 9.27 P=0.0002 DF= 5

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in heart rate post tunnelling are significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	11.38	6.92	3.1	7.1 - 15.7
R	8	-2.6	11.7	4.1	(-8.4) - 3.1

Confidence intervals DO NOT overlap, therefore the mean percentage changes in heart rate post tunnelling are significantly different

95% confidence interval for the difference between the mean percentage changes in heart rate post tunnelling is 2.5 to 25.5

The difference between the mean percentage changes in heart rate post tunnelling IS THEREFORE significant

T test for null hypothesis that the mean percentage changes in heart rate post tunnelling are the same
T= 2.71 P=0.022 DF= 10

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in heart rate post tunnelling are significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	20.0	12.3	3.7	14.8 - 25.1
R	13	-3.5	14.0	3.9	(-8.8) - 1.9

Confidence intervals DO NOT overlap, therefore the mean percentage changes in heart rate post tunnelling are significantly different

95% confidence interval for the difference between the mean percentage changes in heart rate post tunnelling is 12.2 to 34.6

The difference between the mean percentage changes in heart rate post tunnelling IS THEREFORE significant

T test for null hypothesis that the mean percentage changes in heart rate post tunnelling are the same
T= 4.36 P=0.0003 DF= 21

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in heart rate post tunnelling are significantly different

Older Child

	N	Mean	StDev	SE Mean	95% CI
S	13	37.0	26.8	7.4	26.7 - 47.3
R	12	3.6	14.7	4.2	(-2.3) - 9.5

Confidence intervals DO NOT overlap, therefore the mean percentage changes in heart rate post tunnelling are significantly different

95% confidence interval for the difference between the mean percentage changes in heart rate post tunnelling is -51.4 to -15.4

The difference between the mean percentage changes in heart rate post tunnelling IS THEREFORE significant

T test for null hypothesis that the mean percentage changes in heart rate post tunnelling are the same
T= -3.91 P=0.0010 DF= 18

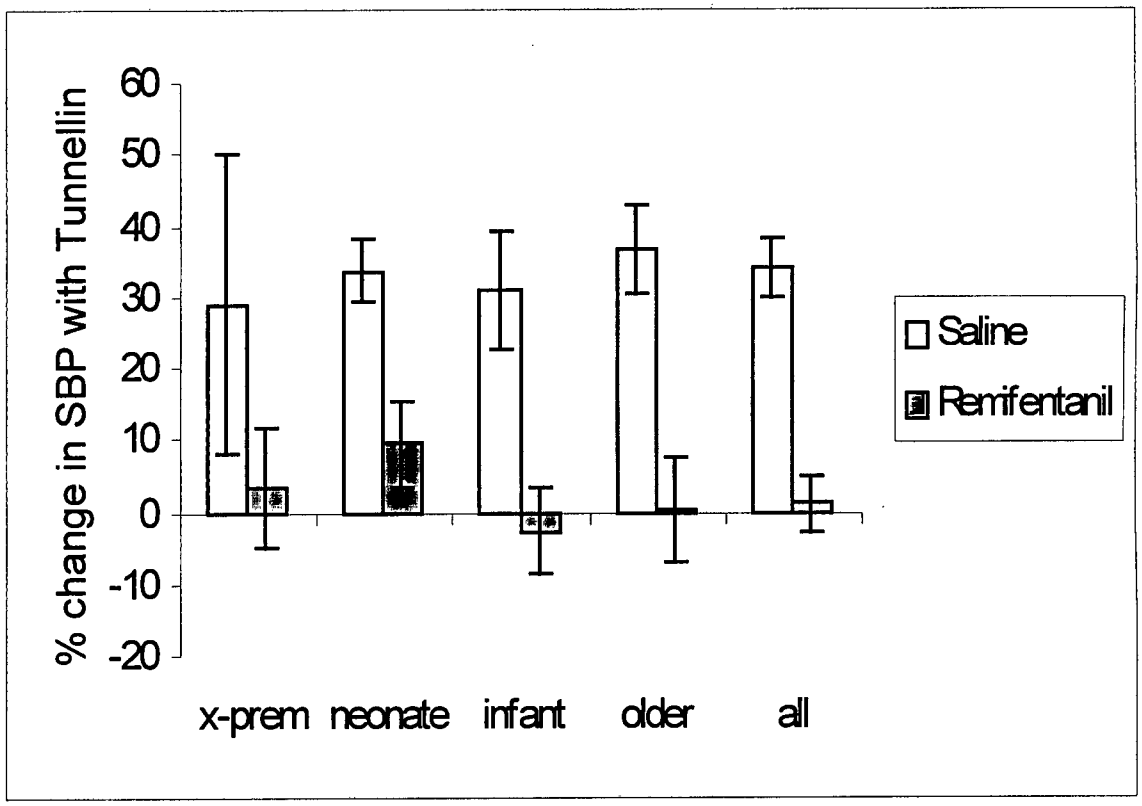
The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in heart rate post tunnelling are significantly different

CONCLUSION:

Analysis of variance, 95% confidence intervals of the means, 95% confidence intervals of the difference between the means, T tests and box and whisker charts show a significant rise in heart rate in the control group, post tunnelling compared to the remifentanil group, at p =0.05, in all age groups. The differences were even greater in the infant and the older child.

Taking all age groups together, the increase in heart rate was + 26.2 (sd=21.8) in the control group and - 0.7 (sd=13.7) in the remifentanil group.

Maximum percentage change in systolic pressure post tunnelling, in mm Hg, & 95% confidence intervals



Basic statistics

Rows contain the number, mean and standard deviation of maximum percentage change in systolic blood pressure post tunnelling in control (S) or remifentanil (R)

Columns contain the age categories: neonate, infant, >1yr old, all ages

		neonate	infant	> 1 year old	all ages
S	number	5	11	12	28
	mean	33.720	30.791	36.725	33.857
	sd	7.281	19.848	15.790	16.212
R	number	7	13	12	32
	mean	9.357	-2.623	0.283	1.087
	sd	12.521	15.567	18.110	16.186
all	number	12	24	24	60
	mean	19.508	12.692	18.504	16.380
	sd	16.192	24.227	24.950	23.016

Analysis of variance for maximum percentage change from baseline in systolic blood pressure, mm Hg, post tunnelling, remifentanil versus control

Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	16036.2	13105.6	13105.6	49.32	**0.000**
agecod	2	578.3	490.9	245.4	0.92	**0.403**
code*agecod	2	289.4	289.4	144.7	0.54	**0.583**
Error	54	14350.4	14350.4	265.7		
Total	59	31254.2				

Thus the anova table shows that the maximum percentage change in systolic pressure from baseline post tunnelling is statistically different between remifentanil and control groups (p=0.000). The control group shows a statistically significant rise in systolic pressure (+33.9%) when compared to the remifentanil group (+1.1%). This finding is consistent amongst the different age groups (p = 0.583).

Confidence intervals and two sample T tests for the maximum percentage change in systolic pressure post tunneling, remifentanil versus control

X-Premie

	N	Mean	StDev	SE Mean	95% CI
S	4	29.0	29.5	15	8 - 50
R	3	3.3	10.3	6.0	(-5.1) - 11.7

Confidence intervals overlap, therefore the mean percentage changes in systolic pressure post tunnelling are not significantly different

95% confidence interval for the difference between the mean percentage changes in systolic pressure post tunnelling is –25 to 76.4

The difference between the mean percentage changes in systolic pressure post tunnelling is therefore not significant

T test for null hypothesis that the mean percentage changes in systolic pressure post tunnelling are the same
T= 1.61 P=0.21 DF= 3

The null hypothesis is proven, thus the mean percentage changes in systolic pressure post tunnelling are not significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	33.72	7.28	3.3	29.2 - 38.3
R	7	9.4	12.5	4.7	3.2 - 15.5

Confidence intervals DO NOT overlap, therefore the mean percentage changes in systolic pressure post tunnelling are significantly different

95% confidence interval for the difference between the mean percentage changes in systolic pressure post tunnelling is 95% C.I. is 11.4 to 37.4

The difference between the mean percentage changes in systolic pressure post tunnelling IS THEREFORE significant

T test for null hypothesis that the mean percentage changes in systolic pressure post tunnelling are the same
T= 4.24 P=0.0022 DF= 9

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in systolic pressure post tunnelling are significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	30.8	19.8	6.0	22.5 - 39.1
R	13	(-2.6)	15.6	4.3	(-8.6) - 3.4

Confidence intervals DO NOT overlap, therefore the mean percentage changes in systolic pressure post tunnelling are significantly different

95% confidence interval for the difference between the mean percentage changes in systolic pressure post tunnelling is 95% C.I. is 17.9 to 48.9

The difference between the mean percentage changes in systolic pressure post tunnelling IS THEREFORE significant

T test for null hypothesis that the mean percentage changes in systolic pressure post tunnelling are the same
T= 4.53 P=0.0003 DF= 18

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in systolic pressure post tunnelling are significantly different

Older Child

	N	Mean	StDev	SE Mean	95% CI
S	12	36.7	15.8	4.6	30.6 - 42.8
R	12	0.3	18.1	5.2	(-7.0) - 7.6

Confidence intervals DO NOT overlap, therefore the mean percentage changes in systolic pressure post tunnelling are significantly different

95% confidence interval for the difference between the mean percentage changes in systolic pressure post tunnelling is -50.9 to -22.0

The difference between the mean percentage changes in systolic pressure post tunnelling IS THEREFORE significant

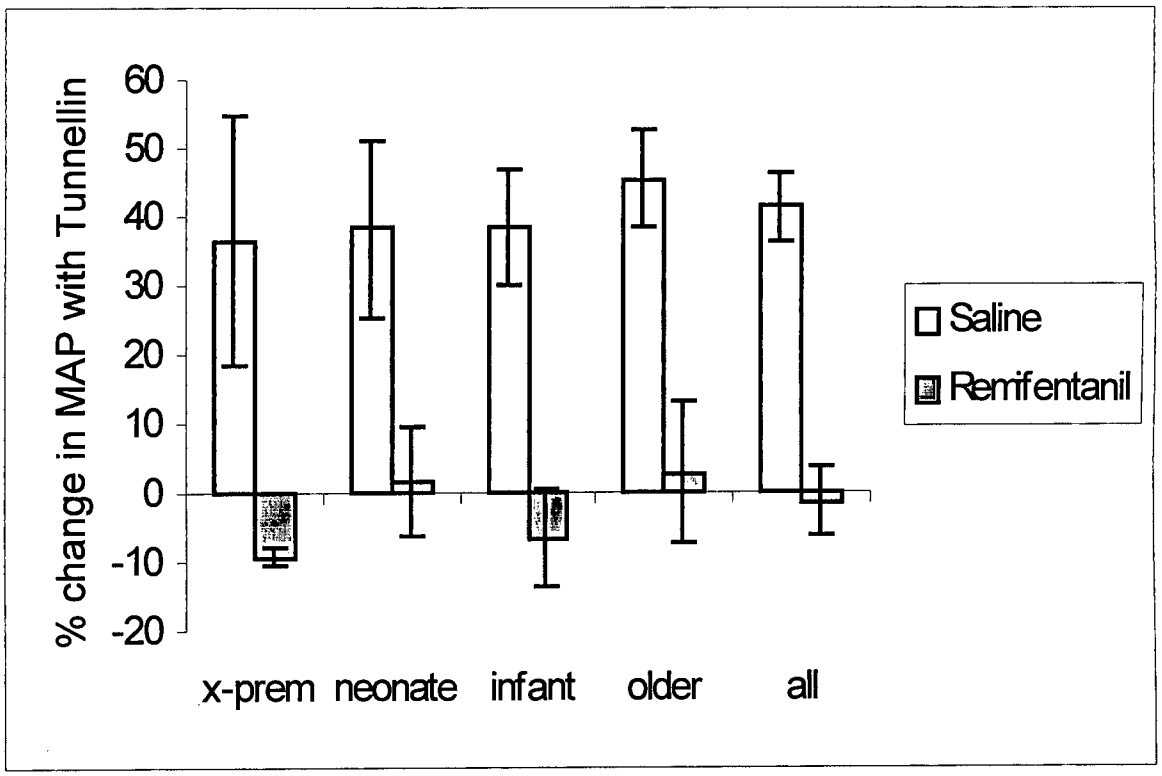
T test for null hypothesis that the mean percentage changes in systolic pressure post tunnelling are the same
T= -5.25 P=0.0000 DF= 21

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in systolic pressure post tunnelling are significantly different

CONCLUSION:

Analysis of variance, confidence intervals of the mean, confidence intervals of the difference between the means, Ttests and box and whisker charts show a significant rise in systolic blood pressure post tunnelling in the control group, compared to the remifentanil group, at p=0.05.
These findings are consistent in all age groups except for the x-premie group, whose numbers are small and who showed a non significant rise of systolic pressure in the control group.
Combining all age groups, the control group showed a mean increase of + 33.9 (sd=16.2) and the remifentanil group a mean increase of only + 1.1 (sd=16.2).

Mean percentage change in mean arterial pressure post tunnelling, in mm Hg, & 95% confidence intervals, remifentanil versus control



Basic statistics

Rows contain the number, mean and standard deviation of maximum percentage change in mean arterial pressure post tunnelling in control (S) or remifentanil (R)

Columns contain the age categories: neonate, infant, >1yr old, all ages

		neonate	infant	> 1 year old	all ages
S	number	5	11	12	28
	mean	38.300	38.336	45.383	41.350
	sd	20.684	19.675	18.774	19.052
R	number	7	13	12	32
	mean	1.571	-6.677	2.717	-1.350
	sd	15.727	18.277	25.388	20.643
All	number	12	24	24	60
	mean	16.875	13.954	24.050	18.577
	sd	25.459	29.453	30.850	29.180

Analysis of variance for maximum percentage change in mean arterial pressure post tunnelling, remifentanil versus control

Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	27227.8	22849.8	22849.8	55.98	**0.000**
agecod	2	833.8	808.1	404.0	0.99	**0.378**
code*agecod	2	134.9	134.9	67.5	0.17	**0.848**
Error	54	22041.9	22041.9	408.2		
Total	59	50238.4				

Thus the anova table shows that percentage change in mean pressure from baseline post tunnelling is statistically different between remifentanil and control groups (p=0.000). The control group shows a statistically significant rise in mean pressure (+41.4%) when compared to the remifentanil group (-1.4%). This finding is consistent amongst the different age groups (p = 0.848).

Two sample T-test and confidence intervals for the maximum percentage change in mean arterial pressure post tunneling, remifentanil versus control

X-Premie

	N	Mean	StDev	SE Mean	95% CI
S	4	36.4	25.4	13	18.2 - 54.6
R	3	(-9.37)	1.82	1.0	(-10.8) - (-8.0)

Confidence intervals DO NOT overlap, therefore the percentage changes in mean pressures post tunnelling are significantly different

95% confidence interval for the difference between the mean percentage changes in mean pressure post tunnelling is 5 to 86.3

The difference between the mean percentage changes in mean pressure post tunnelling IS THEREFORE significant

T test for null hypothesis that the mean percentage changes in mean pressure post tunnelling are the same
T= 3.59 P=0.037 DF= 3

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in mean pressure post tunnelling are significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	38.3	20.7	9.3	25.4 - 51.2
R	7	1.6	15.7	5.9	(-6.2) - 9.3

Confidence intervals DO NOT overlap, therefore the percentage changes in mean pressures post tunnelling are significantly different

95% confidence interval for the difference between the mean percentage changes in mean pressure post tunnelling is 10.7to 62.7

The difference between the mean percentage changes in mean pressure post tunnelling IS THEREFORE significant

T test for null hypothesis that the mean percentage changes in mean pressure post tunnelling are the same
T= 3.34 P=0.012 DF= 7

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in mean pressure post tunnelling are significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	38.3	19.7	5.9	30.1 - 46.6
R	13	-6.7	18.3	5.1	(-13.7) - 0.4

Confidence intervals DO NOT overlap, therefore the percentage changes in mean pressures post tunnelling are significantly different

95% confidence interval for the difference between the mean percentage changes in mean pressure post tunnelling is 28.7 to 61.3

The difference between the mean percentage changes in mean pressure post tunnelling IS THEREFORE significant

T test for null hypothesis that the mean percentage changes in mean pressure post tunnelling are the same
T= 5.77 P=0.0000 DF= 20

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in mean pressure post tunnelling are significantly different

Older Child

	N	Mean	StDev	SE Mean	95% CI
S	12	2.7	25.4	7.3	(-7.5) - 12.9
R	12	45.4	18.8	5.4	38.2 - 52.6

Confidence intervals DO NOT overlap, therefore the percentage changes in mean pressures post tunnelling are significantly different

95% confidence interval for the difference between the mean percentage changes in mean pressure post tunnelling is -61.7 to -23.6

The difference between the mean percentage changes in mean pressure post tunnelling IS THEREFORE significant

T test for null hypothesis that the mean percentage changes in mean pressure post tunnelling are the same
T= -4.68 P=0.0001 DF= 20

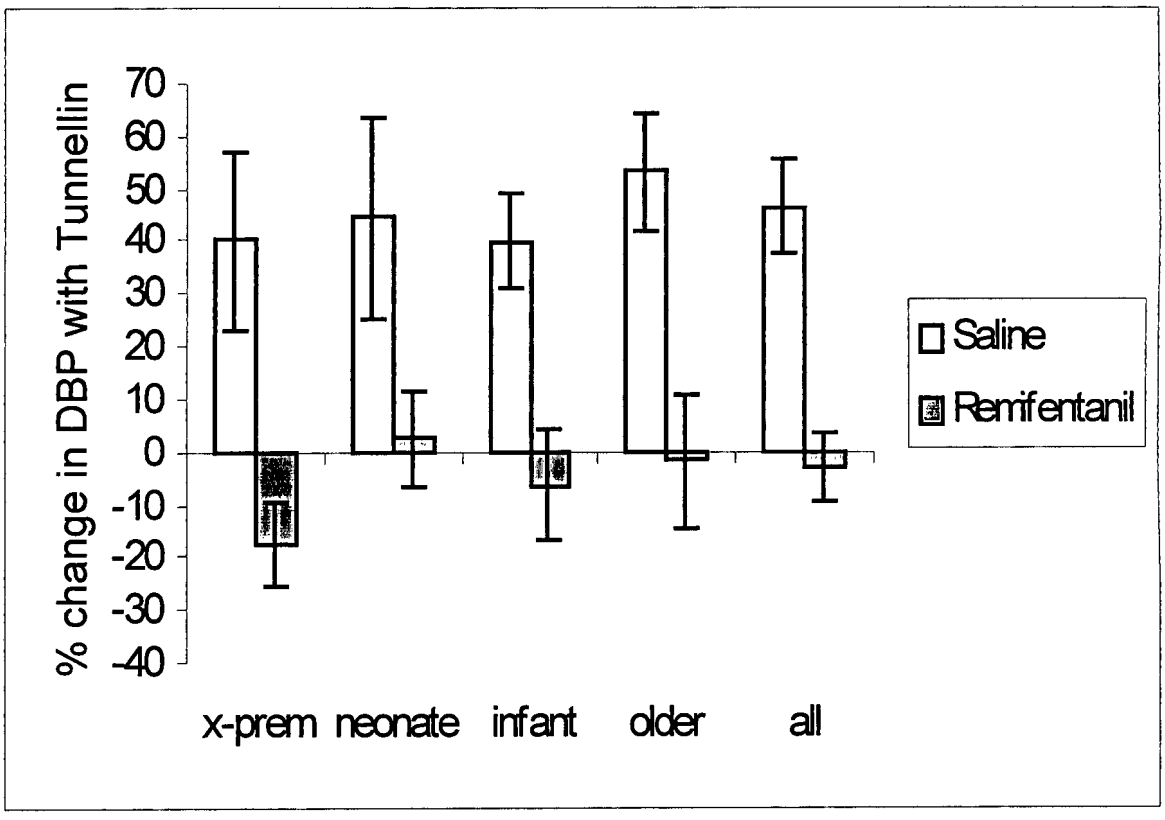
The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in mean pressure post tunnelling are significantly different

CONCLUSION:

Analysis of variance, 95% confidence intervals of the means, 95% confidence intervals of the difference between the means, Ttests and box and whisker charts show a significant increase at p=0.05, in the mean blood pressure, after tunnelling,in the control group compared to the remifentanil group, in all age groups.

Combining all age groups, the control group showed a mean increase of + 41.4 %(sd=19.1) and the remifentanil group - 1.4 % (sd=20.6).

Maximum percentage change in diastolic blood pressure post tunnelling, in mm Hg, & 95 % confidence intervals, remifentanil versus control:



Basic statistics

Rows contain the number, mean and standard deviation of maximum percentage change in diastolic blood pressure post drug administration in control (S) or remifentanil (R)

Columns contain the age categories: neonate, infant, >1yr old, all ages

		neonate	infant	> 1 year old	all ages
S	number	5	11	12	28
	mean	44.420	39.873	52.958	46.293
	sd	31.204	26.253	28.058	27.522
R	number	7	13	12	32
	mean	2.429	-6.446	-2.000	-2.837
	sd	18.400	26.826	31.759	26.721
all	number	12	24	24	60
	mean	19.925	14.783	25.479	20.090
	sd	31.722	35.084	40.581	36.506

Analysis of variance for maximum percentage change in diastolic blood pressure post tunnelling, mm Hg, remifentanil versus control:

Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	36046.0	30303.0	30303.0	39.71	**0.000**
agecod	2	976.8	969.0	484.5	0.63	**0.534**
code*agecod	2	399.1	399.1	199.5	0.26	**0.771**
Error	54	41208.7	41208.7	763.1		
Total	59	78630.6				

Thus the anova table shows that the percentage change in diastolic pressure from baseline post tunnelling is statistically different between remifentanil and control groups (p=0.000). The control group shows a statistically significant rise in diastolic pressure(+46.3%) when compared to the remifentanil group (-2.8%). This finding is consistent amongst the different age groups (p = 0.771).

Confidence intervals and two sample T tests for the maximum percentage change from baseline in diastolic pressure post tunnelling, remifentanil versus control

X-Premie

	N	Mean	StDev	SE Mean	95% CI
S	4	40.0	23.3	12	23.2 - 56.8
R	3	(-17.87)	9.88	5.7	(-25.9) - (-9.9)

Confidence intervals DO NOT overlap, therefore the percentage changes in diastolic pressures post tunnelling are significantly different

95% confidence interval for the difference between the mean percentage changes in diastolic pressure post tunnelling is 22 to 93.9

The difference between the mean percentage changes in diastolic pressure post tunnelling IS THEREFORE significant

T test for null hypothesis that the mean percentage changes in diastolic pressure post tunnelling are the same

T= 4.47 P=0.011 DF= 4

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in diastolic pressure post tunnelling are significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	44.4	31.2	14	25.0 - 63.8
R	7	2.4	18.4	7.0	(-6.6) - 11.5

Confidence intervals DO NOT overlap, therefore the percentage changes in diastolic pressures post tunnelling are significantly different

95% confidence interval for the difference between the mean percentage changes in diastolic pressure post tunnelling is 2 to 82.1

The difference between the mean percentage changes in diastolic pressure post tunnelling IS THEREFORE significant

T test for null hypothesis that the mean percentage changes in diastolic pressure post tunnelling are the same

T= 2.69 P=0.043 DF= 5

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in diastolic pressure post tunnelling are significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	39.9	26.3	7.9	28.9 - 50.9
R	13	-6.4	26.8	7.4	(-16.8) - 3.9

Confidence intervals DO NOT overlap, therefore the percentage changes in diastolic pressures post tunnelling are significantly different

95% confidence interval for the difference between the mean percentage changes in diastolic pressure post tunnelling is 23.7 to 68.9

The difference between the mean percentage changes in diastolic pressure post tunnelling IS THEREFORE significant

T test for null hypothesis that the mean percentage changes in diastolic pressure post tunnelling are the same
T= 4.26 P=0.0003 DF= 21

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in diastolic pressure post tunnelling are significantly different

Older Child

	N	Mean	StDev	SE Mean	95% CI
S	12	53.0	28.1	8.1	42.1 - 63.8
R	12	-2.0	31.8	9.2	(-14.7) - 10.7

Confidence intervals DO NOT overlap, therefore the percentage changes in diastolic pressures post tunnelling are significantly different

95% confidence interval for the difference between the mean percentage changes in diastolic pressure post tunnelling is -80.4 to -29.5

The difference between the mean percentage changes in diastolic pressure post tunnelling IS THEREFORE significant

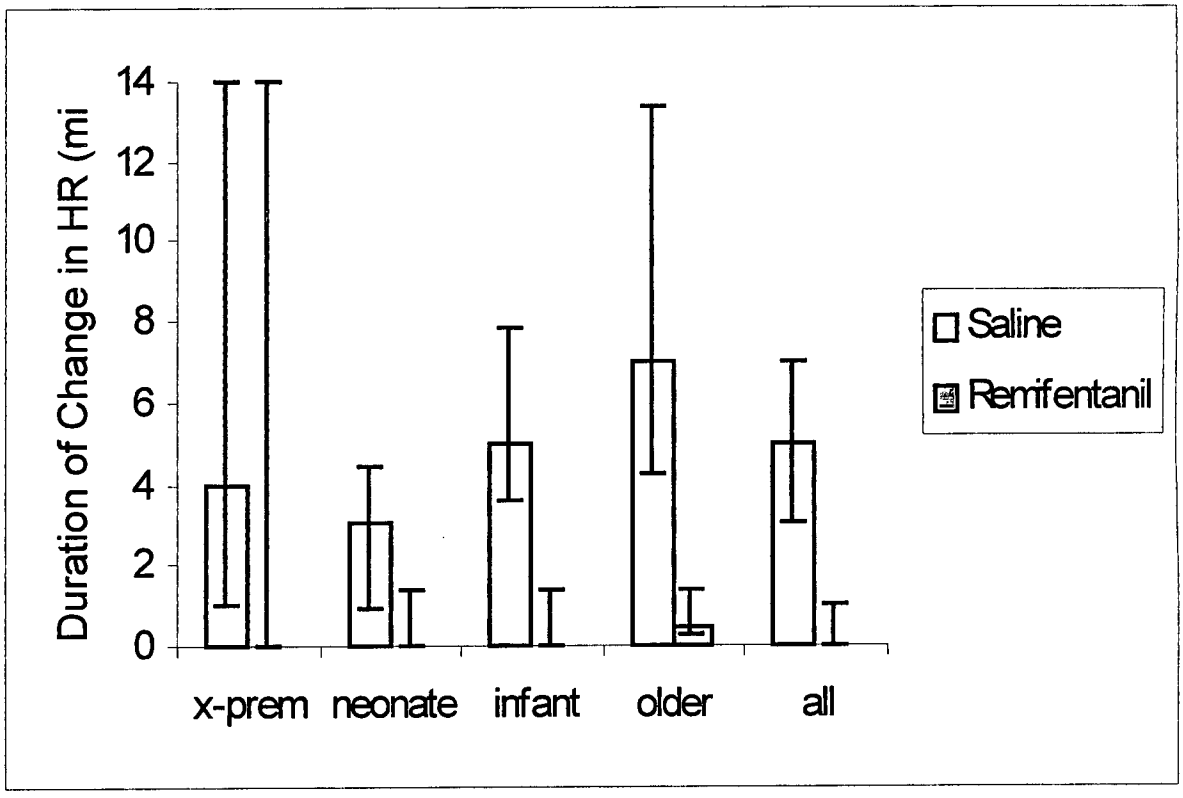
T-test for null hypothesis that the mean percentage changes in diastolic pressure post tunnelling are the same
T= -4.49 P=0.0002 DF= 21

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in diastolic pressure post tunnelling are significantly different

CONCLUSION:

Analysis of variance, 95% confidence intervals of the means, 95% confidence intervals of the difference between the means, Ttests and box and whisker charts show a significant increase, at p=0.05, in the diastolic blood pressure after tunnelling in the control group compared to the remifentanil group, in all ages. Combining all age groups, the control group showed a mean increase of + 46.3 (sd=27.5) and the remifentanil group a mean "increase" of - 2.8 (sd=26.7).

Median duration of change in heart rate post tunnelling, in minutes, & 95% confidence intervals, remifentanil versus control:



Basic statistics for the duration, in minutes, of change in heart rate post tunneling, remifentanil versus control

The first column refers to control (S) or remifentanil (R) . The second column refers to the age group. The third column is the median. The fourth column is the 95% confidence intervals.

TABLES:			
code	agecod	median	+-1.4(se)
S	x-p	4	1.0 - #
S	neonate	3	0.9 - 4.4
S	infant	5	3.6 - 7.8
S	> 1 yr	7	4.2 - 13.4
S	all	5	3 - 7
R	xp	0	0 - #
R	neonate	0	0 - 1.4
R	infant	0	0 - 1.4
R	> 1 yr	0.5	0.3 - 1.4
R	all	0	0 – 1

This data includes "censored" figures, thus non-parametric tests are applied.

COX REGRESSION ANALYSIS FOR "CENSORED" DATA, for the duration of change in heart rate post tunnelling, in minutes, remifentanil versus control

This is similar to an analysis of variance test, but for non-parametric data
In the first column, second row, "code" refers to effect of remifentanil vs control, in the third row "agecode" refers to effect of age category and in the fourth row "code\agecode" refers to the consistency of remifentanil vs control results amongst all age categories

Parameter	Estimate	S.E.	t-ratio	p-value
code	-0.290	0.142	-2.033	**0.042**
agecode	0.379	0.216	1.758	**0.079**
code\agecode	-0.317	0.194	-1.640	**0.101**

Thus the cox regression table shows that there is a significant difference in the duration of change in heart rate post tunnelling between remifentanil(0 minutes) and control groups (5 minutes) (p=0.042) and that this is consistent for all ages (p=0.101)

NON PARAMETRIC LOG-RANK ANALYSIS, for the duration of change in heart rate post tunnelling, in minutes, remifentanil versus control

Test	Age	Chi Sq	DF	p
L-Rank	x-premie	4.20	1	**0.04**
	neonate	4.44	1	**0.035**
	infant	3.27	1	**0.071**
	> 1 yr old	15.15	1	**0.0001**
Wilcox	x-p	4.31	1	0.038
	neonate	7.61	1	0.005
	infant	14.17	1	0.0002
-2LR	x-p	7.73	1	0.005
	neonate	3.94	1	0.047
	infant	44.36	1	0.0001

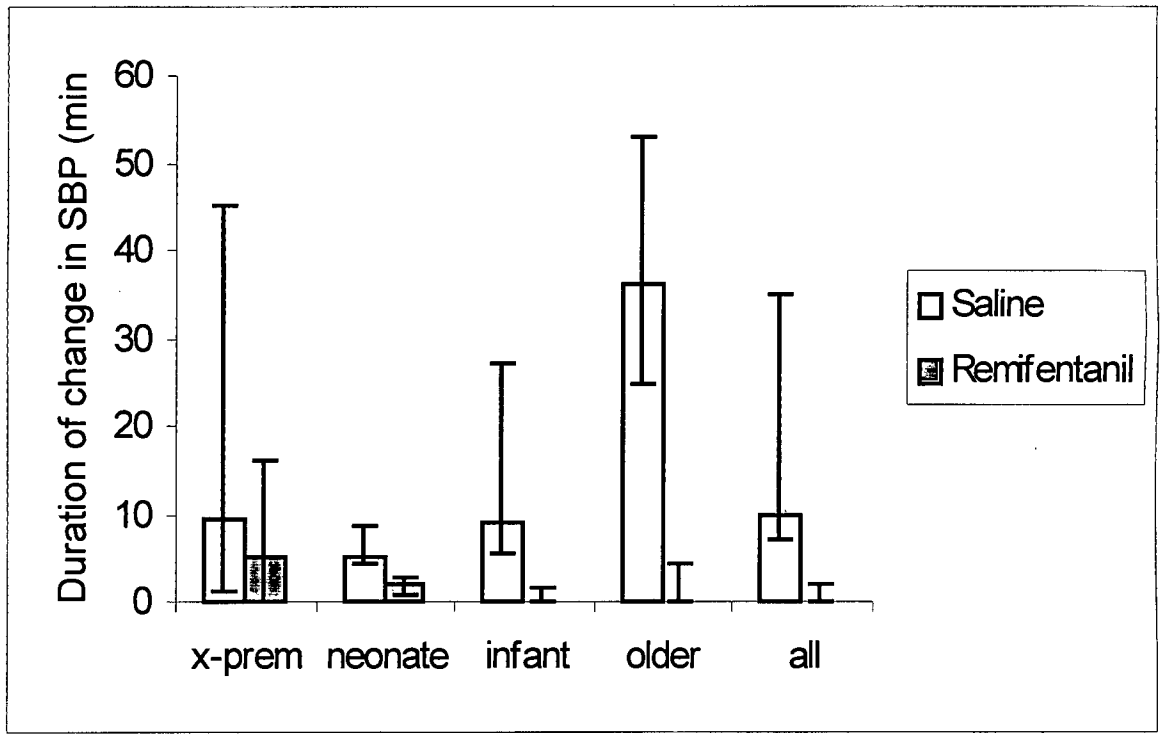
CONCLUSION:

Cox regression tables and log rank tests show that there was a significantly increased duration of change in heart rate post tunnelling in the control group, compared to the remifentanil group, at p=0.05, in all age groups.

The 95% confidence interval box and whisker charts confirm this for the infant, the older child and all ages together and show a non significant difference in the neonate and x-premie.

All ages included, the control groups increase averaged 5 minutes and the remifentanil group had no increase for any duration.

Median duration of change in systolic blood pressure post tunnelling, in minutes, & 95% confidence intervals, remifentanil versus control



Basic statistics for the duration, in minutes, of change in systolic blood pressure post tunnelling, remifentanil versus control

The first column refers to control (S) or remifentanil (R) . The second column refers to the age group. The third column is the median. The fourth column is the 95% confidence intervals.

Code	Agecod	Median	1.4 (se)
S	x-premie	9.5	1.0 - 4.5
S	neonate	5	4.3 - 8.5
S	infant	9	5.5 - 27.2
S	> 1 yr old	36	24.8 - 52.8
S	all ages	10	7 - 35
R	x-premie	5	0 - 16.0
R	neonate	2	0.6 - 2.7
R	infant	0	0 - 1.4
R	> 1 yr old	0	0.3 - 4.2
R	all ages	0	0 - 2

NON PARAMETRIC LOG-RANK ANALYSIS for duration of change in systolic pressure, post tunnelling, remifentanil versus control:

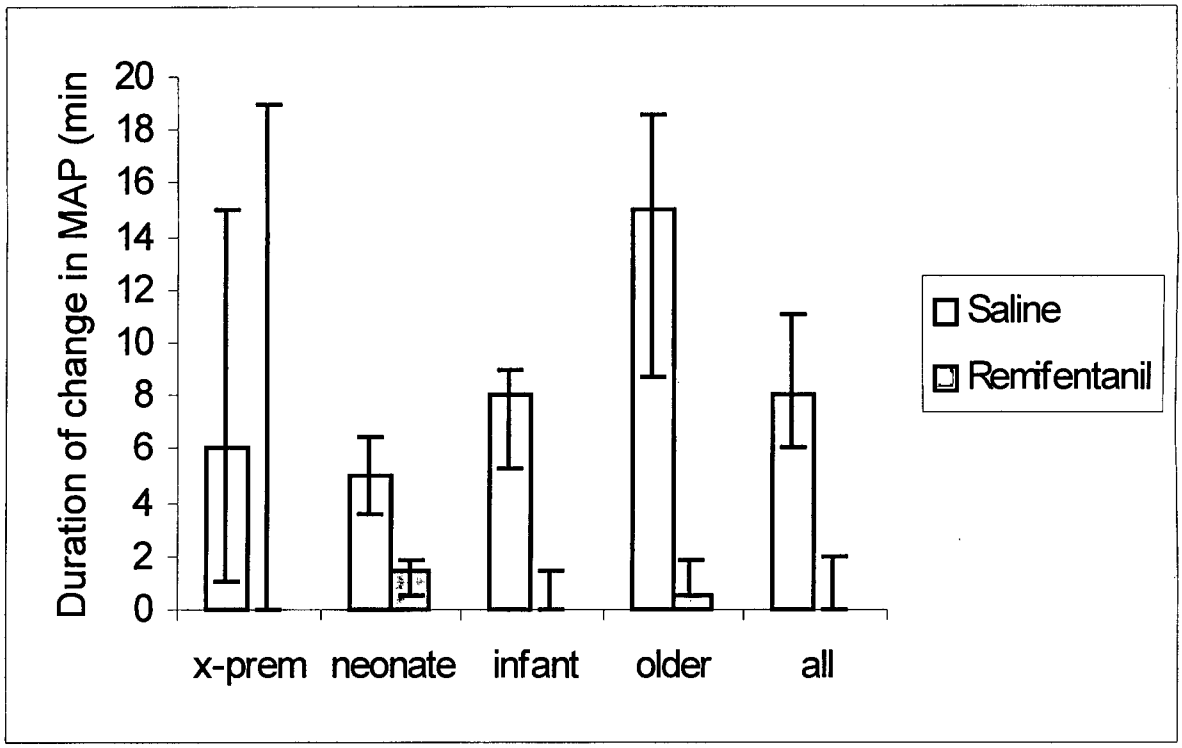
Test	Age	Chi Sq	DF	p
L-Rank	x-premie	0.42	1	**0.52**
	neonate	10.36	1	**0.0013**
	infant	11.03	1	**0.0009**
	> 1 yr old	18.39	1	**0.0001**
Wilcox	neonate	8.84	1	0.003
	infant	12.79	1	0.0003
	> 1 yr old	16.05	1	0.0001
-2LR	neonate	5.31	1	0.021
	infant	22.89	1	0.0001
	> 1 yr old	32.78	1	0.0001

CONCLUSION:

Log rank tables and 95% confidence interval box and whisker charts show a statistically greater duration of increase in systolic blood pressure in the control group compared to the remifentanil group, at p = 0.05, in all age groups except x-premies who show a non significant increase.

All ages included, the control group's increase averaged ten minutes and the remifentanil group had no increase of any duration.

Median duration of the change in mean arterial pressure post tunnelling, in minutes, & 95% confidence intervals



Basic statistics for the duration, in minutes, of change in mean arterial pressure post tunnelling, remifentanil versus control

The first column refers to control (S) or remifentanil (R) . The second column refers to the age group. The third column is the median. The fourth column is the 95% confidence intervals

Code	Agecod	Median	1.4 (se)
S	x-premie	6	1.0 - 15.0
S	neonate	5	3.6 - 6.4
S	infant	8	5.2 - 9.0
S	> 1 yr old	15	8.7 - 18.5
S	all ages	8	6 - 11
R	x-premie	0	0 - #
R	neonate	1.5	0.5 - 1.9
R	infant	0	0.0 - 1.4
R	> 1 yr old	0.5	0.5 - 1.9
R	all ages	0	0 - 2

NON PARAMETRIC LOG-RANK ANALYSIS, for the duration, in minutes, of change in mean arterial pressure post tunnelling, remifentanil versus control

Test	Age	Chi Sq	DF	p
L-Rank	x-premie	0.03	1	**0.85**
	neonate	1.485	1	**0.223**
	infant	18.03	1	**0.0001**
	> 1 yr old	16.43	1	**0.0001**
Wilcox	x-premie	4.865	1	0.027
	neonate	15.77	1	0.0001
	infant	13.5	1	0.0002
-2LR	x-premie	0.913	1	0.339
	neonate	31.06	1	0.0001
	infant	25.14	1	0.0001

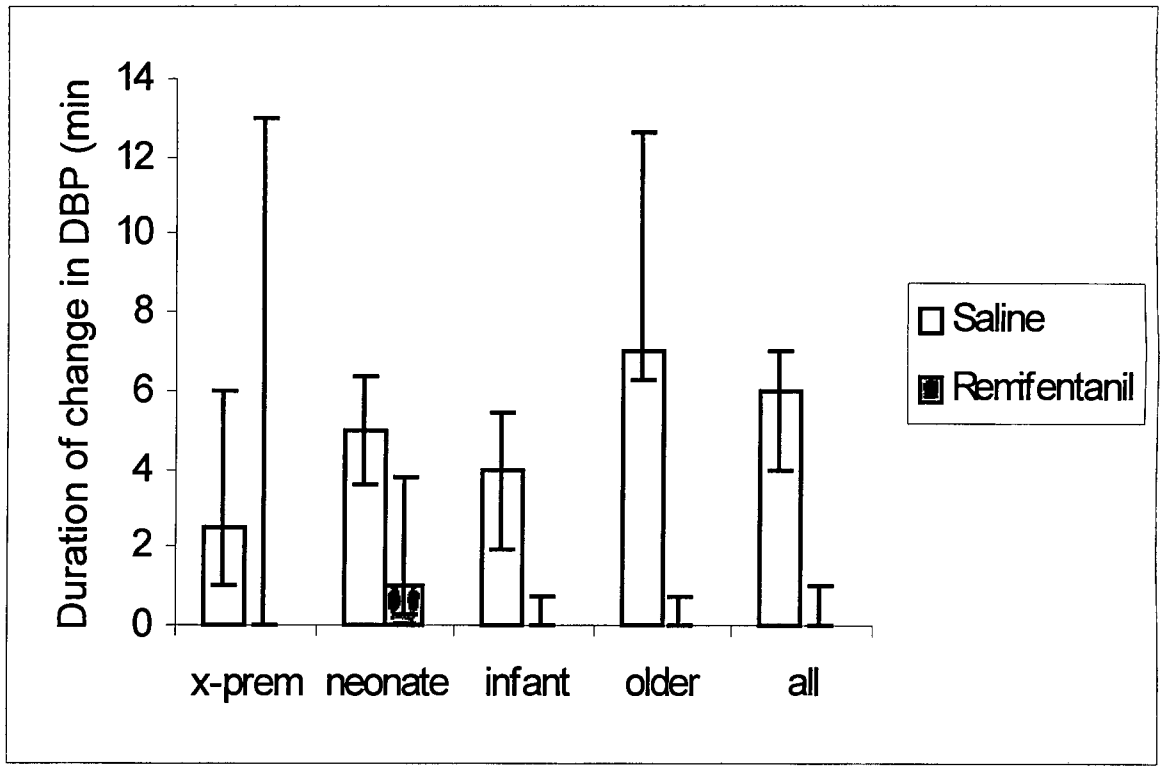
CONCLUSION:

95% confidence interval box and whisker charts show that there is a significantly longer duration of change in mean arterial pressure post tunnelling, in the control group, at p=0.05, compared to the remifentanil group, in all age groups except x-premies who show a non significant increase in duration.

Log rank tests show a significant increase in duration in the control group, in infants and older children and a non significant increase in neonates and x-premies.

All ages included, the control group's increase averaged eight minutes and the remifentanil's group had no increase of any duration.

Mean duration of change in diastolic pressure post tunnelling, in minutes, & 95% confidence intervals:



Basic statistics for the duration, in minutes, of change in diastolic blood pressure post tunnelling, remifentanil versus control

The first column refers to control (S) or remifentanil (R) . The second column refers to the age group. The third column is the median. The fourth column is the 95% confidence intervals.

Code	Agecode	Median	1.4(se)
S	x-premie	2.5	1.0 - 6.0
S	neonate	5	3.6 - 6.4
S	infant	4	1.9 - 5.4
S	> 1 yr old	7	6.3 - 12.6
S	all ages	6	4 - 7
R	x-premie	0	0 - #
R	infant	1	0.3 - 3.8
R	infant	0	0.0 - 0.7
R	> 1 yr old	0	0.0 - 0.7
R	all ages	0	0 - 1

NON PARAMETRIC LOG-RANK ANALYSIS, for the duration, in minutes, of change in diastolic blood pressure post tunnelling, remifentanil versus control

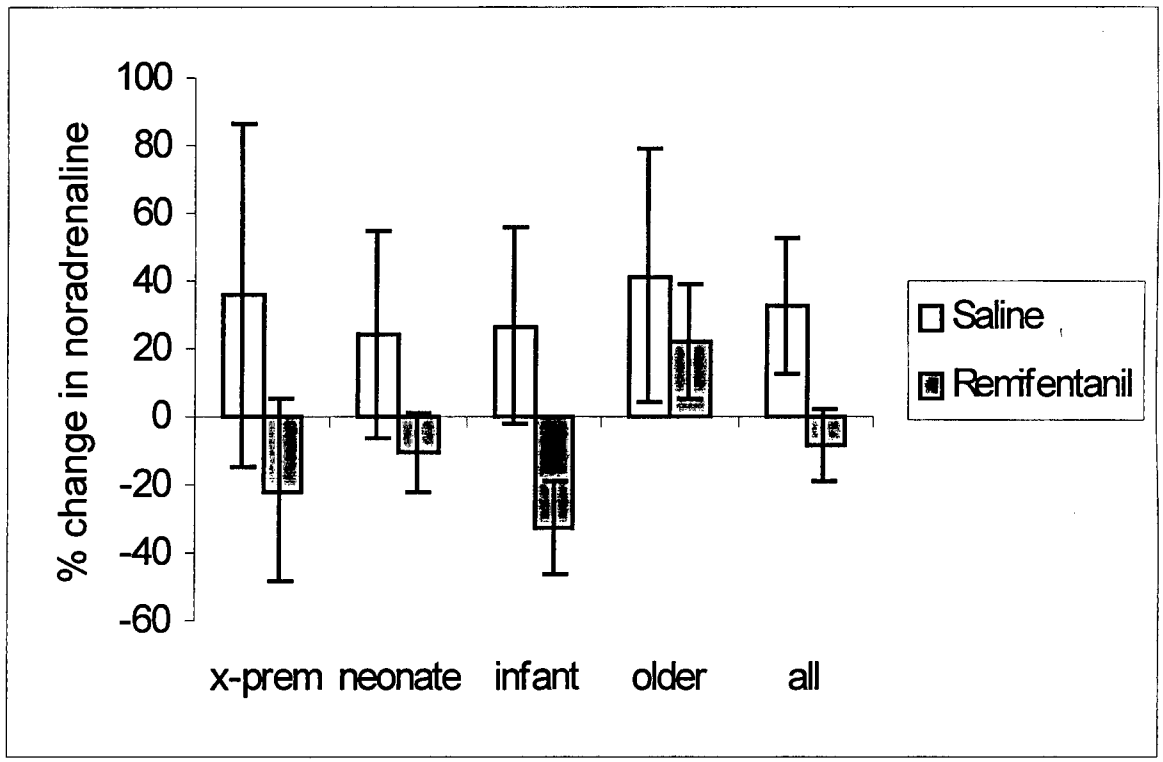
Test	Age	Chi Sq	DF	p
L-Rank	x-premie	0.06	1	**0.81**
	neonate	0.813	1	**0.367**
	infant	10.69	1	**0.0011**
	> 1 yr old	22.59	1	**0.0001**
Wilcox	neonate	3.378	1	0.066
	infant	11.86	1	0.0006
	> 1 yr old	17.658	1	0.0001
-2LR	neonate	1.014	1	0.3141
	infant	18.20	1	0.0001
	> 1 yr old	34.67	1	0.0001

CONCLUSION:

95% confidence interval box and whisker charts and log rank tests show a significantly greater duration of change in diastolic blood pressure, at p = 0.05, in the control group post tunnelling compared to the remifentanil group in all age groups except neonates and x-premies who show a non significant increase.

All ages included, the control groups' increase averaged six minutes and the remifentanil groups had no increase of any duration.

Mean percentage change from baseline in plasma noradrenaline levels in response to tunnelling, & 95% confidence intervals:



Basic statistics for the percentage change from baseline in plasma noradrenaline levels in response to tunnelling, remifentanil versus control

Rows contain the number, mean and standard deviation of percentage change from baseline in plasma noradrenaline levels post tunnelling in control (S) or remifentanil (R)

Columns contain the age categories: neonate, infant, >1yr old, all ages

		neonate	infant	> 1 yr old	all ages
S	number	5	11	13	29
	mean	23.960	26.645	41.346	32.772
	sd	49.495	68.872	96.748	78.220
R	number	8	13	11	32
	mean	-10.825	-32.731	22.000	-8.441
	sd	23.814	36.130	42.219	42.262
all	number	13	24	24	61
	mean	2.554	-5.517	32.479	11.152
	sd	38.179	60.471	75.865	64.874

Analysis of variance for percentage change in plasma noradrenaline post tunnelling, remifentanil versus control :

Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	25840	19501	19501	5.18	**0.027**
agecod	2	14840	14949	7474	1.99	**0.147**
code*agecod	2	4825	4825	2413	0.64	**0.531**
Error	55	207014	207014	3764		
Total	60	252519				

Thus the anova table shows that percentage change in plasma noradrenaline levels from baseline post tunnelling is statistically greater in the control group than in the remifentanil group (p=0.027). The control group shows a statistically significant rise in plasma noradrenaline at + 32.7% when compared to the remifentanil group at – 8.4%.
This finding is consistent amongst the different age groups (p = 0.531).

Confidence intervals and two sample T tests for the percentage change in plasma noradrenaline due to tunneling, remifentanil versus control

X-Premie

	N	Mean	StDev	SE Mean	95% CI
S	4	35.8	72.4	36	(-14.6) - 86.2
R	4	(-21.8)	38.4	19	(-48.4) - 4.8

Confidence intervals overlap, therefore the percentage changes in plasma catecholamines post tunnelling are not significantly different

95% confidence interval for the difference between the mean percentage changes in plasma noradrenaline post tunnelling is –56 to 171

The difference between the mean percentage changes in plasma noradrenaline post tunnelling is therefore not significant

T test for null hypothesis that the mean percentage changes in plasma catecholamines post tunnelling are the same

T= 1.41 P=0.23 DF= 4

The null hypothesis is proven, thus the mean percentage changes in plasma noradrenaline post tunnelling are not significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	24.0	49.5	22	(-6.8) - 54.7
R	8	(-10.8)	23.8	8.4	(-22.5) - 0.9

Confidence intervals overlap, therefore the percentage changes in plasma catecholamines post tunnelling are not significantly different

95% confidence interval for the difference between the mean percentage changes in plasma noradrenaline post tunnelling is -26 to 95.7

The difference between the mean percentage changes in plasma noradrenaline post tunnelling is therefore not significant

T test for null hypothesis that the mean percentage changes in plasma catecholamines post tunnelling are the same

T= 1.47 P=0.20 DF= 5

The null hypothesis is proven, thus the mean percentage changes in plasma noradrenaline post tunnelling are not significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	26.6	68.9	21	(-2.2) - 55.5
R	13	-32.7	36.1	10	(-46.7) - (-18.8)

Confidence intervals DO NOT overlap, therefore the percentage changes in plasma catecholamines post tunnelling are significantly different

95% confidence interval for the difference between the mean percentage changes in plasma noradrenaline post tunnelling is 10 to 109

The difference between the mean percentage changes in plasma noradrenaline post tunnelling IS THEREFORE significant

T test for null hypothesis that the mean percentage changes in plasma catecholamines post tunnelling are the same
T= 2.58 P=0.022 DF= 14

The ALTERNATIVE hypothesis is proven, thus the mean percentage changes in plasma noradrenaline post tunnelling are significantly different

Older Child

	N	Mean	StDev	SE Mean	95% CI
S	13	41.3	96.7	27	4.1 - 78.6
R	11	22.0	42.2	13	5.1 - 38.9

Confidence intervals overlap, therefore the percentage changes in plasma catecholamines post tunnelling are not significantly different

95% confidence interval for the difference between the mean percentage changes in plasma noradrenaline post tunnelling is -82 to 44

The difference between the mean percentage changes in plasma noradrenaline post tunnelling is therefore not significant

T test for null hypothesis that the mean percentage changes in plasma catecholamines post tunnelling are the same
T= -0.65 P=0.52 DF= 16

The null hypothesis is proven, thus the mean percentage changes in plasma noradrenaline post tunnelling are not significantly different

CONCLUSION:

Analysis of variance suggests a significant rise in plasma noradrenaline levels in the control group, compared to the remifentanil group, at p = 0.05, post tunnelling, in all age groups.

95% confidence intervals of the mean, 95% confidence intervals of the difference between the means, box and whisker charts and T tests confirm this in the infant and all ages together and showed a non significant increase in noradrenaline in the x-premie, neonate and older child.

All ages included, the controls groups' average change in noradrenaline was + 33.8 % and the remifentanil group - 8.4 %

Plasma adrenaline levels were also measured but quantities assayed were too low to be regarded of any significance, i.e. the levels were less than than the High Performance Liquid Chromatogram's degree of accuracy.

OVERALL CONCLUSIONS:

The control group generally showed a statistically greater degree and duration of increase in heart rate and blood pressure and increase in plasma catecholamines post tunnelling than the remifentanil group, in all age groups.

The heart rate changes were greater the older the child, as were the durations of all the changes. Analysis of variance, with it's use of pooled data and it's greater power, suggests that the responses are the same in all age groups. The individual Ttests and confidence intervals were less conclusive in the younger age groups. I would suggest that greater numbers in each group would confirm the anova findings. It may be, however, that the neonate or young infant respond differently to both stress and to remifentanil when compared to the older child. Further work is warranted in these age groups.

Haemodynamic measurements and catecholamine levels increased by 30 – 45% in the control group for between 5 – 10 minutes.
The remifentanil showed almost no change from the baseline. In the young brain with immature autoregulation and compromised cerebral perfusion this is likely to be clinically very significant, for the reasons discussed in the chapter one.

Recovery profiles

Recovery profiles are compared in the remifentanil and control groups, in each age group, using box and whisker charts, analysis of variance, T tests and 95% confidence intervals. Recovery criteria were time from end of surgery, in minutes, until fulfilling the criteria for extubation, the criteria for transfer to recovery and the criteria for discharge to the ward.

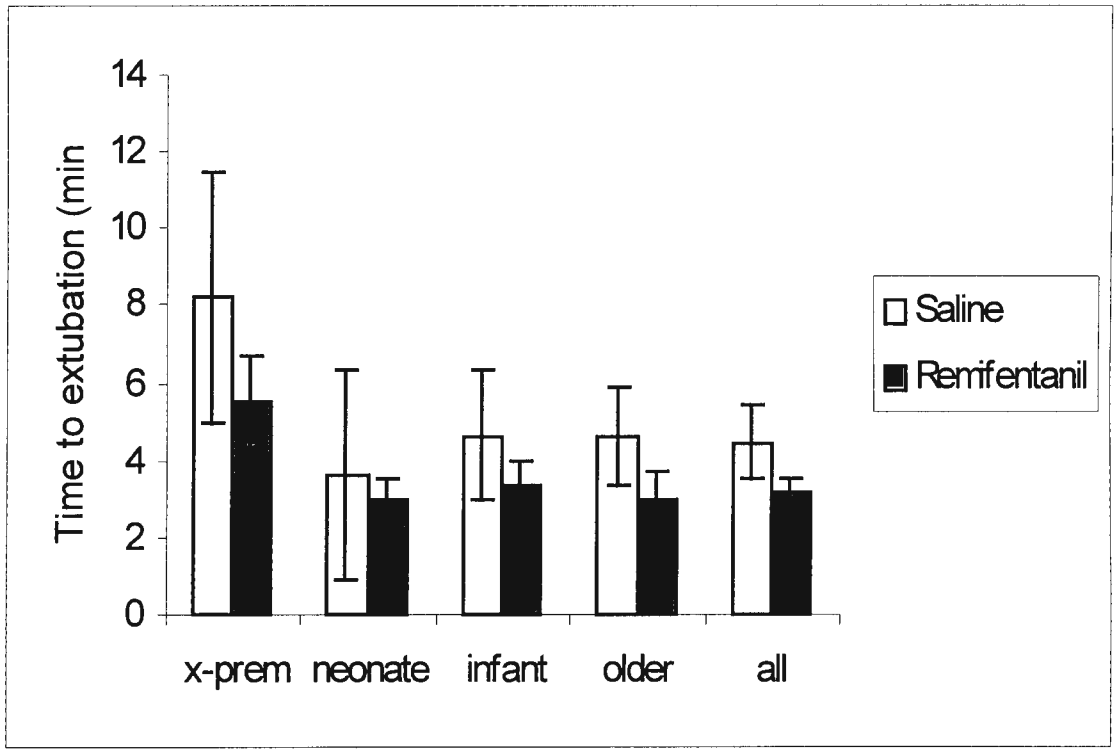
There was no delay in recovery in the remifentanil group, in all age groups, when compared to control. In fact, times to fitness for transfer to recovery and for discharge to the ward appeared to be faster in the remifentanil group. This unexpected finding is discussed below.

This "All ages combined" table shows the means, standard errors of the mean and p values testing the null hypothesis that the remifentanil and control groups had the same recovery profile:

	Time from end of surgery to extubation in minutes	Time from end of surgery till fit for transfer to recovery area in minutes	Time from end of surgery till fit for discharge to ward in minutes
Saline	4.4 (0.7)	6.6 (0.7)	15.4 (1.5)
Remifentanil	3.1 (0.3)	4.7 (0.3)	10.6 (0.9)
P value	$p > 0.05$	$p < 0.05$	$p < 0.05$

On the following pages numbered A to N are the detailed statistics for each variable in each age category

Mean duration between "end of surgery" and "fulfilling criteria for extubation", in minutes & 95% confidence intervals, remifentanil versus control:



Basic statistics

Rows contain the number, mean and standard deviation of time, in minutes, from the end of surgery until fullfilling criteria for extubation in control (S) or remifentanil (R)

Columns contain the age categories: neonate, infant, >1yr old, all ages

		neonate	infant	> 1 yr	all ages
S	number	5	11	13	29
	mean	3.6000	4.6364	4.6154	4.4483
	sd	4.2778	3.9312	3.4044	3.6409
R	number	8	13	12	33
	mean	3.0000	3.3077	3.0000	3.1212
	sd	1.0690	1.8879	1.6514	1.5960
all	number	13	24	25	62
	mean	3.2308	3.9167	3.8400	3.7419
	sd	2.6190	3.0060	2.7791	2.8048

Analysis of variance for time to extubation, in minutes, remifentanil versus control:

Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	27.183	19.232	19.232	2.41	**0.126**
agecod	2	2.963	3.727	1.863	0.23	**0.793**
code*agecod	2	2.133	2.133	1.067	0.13	**0.875**
Error	56	447.592	447.592	7.993		
Total	61	479.871				

Thus the anova table shows that there is no significant difference between the time from the end of surgery to extubation in the remifentanil (3.1 minutes) and control groups (4.4 minutes) (p=0.126). This finding is consistent amongst the different age groups (p = 0.875).

Confidence intervals and two sample tests for the time, in minutes, from the end of surgery to extubation, remifentanil versus control

X-Premie

	N	Mean	StDev	SE Mean	95% CI
S	4	8.25	4.57	2.3	5.0 - 11.5
R	4	5.50	1.73	0.87	4.3 - 6.7

Confidence intervals overlap, therefore the mean times to extubation are not significantly different

95% confidence interval for the difference between the mean times to extubation is -5.0 to 10.53

The difference between the mean times to extubation is therefore not significant

T test for null hypothesis that the mean times to extubation are the same
T= 1.12 P=0.34 DF= 3

The null hypothesis is proven, thus the mean times to extubation are not significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	3.60	4.28	1.9	0.9 - 6.3
R	8	3.00	1.07	0.38	2.5 - 3.5

Confidence intervals overlap, therefore the mean times to extubation are not significantly different

95% confidence interval for the difference between the mean times to extubation is -4.8 to 6.02

The difference between the mean times to extubation is therefore not significant

T test for null hypothesis that the mean times to extubation are the same
T= 0.31 P=0.77 DF= 4

The null hypothesis is proven, thus the mean times to extubation are not significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	4.64	3.93	1.2	3.0 - 6.3
R	13	3.31	1.89	0.52	2.6 - 4.0

Confidence intervals overlap, therefore the mean times to extubation are not significantly different

95% confidence interval for the difference between the mean times to extubation is -1.5 to 4.13

The difference between the mean times to extubation is therefore not significant

T test for null hypothesis that the mean times to extubation are the same
T= 1.03 P=0.32 DF= 13

The null hypothesis is proven, thus the mean times to extubation are not significantly different

Older Child

	N	Mean	StDev	SE Mean	95% CI
S	13	4.62	3.40	0.94	3.3 - 5.9
R	12	3.00	1.65	0.48	2.3 - 3.7

Confidence intervals overlap, therefore the mean times to extubation are not significantly different

95% confidence interval for the difference between the mean times to extubation is -3.85 to 0.62

The difference between the mean times to extubation is therefore not significant

T test for null hypothesis that the mean times to extubation are the same
T= -1.53 P=0.15 DF= 17

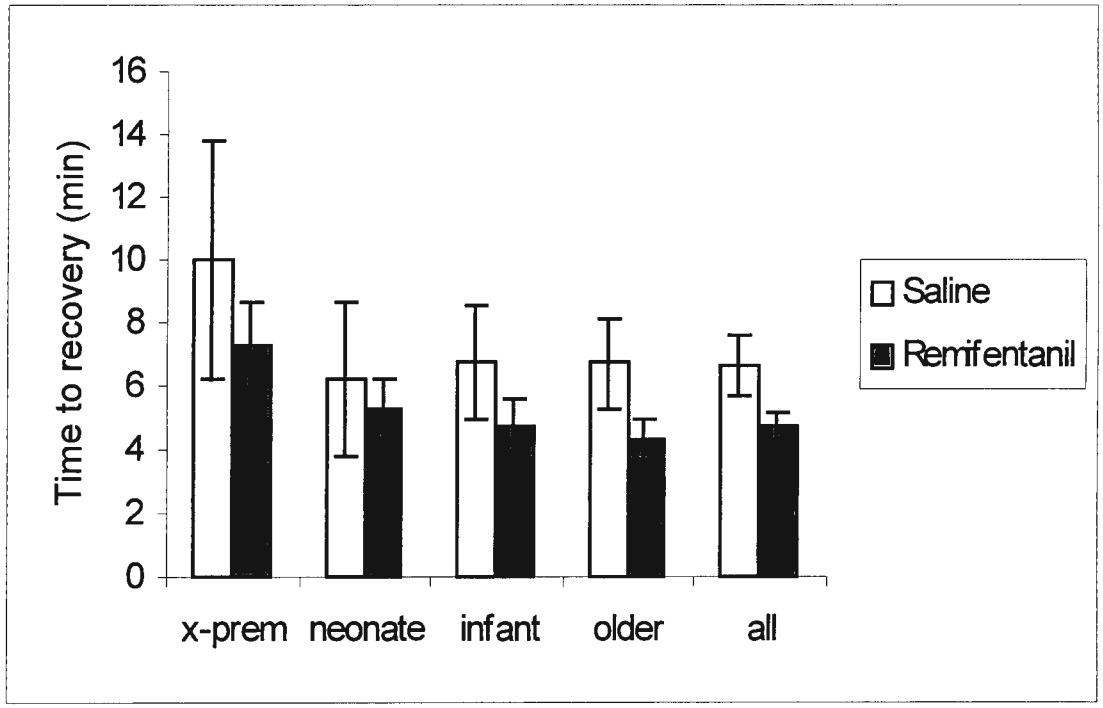
The null hypothesis is proven, thus the mean times to extubation are not significantly different

CONCLUSION:

Analysis of variance, confidence intervals of the means and confidence intervals of the difference between the means, Ttests and box and whisker charts show that there is no statistical difference, at p= 0.05,in the time from the end of surgery to extubation, between remifentanil and control groups, in all age groups.

In fact, there was a non-significant tendency for extubation to be faster in the remifentanil group. All ages included, the mean time for the remifentanil group was 3.1 min (sd=1.6) and the control group 4.4 (sd=3.6). Possible explanations include chance, observer bias or altered depth of anaesthesia due to the haemodynamic surge. This is discussed further in the conclusion.

Mean duration of time from "end of surgery" to "fulfilling criteria for discharge to recovery", in minutes, & 95% confidence intervals, remifentanil versus control:



Basic statistics

Rows contain the number, mean and standard deviation of time taken, in minutes, to fulfil criteria for moving to recovery, in control (S) or remifentanil (R)

Columns contain the age categories: neonate, infant, >1yr old, all ages

		neonate	infant	> 1 yr old	all ages
S	number	5	11	13	29
	mean	6.2000	6.7273	6.6923	6.6207
	sd	3.8341	4.2448	3.7055	3.8024
R	number	8	13	12	33
	mean	5.2500	4.7692	4.3333	4.7273
	sd	1.8323	2.1274	1.5570	1.8418
all	number	13	24	25	62
	mean	5.6154	5.6667	5.5600	5.6129
	sd	2.6627	3.3449	3.0697	3.0534

Analysis of variance for time to recovery, in minutes, remifentanil versus control

Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	55.337	42.477	42.477	4.68	**0.035**
agecod	2	1.042	0.769	0.384	0.04	**0.959**
code*agecod	2	4.106	4.106	2.053	0.23	**0.798**
Error	56	508.225	508.225	9.075		
Total	61	568.710				

The anova table shows that there is a statistically significant difference in the time taken to fulfil criteria for moving to recovery between remifentanil and control groups (p = 0.035) and that this is consistent amongst the different age groups (p = 0.798). Surprisingly, the remifentanil (4.7 minutes) group appeared to fulfil the criteria for moving to recovery faster than the control group (6.6 minutes). Possible explanations for this phenomenon are mentioned below, in the conclusion.

Confidence intervals and two sample T tests for the time taken, in minutes, to fulfill criteria for moving to recovery, remifentanil versus control

X-Premie

	N	Mean	StDev	SE Mean	95% CI
S	4	10.00	5.35	2.7	6.2 - 13.8
R	4	7.25	1.89	0.95	5.9 - 8.6

Confidence intervals overlap, therefore the mean times to recovery are not significantly different

95% confidence interval for the difference between the mean times to recovery is -6.3 to 11.79

The difference between the mean times to recovery is therefore not significant

T test for null hypothesis that the mean times to recovery are the same
T= 0.97 P=0.40 DF= 3

The null hypothesis is proven, thus the mean times to recovery are not significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	6.20	3.83	1.7	3.8 - 8.6
R	8	5.25	1.83	0.65	4.4 - 6.2

Confidence intervals overlap, therefore the mean times to recovery are not significantly different

95% confidence interval for the difference between the mean times to recovery is -3.8 to 5.66

The difference between the mean times to recovery is therefore not significant

T test for null hypothesis that the mean times to recovery are the same
T= 0.52 P=0.63 DF= 5

The null hypothesis is proven, thus the mean times to recovery are not significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	6.73	4.24	1.3	5.0 - 8.5
R	13	4.77	2.13	0.59	4.0 - 5.6

Confidence intervals overlap, therefore the mean times to recovery are not significantly different

95% confidence interval for the difference between the mean times to recovery is -1.1 to 4.98

The difference between the mean times to recovery is therefore not significant

T test for null hypothesis that the mean times to recovery are the same
T= 1.39 P=0.19 DF= 14

The null hypothesis is proven, thus the mean times to recovery are not significantly different

Older Child

	N	Mean	StDev	SE Mean	95% CI
S	13	6.69	3.71	1.0	5.3 - 8.1
R	12	4.33	1.56	0.45	3.7 - 5.0

Confidence intervals DO NOT overlap, therefore the mean times to recovery are significantly different

95% confidence interval for the difference between the mean times to recovery is -4.74 to 0.0

The difference between the mean times to recovery is therefore not significant

T test for null hypothesis that the mean times to recovery are the same
T= -2.10 P=0.052 DF= 16

The null hypothesis is proven, thus the mean times to recovery are not significantly different

CONCLUSION:

Analysis of variance surprisingly suggest that early recovery is actually faster in the remifentanil group, in all ages (4.7 versus 6.6 minutes)

T tests and 95% confidence intervals of the difference between the means however, show no significant difference, in all age groups.

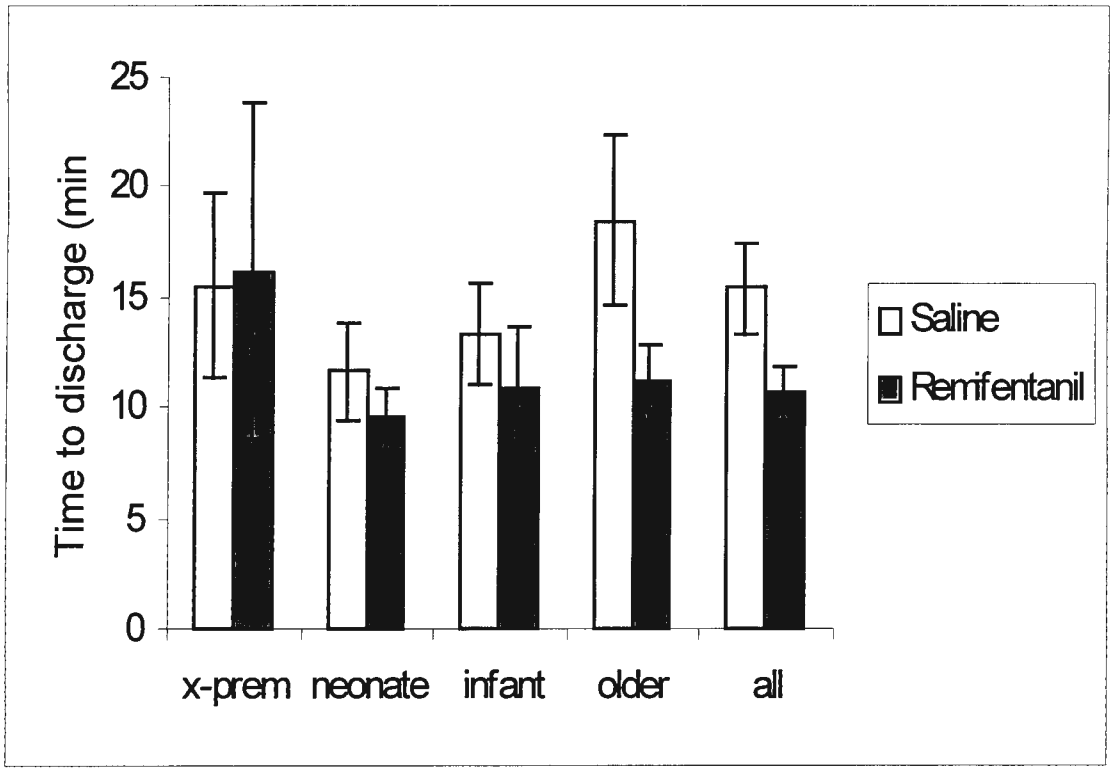
The 95% confidence intervals of the means show no difference in the x-premie, neonate and infant, but the remifentanil group show a significantly faster recovery in the older child and in all age groups together

The analysis of variance test has a higher power than the individual T tests due to the use of increased numbers and pooled data.

In these > one year olds, the mean time required for patients in the control group to fulfill criteria for transfer to recovery was 6.6 (sd= 3.8) minutes and the remifentanil group 4.7 minutes (sd= 1.8)
Possible explanations for this surprising phenomenon include observer bias, chance or increased depth of anaesthesia in the control group due to the increased cardiac output after tunnelling, although this seems very unlikely (see discussion section-chapter 4).

The clinical significance of theses findings are very limited due to the small times involved, when compared to the overall duration of surgery (approximately 2 hours)

Mean duration of time from "end of surgery" to "fulfilling criteria for discharge to the ward", in minutes, & 95% confidence intervals, remifentanil versus control



Basic statistics

Rows contain the number, mean and standard deviation of the time, in minutes, from the end of surgery intil fulfilling criteria for discharge to the ward in control (S) or remifentanil (R)

Columns contain the age categories: neonate, infant, >1yr old, all ages

		neonate	infant	> 1 yr old	all ages
S	number	5	11	13	29
	mean	11.600	13.364	18.538	15.379
	sd	3.578	5.446	10.138	8.077
R	number	8	13	12	33
	mean	9.500	10.846	11.167	10.636
	sd	2.777	7.358	4.282	5.361
all	number	13	24	25	62
	mean	10.308	12.000	15.000	12.855
	sd	3.146	6.541	8.597	7.122

Analysis of variance for time required, in minutes to fulfill discharge criteria, remifentanil versus control:

Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	347.23	220.10	220.10	4.96	**0.030**
agecod	2	167.63	178.18	89.09	2.01	**0.144**
code*agecod	2	92.50	92.50	46.25	1.04	**0.360**
Error	56	2486.34	2486.34	44.40		
Total	61	3093.69				

The anova table shows that there is a statistically significant difference in the time taken to fulfil criteria for discharge to the ward between remifentanil and control groups (p = 0.030) and that this is consistent amongst the different age groups (p = 0.360). Surprisingly, the remifentanil group (10.6 minutes) appeared to fulfil the criteria for discharge faster than the control group (15.4 minutes). Possible explanations for this phenomenon are mentioned below, in the conclusion.

Confidence intervals and two sample T tests for the time, in minutes, to fulfill discharge criteria, remifentanil versus control

X-Premie

	N	Mean	StDev	SE Mean	95% CI
S	4	15.50	5.92	3.0	11.3 - 19.7
R	4	16.2	10.9	5.4	8.6 - 23.8

Confidence intervals overlap, therefore the mean times to discharge are not significantly different

95% confidence interval for the difference between the mean times to discharge is -17.9 to 16.4

The difference between the mean times to discharge is therefore not significant

T test for null hypothesis that the mean times to discharge are the same
T= -0.12 P=0.91 DF= 4

The null hypothesis is proven, thus the mean times to discharge are not significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	11.60	3.58	1.6	9.4 - 13.8
R	8	9.50	2.78	0.98	8.1 - 10.9

Confidence intervals overlap, therefore the mean times to discharge are not significantly different

95% confidence interval for the difference between the mean times to discharge is -2.3 to 6.54

The difference between the mean times to discharge is therefore not significant

T test for null hypothesis that the mean times to discharge are the same
T= 1.12 P=0.30 DF= 7

The null hypothesis is proven, thus the mean times to discharge are not significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	13.36	5.45	1.6	11.1 - 15.7
R	13	10.85	7.36	2.0	8.0 - 13.7

Confidence intervals overlap, therefore the mean times to discharge are not significantly different

95% confidence interval for the difference between the mean times to discharge is -2.9 to 8.0

The difference between the mean times to discharge is therefore not significant

T test for null hypothesis that the mean times to discharge are the same
T= 0.96 P=0.35 DF= 21

The null hypothesis is proven, thus the mean times to discharge are not significantly different

Older Child

	N	Mean	StDev	SE Mean	95% CI
S	13	18.5	10.1	2.8	14.6 - 22.4
R	12	11.17	4.28	1.2	9.5 - 12.9

Confidence intervals DO NOT overlap, therefore the mean times to discharge are significantly different

95% confidence interval for the difference between the mean times to discharge is -13.9 to -0.9

The difference between the mean times to discharge is therefore significant

T test for null hypothesis that the mean times to discharge are the same
T= -2.40 P=0.029 DF= 16

The ALTERNATIVE hypothesis is proven, thus the mean times to discharge are significantly different

CONCLUSION:

Analysis of variance again surprisingly shows a faster time to fulfilling criteria for discharge in the remifentanil group, at p = 0.05, in all age groups, when compared to control.

T tests show no difference except in the older child.

95% confidence intervals of the means, 95% confidence intervals of the difference between the means and box and whisker charts show no difference in the x-premie, neonate and infant, but a faster time to discharge in the older child in the remifentanil group.

Mean times for all ages combined was 10.6 (sd=5.4) minutes in the remifentanil group and 15.4 (sd=8.1) minutes in the control group.

Again observer bias, chance or altered depth of anaesthesia appear to be the likely explanations.

OVERALL CONCLUSIONS

The times involved are all small in relation to the overall duration of surgery, thus any small differences have limited clinical significance. The surprising finding of the slightly faster recovery in certain age groups receiving remifentanil is discussed in the discussion section.

There is certainly no delay in recovery caused by the use of remifentanil in this clinical scenario.

Respiratory Depression

Post-operative respiratory depression is compared in the remifentanil and control groups, in each age group, using box and whisker charts, analysis of variance, T tests and 95% confidence intervals.

The respiratory parameters looked at were the maximum percentage change post-operatively of the transcutaneous carbon dioxide partial pressure from the pre-operative baseline; the time in minutes for the transcutaneous carbon dioxide partial pressure, in kPa, to return to < 6.0 kPa post-operatively; the time for the transcutaneous carbon dioxide to return to < 5.3 kPa post-operatively; the time for carbon dioxide partial pressure to become steady; the amount of time, in minutes, that additional oxygen is required to keep the oxygen saturation above 95%; the maximum percentage change from pre-operative baseline of respiratory rate post-operatively.

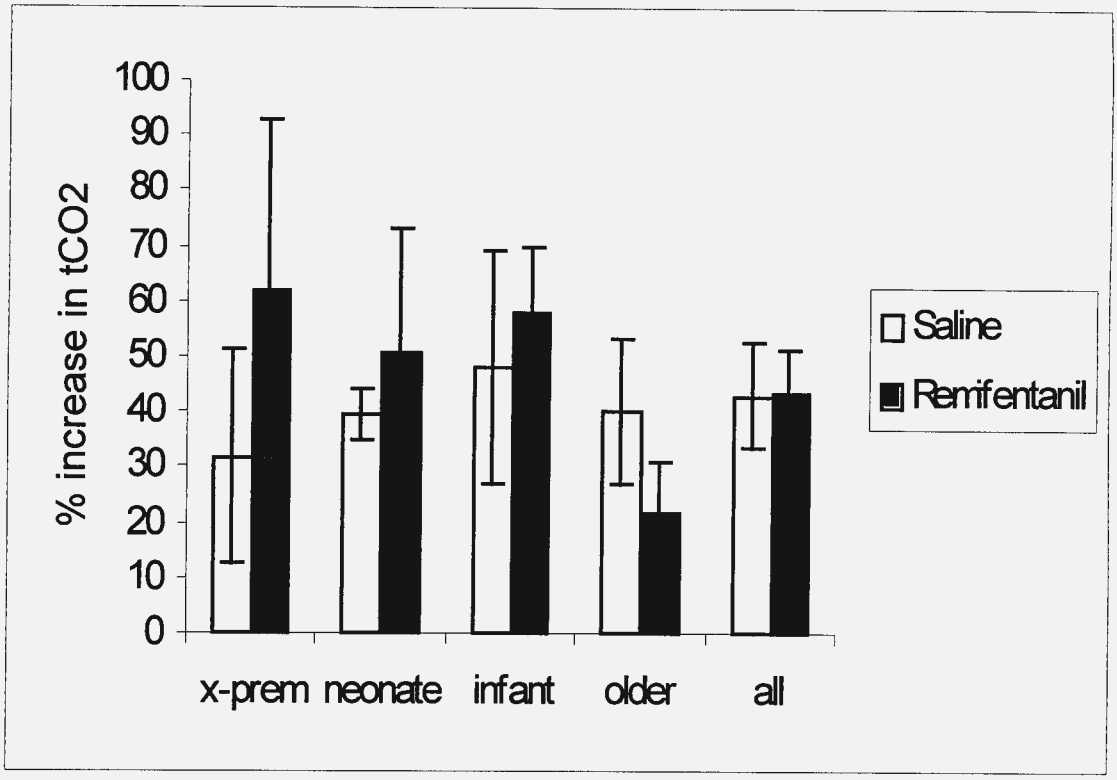
This "All ages combined" table shows the means, standard errors of the mean and p values testing the null hypothesis that the remifentanil and control groups had the same degree of post-operative respiratory depression (bold, underlined figures are medians, as they used censored results):

	Percentage change in CO2, post-op, from pre-operative baseline	Time till CO2 returns to baseline post-op, in minutes	Time till CO2 decreases post-op to < 6 kPa, in minutes	Time till CO2 decreases post-op to < 5.3 kPa, in minutes
Control	43 (7.0)	**32**	**7**	**22**
Remi	43.1 (6.1)	**60**	**4**	**17**
P value	> 0.05	> 0.05	> 0.05	> 0.05

	Time till CO2 steady post-op, in minutes	Maximum percentage change in resp rate post op, from pre-op baseline	Time till resp rate returns to baseline, post-op, in minutes	Time till room air sufficient to keep sats> 95% post op, in minutes
Control	**17**	24.3 (7.1)	0.2 (0.2)	15.9 (3.6)
Remi	**17**	33.2 (7.3)	0.2 (0.1)	13.6 (2.8)
P value	> 0.05	> 0.05	> 0.05	> 0.05

On the following pages numbered A to W are the detailed statistics for each variable in each age category

Maximum percentage change in transcutaneous carbon dioxide partial pressure post operatively, in kPa, & 95% confidence intervals, remifentanil versus control



Basic statistics

Rows contain the number of patients, mean and standard deviation of the maximum percentage change in transcutaneous carbon dioxide partial pressure post-operatively in control (S) or remifentanil (R)

Columns contain the age categories: neonate, infant, >1yr old, all ages

		neonate	infant	> 1 yr old	all ages
S	number	5	11	13	29
	mean	39.460	48.064	40.177	43.045
	sd	7.272	49.917	34.132	37.587
R	number	8	13	12	33
	mean	50.875	57.900	21.867	43.094
	sd	44.610	30.693	23.301	35.333
all	number	13	24	25	62
	mean	46.485	53.392	31.388	43.071
	sd	34.813	39.999	30.307	36.103

Analysis of variance for the maximum percentage change from pre-operative baseline in transcutaneous carbon dioxide partial pressure post operatively, remifentanil versus control

Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	0	13	13	0.01	**0.919**
agecod	2	6148	5994	2997	2.39	**0.101**
code*agecod	2	3042	3042	1521	1.21	**0.306**
Error	56	70317	70317	1256		
Total	61	79507				

The anova table concludes that there is no statistical difference between the maximum percentage changes in transcutaneous carbon dioxide partial pressure post operatively, in remifentanil (43 minutes) and control groups (43 minutes) (p = 0.919) and that this is consistent amongst the different age groups (p = 0.306).

Confidence intervals and two sample T tests for the maximum percentage change from pre-operative baseline of transcutaneous carbon dioxide partial pressure, in kPa, remifentanil versus control

X-premie

	N	Mean	StDev	SE Mean	95% CI
S	4	31.9	27.9	14	12.3 - 51.5
R	4	61.7	44.3	22	30.9 - 92.5

Confidence intervals overlap, therefore the maximum percentage changes in carbon dioxide partial pressure are not significantly different

95% confidence interval for the difference between maximum percentage changes in carbon dioxide partial pressure is -97 to 37

The difference between the maximum percentage changes in carbon dioxide partial pressure is therefore not significant

T test for null hypothesis that the maximum percentage changes in carbon dioxide partial pressures are the same
T= -1.14 P=0.31 DF= 5

The null hypothesis is proven, thus the maximum percentage changes in carbon dioxide partial pressure are not significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	39.46	7.27	3.3	34.9 - 44.0
R	8	50.9	44.6	16	29.0 - 72.8

Confidence intervals overlap, therefore the maximum percentage changes in carbon dioxide partial pressure are not significantly different

95% confidence interval for the difference between maximum percentage changes in carbon dioxide partial pressure is -49.5 to 27

The difference between the maximum percentage changes in carbon dioxide partial pressure is therefore not significant

T test for null hypothesis that the maximum percentage changes in carbon dioxide partial pressures are the same
T= -0.71 P=0.50 DF= 7

The null hypothesis is proven, thus the maximum percentage changes in carbon dioxide partial pressure are not significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	48.1	49.9	15	27.1 - 69.0
R	13	57.9	30.7	8.5	46.1 - 69.7

Confidence intervals overlap, therefore the maximum percentage changes in carbon dioxide partial pressure are not significantly different

95% confidence interval for the difference between maximum percentage changes in carbon dioxide partial pressure is -47 to 26.8

The difference between the maximum percentage changes in carbon dioxide partial pressure is therefore not significant

T test for null hypothesis that the maximum percentage changes in carbon dioxide partial pressures are the same

T= -0.57 P=0.58 DF= 16

The null hypothesis is proven, thus the maximum percentage changes in carbon dioxide partial pressure are not significantly different

Older Child

	N	Mean	StDev	SE Mean	95 % CI
S	13	40.2	34.1	9.5	27.0 - 53.3
R	12	21.9	23.3	6.7	12.5 - 31.2

Confidence intervals overlap, therefore the maximum percentage changes in carbon dioxide partial pressure are not significantly different

95% confidence interval for the difference between maximum percentage changes in carbon dioxide partial pressure is -42.5 to 5.8

The difference between the maximum percentage changes in carbon dioxide partial pressure is therefore not significant

T test for null hypothesis that the maximum percentage changes in carbon dioxide partial pressures are the same

T= -1.58 P=0.13 DF= 21

The null hypothesis is proven, thus the maximum percentage changes in carbon dioxide partial pressure are not significantly different

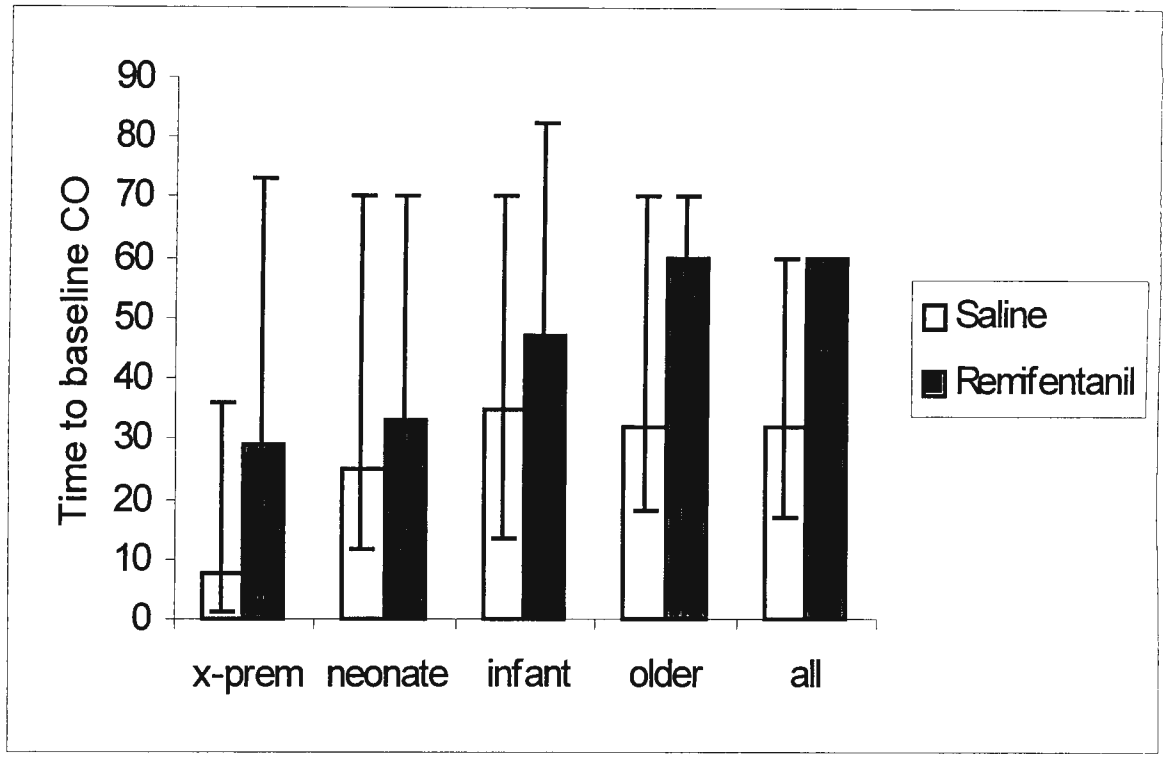
CONCLUSION:

Analysis of variance, T tests, 95% confidence intervals of the means, 95% confidence intervals of the difference between the means and box and whisker charts show no statistical difference, at p=0.05, between remifentanil and control groups, in the percentage increase in transcutaneous carbon dioxide partial pressure post-operatively, in all age groups.

There is a tendency, as seen in the box and whisker charts, for higher carbon dioxide partial pressures to be reached in the x-premie group. This was not significant, but if sample numbers were larger, a more conclusive result could be achieved.

All ages together, the remifentanil group percentage change of transcutaneous carbon dioxide partial pressure was + 43.1% (sd=35) and the control + 43.0% (sd=37).

Median duration of time until transcutaneous carbon dioxide partial pressure falls to within 5 % of pre-op baseline, in minutes, & 95% confidence intervals, remifentanil versus control



Basic statistics for the duration of time post-operatively, in minutes, until the transcutaneous carbon dioxide partial pressure falls to within 5 % of pre-op baseline, remifentanil versus control

The first column refers to control (S) or remifentanil (R) . The second column refers to the age group. The third column is the median. The fourth column is the 95% confidence interval.

Code	Agecod	Median	95% CI
S	x-premie	7.5	1 - 35
S	neonate	25	11.7 - 70
S	infant	35	13.4 - 70
S	< 1 yr old	32	18.0 - 70
S	all ages	32	17 - 60
R	x-premie	29	3 - #
R	neonate	33	11.0 - 70
R	infant	47	36.4 - 72.2
R	> 1 yr old	60	0 - 70
R	all ages	60	44 - 60

The confidence intervals overlap in each age group overlap, showing no statistical difference.

NON PARAMETRIC LOG-RANK ANALYSIS for the duration of time post-operatively until transcutaneous carbon dioxide partial pressure falls to within 5 % of pre-op baseline:

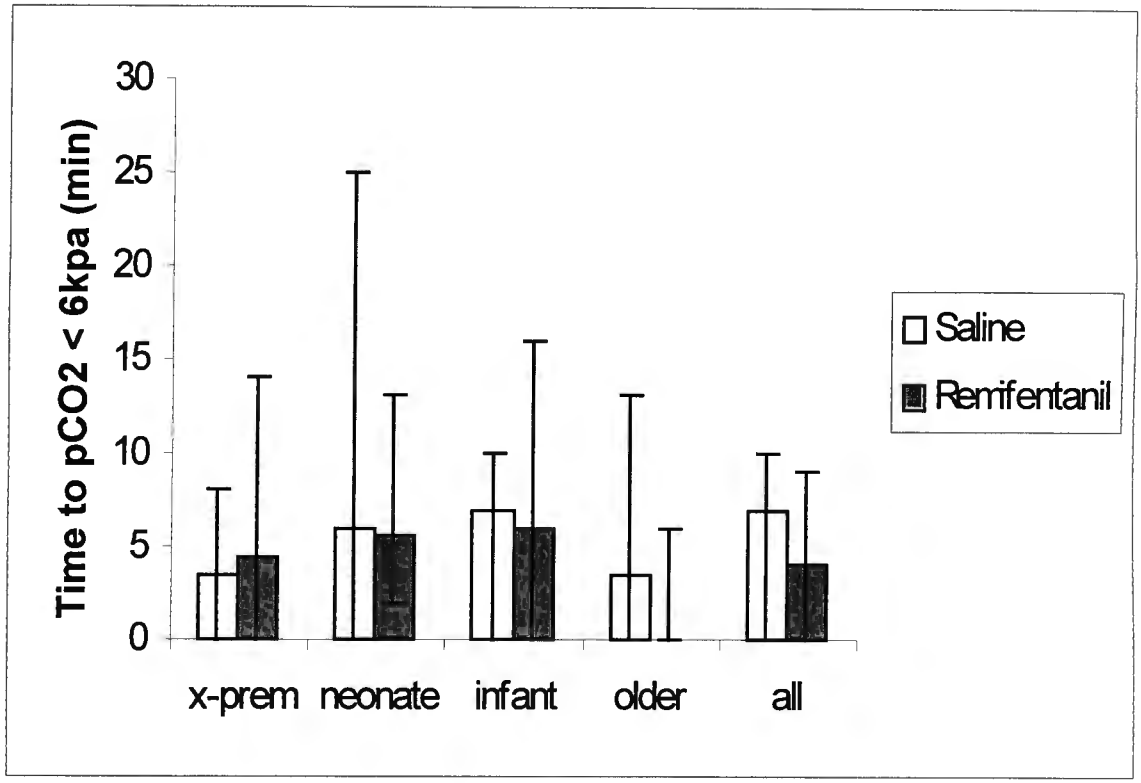
Test	Age	Chi Sq	DF	p
L-Rank	xp	1.81	1	**0.18**
	1	0.313	1	**0.576**
	2	0.548	1	**0.459**
	3	0.635	1	**0.426**
Wilcox	1	0.424	1	0.515
	2	1.09	1	0.296
	3	0.955	1	0.329
-2LR	1	0.182	1	0.670
	2	0.47	1	0.492
	3	0.428	1	0.513

Thus in each individual age group, there is no statistical difference, at p = 0.05, between the remifentanil and control groups in the time taken for the transcutaneous carbon dioxide partial pressure to fall to within 5% of pre-operative baseline, post-operatively.

CONCLUSION:

Log rank tests, 95% confidence intervals of the medians and box and whisker charts show no statistical difference, at p = 0.05, between remifentanil (60 minutes) and control groups (32 minutes), in the time taken for transcutaneous carbon dioxide partial pressure to return to baseline post operatively, in all age groups.

Median duration of time post-operatively, in minutes, until the transcutaneous carbon dioxide partial pressure decreases to < 6.0 kpa, & 95% confidence intervals, remifentanil versus control



Basic statistics for the duration of time post-operatively, in minutes, until the transcutaneous carbon dioxide partial pressure falls to within < 6.0 kPa, remifentanil versus control

The first column refers to control (S) or remifentanil (R) . The second column refers to the age group. The third column is the median. The fourth column is the 95% confidence interval

Code	Agecod	Median	95% conf. limits
S	x-premie	3.5	0 - 8
S	neonate	6	0 - 25
S	infant	7	0 - 10
S	> 1 yr old	3.5	0 - 13
S	all ages	7	0 - 10
R	x-premie	4.5	0 - 14
R	neonate	5.5	2 - 13
R	infant	6	0 - 16
R	> 1 yr old	0	0 - 6
R	all ages	4	0 – 9

Confidence intervals overlap in each age group, thus there is no statistical difference.

Non parametric tests to assess the duration of time post-operatively, in minutes, until the transcutaneous carbon dioxide partial pressure falls to < 6.0 kPa., remifentanil versus control:

Test	Age	Chi Sq	DF	p
L-Rank	x-premie	0.13	1	**0.72**
	neonate	0.003	1	**0.958**
	infant	0.059	1	**0.808**
	> 1 yr old	0.159	1	**0.689**
Wilcox	neonate	0.005	1	0.942
	infant	0.031	1	0.860
	> 1 yr old	0.865	1	0.352
-2LR	neonate	0.096	1	0.757
	infant	0.069	1	0.793
	> 1 yr old	0.277	1	0.599

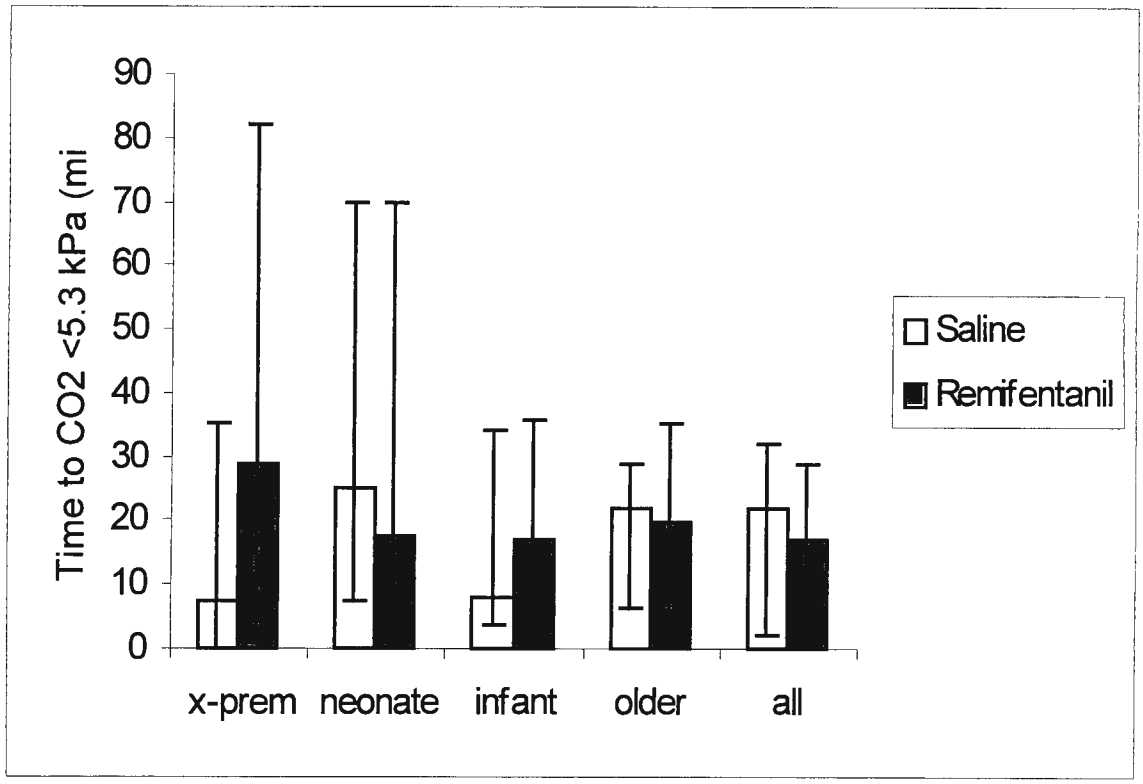
Thus in each individual age group, there is no statistical difference, at p = 0.05, between the remifentanil (4 minutes) and control groups (7 minutes) in the time taken for the transcutaneous carbon dioxide partial pressure to fall to < 6.0 kPa, post-operatively.

CONCLUSION:

Log rank tests, 95% confidence intervals of the medians and box and whisker charts show no statistical difference, at p= 0.05, between remifentanil and control groups, in the duration of time until the transcutaneous carbon dioxide partial pressure falls to < 6.0 kPa post operatively, in all age groups.

The control group had a median of seven minutes and the remifentanil group four minutes, till carbon dioxide levels fell to < 6.0 kPa

Median duration of time post-operatively, in minutes, until the transcutaneous carbon dioxide partial pressure falls to < 5.3 kPa, & 95% confidence intervals, remifentanil versus control



Basic statistics for the duration of time post-operatively, in minutes, until the transcutaneous carbon dioxide partial pressure falls to < 5.3 kPa, remifentanil versus control

The first column refers to control (S) or remifentanil (R) . The second column refers to the age group. The third column is the median. The fourth column is the 95% confidence interval

Code	Agecod	Median	95% CI
S	x-premie	7.5	0 - 35
S	neonate	25	7.5 - 70
S	infant	8	3.8 - 33.9
S	> 1 yr old	22	6.6 - 29.0
S	all ages	22	2 - 32
R	x-premie	29	3 - #
R	neonate	17.5	4.4 -70.0
R	infant	17	14.9 - 35.9
R	> 1 yr old	19.5	5.9 - 35.2
R	all ages	17	13 – 29

Confidence intervals overlap, therefore there is no statistical difference between remifentanil and control.

Non parametric tests to assess the duration of time post-operatively, in minutes, until the transcutaneous carbon dioxide partial pressure falls to < 5.3 kPa., remifentanil versus control:

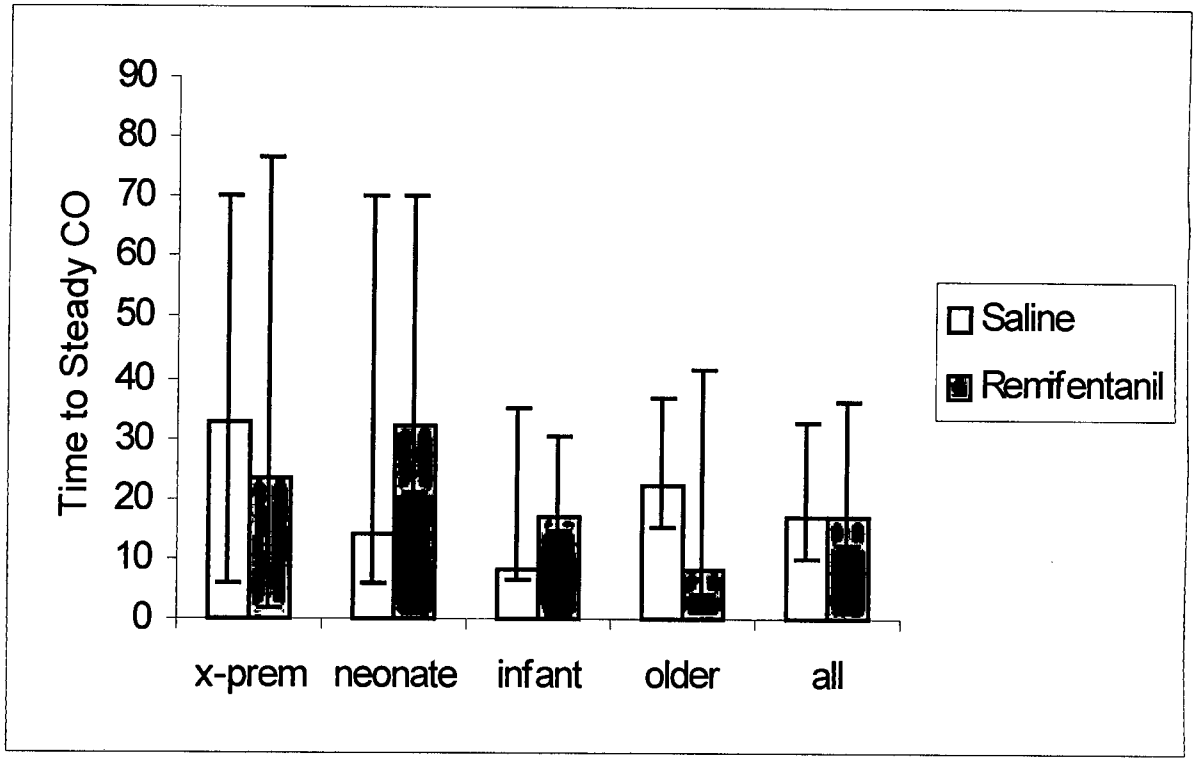
Test	Age	Chi Sq	DF	p
L-Rank	x-premie	1.81	1	**0.18**
	neonate	0.007	1	**0.935**
	infant	0.300	1	**0.584**
	> 1 yr old	0.044	1	**0.835**
Wilcox	neonate	0.000	1	1.000
	infant	0.626	1	0.429
	> 1 yr old	0.049	1	0.824
-2LR	neonate	0.002	1	0.965
	infant	0.274	1	0.601
	> 1 yr old	0.121	1	0.728

Thus in each individual age group, there is no statistical difference, at p = 0.05, between the remifentanil and control groups in the time taken for the transcutaneous carbon dioxide partial pressure to fall to < 5.3 kPa, post-operatively.

CONCLUSION:

Non-parametric tests, 95% confidence intervals of the medians and box and whisker charts show no statistical difference, at p= 0.05, between remifentanil and control groups, in the duration of time until transcutaneous carbon dioxide partial pressures fall to < 5.3 kPa post operatively, in all age groups. Overall the control group averaged 22 minutes and the remifentanil groups 17 minutes

Median duration of time post-operatively, in minutes, until the transcutaneous carbon dioxide partial pressure reaches steady state & 95% confidence intervals, remifentanil versus control



Basic statistics for the duration of time post-operatively, in minutes, until the transcutaneous carbon dioxide partial pressure reaches a steady state, remifentanil versus control

The first column refers to control (S) or remifentanil (R) . The second column refers to the age group. The third column is the median. The fourth column is the 95% confidence interval

Code	Agecod	Median	95% CI
S	x-premie	32.5	6 - #
S	neonate	14	5.6 - 70
S	infant	8	6.6 - 35.3
S	> 1 yr old	22	15 - 36.7
S	all	17	10 - 33
R	x-premie	23.5	2 - 38
R	neonate	32	20.8 - 70
R	infant	17	14.9 - 30.3
R	> 1 yr old	8	3.8 - 41.6
R	all	17	12 – 36

Confidence intervals overlap, therefore there is no statistical difference between remifentanil and control.

Non parametric tests to assess the duration of time post-operatively, in minutes, until the transcutaneous carbon dioxide partial pressure reached a steady state, remifentanil versus control:

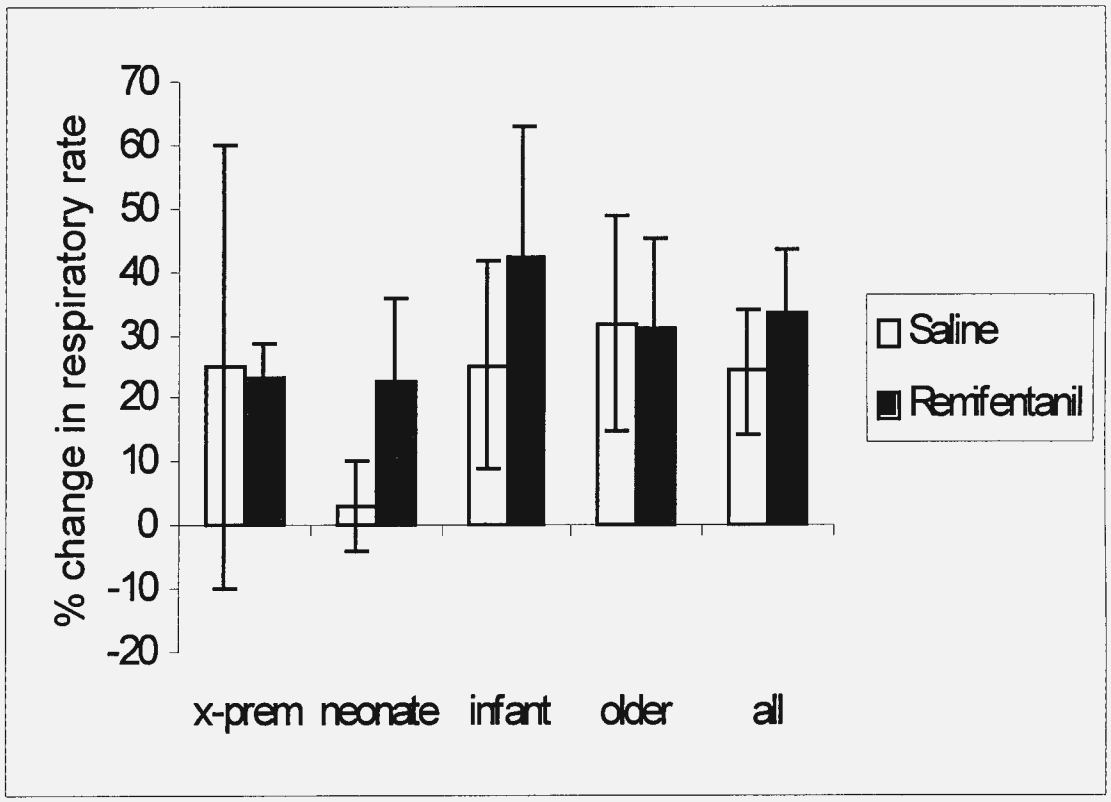
Test	Age	Chi Sq	DF	p
L-Rank	x-premie	0.89	1	**0.35**
	neonate	0.524	1	**0.469**
	infant	0.659	1	**0.417**
	> 1 yr old	0.149	1	**0.699**
Wilcox	neonate	0.975	1	0.323
	infant	0.718	1	0.397
	> 1 yr old	1.868	1	0.172
-2LR	neonate	0.331	1	0.561
	infant	0.614	1	0.433
	> 1 yr old	0.048	1	0.826

Thus in each individual age group, there is no statistical difference, at p = 0.05, between the remifentanil and control groups in the time taken for the transcutaneous carbon dioxide partial pressure to reach a steady state, post-operatively.

CONCLUSION:

Non-parametric tests, 95% confidence intervals of the medians and box and whisker charts show no statistical difference, at p= 0.05, between remifentanil and control groups, in the duration of time until the transcutaneous carbon dioxide partial pressure reaches a steady state post operatively, in all age groups. The average time for the both the remifentanil and control groups was 17 minutes.

Mean percentage change in the respiratory rate post operatively, when compared to pre-op baseline, in breaths per minute, & 95% confidence intervals, remifentanil versus control



Basic statistics

Rows contain the number of patients, mean and standard deviation of the maximum percentage change in respiratory rate post-operatively in control (S) or remifentanil (R)

Columns contain the age categories: neonate, infant, >1yr old, all ages

		neonate	infant	> 1yr	all ages
S	number	5	11	13	29
	mean	2.980	25.182	31.677	24.266
	sd	11.576	39.184	43.270	38.427
R	number	8	13	12	33
	mean	22.763	41.908	30.683	33.185
	sd	25.609	54.648	36.582	42.235
all	number	13	24	25	62
	mean	15.154	34.242	31.200	29.013
	sd	22.969	47.939	39.367	40.419

Analysis of variance for the maximum percentage change in respiratory rate post – operatively, when compared to pre-operative baseline, remifentanil versus control

Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	1228	1931	1931	1.16	**0.287**
agecod	2	3604	3792	1896	1.14	**0.329**
code*agecod	2	1318	1318	659	0.39	**0.676**
Error	56	93504	93504	1670		
Total	61	99654				

The anova table suggests that there is no statistically significant difference in the post-operative changes in respiratory rate between the remifentanil and control groups (p = 0.287) and that this is consistent amongst the different age groups (p = 0.676).

95% Confidence intervals and two sample T tests for the maximum percentage changes in respiratory rate post-operatively

X-Premie

	N	Mean	StDev	SE Mean	95% CI
S	4	25.0	50.0	25	0 - 60
R	4	23.12	8.03	4.0	17.5 - 28.5

Confidence intervals overlap, therefore the mean percentage changes in respiratory rate are not significantly different

95% confidence interval for the difference between the mean percentage change in respiratory rates is –79 to 82.5

The difference between the mean percentage changes in respiratory rate is therefore not significant

T test for null hypothesis that the mean changes in respiratory rate are the same
T= 0.07 P=0.95 DF= 3

The null hypothesis is proven, thus the mean percentage changes in respiratory rate are not significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	3.0	11.6	5.2	(-4.2) - 10.2
R	8	22.8	25.6	9.1	10.2 - 35.4

Confidence intervals overlap, therefore the mean percentage changes in respiratory rate are not significantly different

95% confidence interval for the difference between the mean percentage change in respiratory rates is -43.0 to 3.5

The difference between the mean percentage changes in respiratory rate is therefore not significant

T test for null hypothesis that the mean changes in respiratory rate are the same
T= -1.90 P=0.087 DF= 10

The null hypothesis is proven, thus the mean percentage changes in respiratory rate are not significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	25.2	39.2	12	8.8 - 41.6
R	13	41.9	54.6	15	20.8 - 63.0

Confidence intervals overlap, therefore the mean percentage changes in respiratory rate are not significantly different

95% confidence interval for the difference between the mean percentage change in respiratory rates is -57 to 23

The difference between the mean percentage changes in respiratory rate is therefore not significant

T test for null hypothesis that the mean changes in respiratory rate are the same
T= -0.87 P=0.39 DF= 21

The null hypothesis is proven, thus the mean percentage changes in respiratory rate are not significantly different

Older Child

	N	Mean	StDev	SE Mean	95% CI
S	13	31.7	43.3	12	15.0 - 48.4
R	12	30.7	36.6	11	16.0 - 45.4

Confidence intervals overlap, therefore the mean percentage changes in respiratory rate are not significantly different

95% confidence interval for the difference between the mean percentage change in respiratory rates is -34 to 32

The difference between the mean percentage changes in respiratory rate is therefore not significant

T test for null hypothesis that the mean changes in respiratory rate are the same
T= -0.06 P=0.95 DF= 22

The null hypothesis is proven, thus the mean percentage changes in respiratory rate are not significantly different

CONCLUSION:

Analysis of variance, 95% confidence intervals, T tests and box and whisker charts show no statistical difference, at p= 0.05, between remifentanil and control groups in the maximum percentage change in respiratory rate post operatively, in all age groups.

All ages included, the remifentanil group had a maximum percentage change of +33.2 (sd=42.2) and the control group +24.3 (sd=38.4).

Mean time for the respiratory rate to return to baseline post-operatively, in minutes, remifentanil versus control.

Basic statistics

Rows contain the number of patients, mean and standard deviation of the time taken post-operatively, in minutes, for the respiratory rate to return to pre-operative baseline in control (S) or remifentanil (R)

Columns contain the age categories: neonate, infant, >1yr old, all ages

		neonate	infant	> 1 yr old	all ages
S	number	5	11	13	29
	mean	0.0000	0.4545	0.1538	0.2414
	sd	0.0000	1.5076	0.5547	0.9876
R	number	8	13	12	33
	mean	0.0000	0.4615	0.0000	0.1818
	sd	0.0000	1.1266	0.0000	0.7269
all	number	13	24	25	62
	mean	0.0000	0.4583	0.0800	0.2097
	sd	0.0000	1.2847	0.4000	0.8519

Analysis of variance for time, in minutes, till post-operative respiratory rate returns to baseline, remifentanil versus control

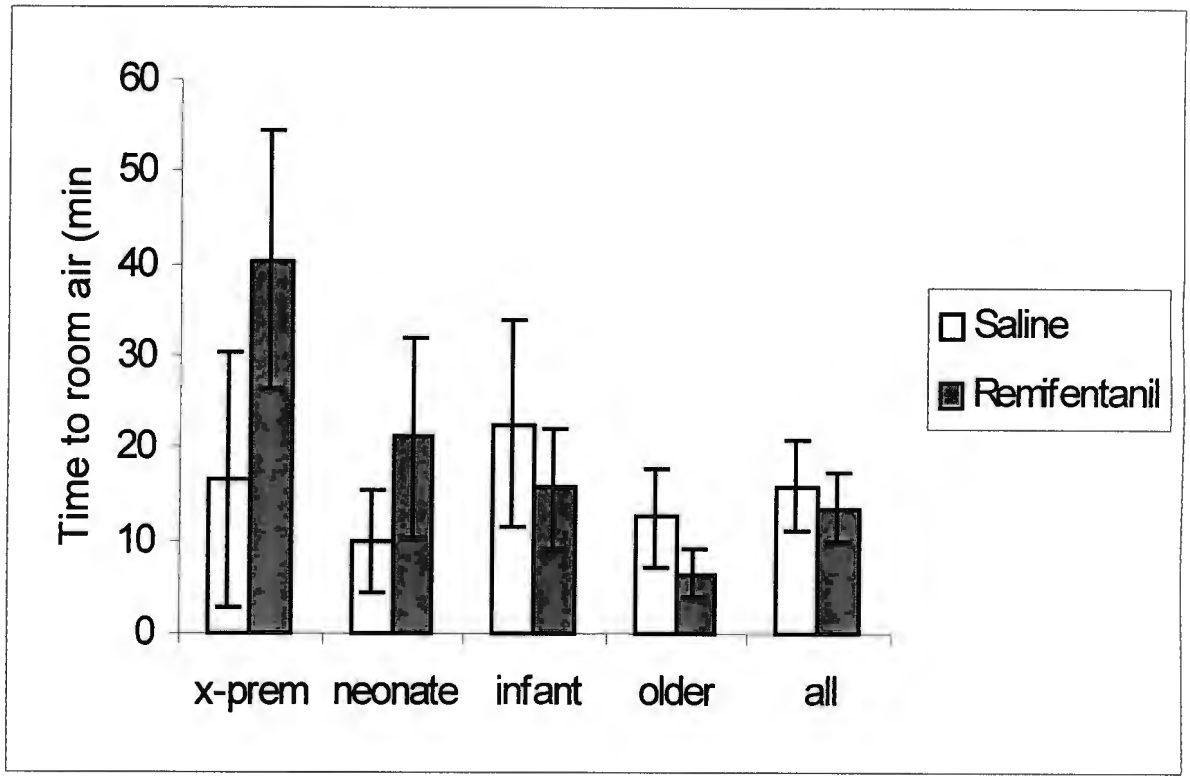
Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	0.0548	0.0330	0.0330	0.04	**0.834**
agecod	2	2.4763	2.4511	1.2256	1.65	**0.202**
code*agecod	2	0.0928	0.0928	0.0464	0.06	**0.940**
Error	56	41.6503	41.6503	0.7438		
Total	61	44.2742				

The anova table suggests that there is no statistically significant difference in the time taken for the respiratory rate to return to baseline between the remifentanil and control groups (p = 0.834) and that this is consistent amongst the different age groups (p = 0.940).

CONCLUSION:

Analysis of variance show no statistical difference, at p= 0.05, in the time taken for the respiratory rate to return to baseline post operatively, between remifentanil and control groups (p=0.834).
This was consistent amongst all age groups (p=0.940).
All ages included, the remifentanil group took 0.2 (sd=0.7) and the control group 0.2 (sd=1.0) minutes.

Mean time required, in minutes, until room air alone is sufficient to maintain peripheral oxygen saturation above 95% post operatively & 95% confidence intervals, remifentanil versus control:



Basic statistics

Rows contain the number of patients, mean and standard deviation of the time required post-operatively, until room air alone is sufficient in control (S) or remifentanil (R)

Columns contain the age categories: neonate, infant, >1yr old, all ages

		neonate	infant	> 1 yr old	all ages
S	number	5	11	13	29
	mean	9.800	22.636	12.538	15.897
	sd	8.729	26.834	13.283	19.323
R	number	8	13	12	33
	mean	21.250	15.615	6.333	13.606
	Sd	22.070	16.520	6.485	16.107
all	number	13	24	25	62
	mean	16.846	18.833	9.560	14.677
	sd	18.524	21.639	10.840	17.573

Analysis of variance for the time required post-operatively, in minutes, until room air alone is sufficient to maintain peripheral oxygen saturation above 95%, remifentanil versus control.

Source	DF	Seq SS	Adj SS	Adj MS	F	P
code	1	81.0	4.8	4.8	0.02	**0.899**
agecod	2	1183.9	1162.8	581.4	1.94	**0.153**
code*agecod	2	802.9	802.9	401.4	1.34	**0.270**
Error	56	16769.8	16769.8	299.5		
Total	61	18837.5				

The anova table concludes that there is no statistically significant difference in the time required until air alone is sufficient to maintain peripheral oxygen saturations above 95% between the remifentanil (13.6 minutes) and control groups (15.9 minutes) (p = 0.899) and that this is consistent amongst the different age groups (p = 0.270).

Confidence intervals and two sample tests to assess the time required post-operatively until room air alone is sufficient, remifentanil versus control

X-Premie

	N	Mean	StDev	SE Mean	95% CI
S	4	16.5	19.5	9.8	2.8 - 30.2
R	4	40.3	20.2	10	26.3 - 54.3

Confidence intervals overlap, therefore the times required for air alone to be sufficient are not significantly different

95% confidence interval for the difference between the times required for air to be sufficient is -59.9, to 12

The difference between the times required for air to be sufficient is therefore not significant

T test for null hypothesis that the times required for air to be sufficient are the same
T= -1.69 P=0.15 DF= 5

The null hypothesis is proven, thus the times required for air to be sufficient are not significantly different

Neonate

	N	Mean	StDev	SE Mean	95% CI
S	5	9.80	8.73	3.9	4.4 - 15.2
R	8	21.2	22.1	7.8	10.4 - 32.1

Confidence intervals overlap, therefore the times required for air alone to be sufficient are not significantly different

95% confidence interval for the difference between the times required for air to be sufficient is -31.2 to 8.3

The difference between the times required for air to be sufficient is therefore not significant

T test for null hypothesis that the times required for air to be sufficient are the same
T= -1.31 P=0.22 DF= 9

The null hypothesis is proven, thus the times required for air to be sufficient are not significantly different

Infant

	N	Mean	StDev	SE Mean	95% CI
S	11	22.6	26.8	8.1	11.4 - 33.9
R	13	15.6	16.5	4.6	9.3 - 22.0

Confidence intervals overlap, therefore the times required for air alone to be sufficient are not significantly different

95% confidence interval for the difference between the times required for air to be sufficient is -12.7 to 26.7

The difference between the times required for air to be sufficient is therefore not significant

T test for null hypothesis that the times required for air to be sufficient are the same
T= 0.76 P=0.46 DF= 16

The null hypothesis is proven, thus the times required for air to be sufficient are not significantly different

Older child

	N	Mean	StDev	SE Mean	95% CI
S	13	12.5	13.3	3.7	7.4 - 17.7
R	12	6.33	6.49	1.9	3.7 - 8.9

Confidence intervals overlap, therefore the times required for air alone to be sufficient are not significantly different

95% confidence interval for the difference between the times required for air to be sufficient is -14.9 to 2.5

The difference between the times required for air to be sufficient is therefore not significant

T test for null hypothesis that the times required for air to be sufficient are the same
T= -1.50 P=0.15 DF= 17

The null hypothesis is proven, thus the times required for air to be sufficient are not significantly different

CONCLUSION:

Analysis of variance, 95% confidence intervals of the means, 95% confidence intervals of the difference between the means, T tests and box and whisker charts show no statistical difference, at p= 0.05, between remifentanil and control groups, in the time taken for room air to be sufficient post-operatively to maintain peripheral oxygen saturation > 95%, in all age groups.

All ages included, the remifentanil group required 13.6 (sd=16.1) and the control group 15.9 (sd=19.3) minutes.

OVERALL CONCLUSIONS:

There is some degree of respiratory depression exhibited in patients of all ages post-operatively, as assessed by the degree and duration of changes in transcutaneous carbon dioxide partial pressures, respiratory rate and oxygen requirements, but no difference between the patients receiving remifentanil and the control.

This is consistent amongst all age groups. It does appear that x-premies receiving remifentanil may require oxygen for longer than older children, but numbers are too small and further work is required in this age group to make definitive conclusions.

This "routine" post-operative respiratory depression is predictable, temporary and is usually of very limited clinical significance in both the remifentanil and control groups, providing basic standards of monitoring and care are applied in the recovery area.

Pre-operative respiratory parameters are returned to 15 - 60 minutes post-operatively.

Analgesia, Blood Loss, Chest Wall Rigidity:

Only two patients out of 62 required analgesia in the immediate recovery period.
Blood loss was minimal in all patients.
There was no evidence of chest wall rigidity in any patient.
Thus there is no evidence that remifentanil causes any difference in these parameters, when compared to control.

5. DISCUSSION & CONCLUSIONS

The aim of the study was to see if remifentanil is an appropriate analgesic to cover the tunnelling phase of ventriculoperitoneal shunt insertion in children of all ages, including x-premies and neonates. Present day practice is to either give nothing, to briefly increase the inspired isoflurane concentration or to give a short acting opioid.

As has been extensively discussed in the preceding chapters, it is now understood that young children experience a heightened response to a wide variety of noxious stimuli, that their metabolic stability is harder to maintain, that uncontrolled stress responses can possibly worsen outcome and that good analgesia may improve outcome. The dangers of an uncontrolled stress response are of particular importance in this scenario due to the risks of intracranial haemorrhage in the face of immature cerebral autoregulation. It is thus imperative that we look to providing the best cover for such events.

As has also been discussed, we know that young children and babies are at greater risk of respiratory depression from the use of opioids. This means that attention to kinetic and dynamic factors of agents used is of utmost importance. This is particularly true in the neurosurgical patient, where respiratory depression and sedation may compromise postoperative recovery and vital signs monitoring.

Remifentanil is a new agent, still finding its' place in the clinicians' armoury, as a rapidly titratable analgesic, with more work required both in neurosurgical patients and in the paediatric population.

In this study, the administration of remifentanil to cover the tunnelling phase of shunt insertion in children caused good attenuation of haemodynamic and endocrine markers of stress, no delay in recovery and no additional post operative respiratory depression in all age groups, including x-premies and neonates.

There was some degree of respiratory depression exhibited in patients of all ages post operatively, but no difference between the patients receiving remifentanil and patients receiving control, in all age groups. This is probably the normal level of respiratory depression that routinely occurs post-operatively, due to predictable effects of the volatile agents. There is always a depression of the hypoxic and hypercarbic ventilatory drive, due to a direct effect of the volatile agent on the respiratory centre. In addition, lying supine, general anaesthesia, endotracheal intubation and positive pressure ventilation all causes temporary changes in other respiratory parameters such as functional residual capacity, respiratory rate and tidal volume, gas exchange, dead space and ciliary function. These changes are predictable and readily reversible and usually not of concern to an otherwise healthy patient. The x-premie group is, of course, at the greatest risk of this and special care is required, with the use of respiratory stimulants and more intensive post-operative monitoring.
In this study, other reasons for respiratory depression were excluded by vigilantly maintaining normothermia, by achieving full reversal of neuromuscular blockade using a peripheral nerve stimulator and by maintaining an inspired isoflurane partial pressure of 1kPa in all patients, using a calibrated agent monitor. The same inspired partial pressure of isoflurane was given to all age groups, in spite of the changing minimal alveolar concentration for isoflurane with age. This was felt appropriate, because the same concentration was being given to both remifentanil and control groups and comparisons were being made within individual age groups. Altering the levels for each age group could have confused and complicated the study. There was no rebound respiratory depression in either group (defined for the purposes of the study as an increase in transcutaneous C02 partial pressure of > 1 kPa from the post operative steady state value).

There was some evidence of cardiovascular depression; thus attention to correct dosage, to preload and to timing of dose to coincide with the noxious stimulus would appear to be prudent.

There was no evidence of adverse effects, such as muscle rigidity (the patients were all paralysed, of course). There was also no difference in postoperative analgesic requirements or intraoperative blood loss between the two groups.

Thus the agent remifentanil appears to have an appropriate kinetic and dynamic profile to be safe and effective in this setting, in children of all ages.

The use of percentage changes of parameters from baseline was used to compare certain the response of parameters in the remifentanil and control groups. Although it was not the mandate of this study to compare one age group with another, this mode of comparison does at least allow some sort of cross age group comparison. Hard data changes of course are not comparable across age groups due to the differing baselines of different age groups.

Why did remifentanil patients recover faster? - Could the increased delivery of isoflurane to the brain in the control group due to cardiovascular stimulation have caused a significant deepening of anaesthesia and thus a slower recovery? Was it just chance, or observer bias? Observer bias is always a possibility, but the study was specifically designed to minimise this risk. The anaesthesia was rigidly standardised, the partia

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Why did remifentanil patients recover faster? - Could the increased delivery of isoflurane to the brain in the control group due to cardiovascular stimulation have caused a significant deepening of anaesthesia and thus a slower recovery? Was it just chance, or observer bias? Observer bias is always a possibility, but the study was specifically designed to minimise this risk. The anaesthesia was rigidly standardised, the partial pressure of the volatile anaesthetic controlled against an end-tidal monitor, and the anaesthetist blinded as to the agent given (saline or remifentanil). However, remifentanil produced a consistent bradycardia, and this partially confounded the attempted blinding. There is therefore a possibility that subconscious bias may have contributed to the apparent faster wakening in the remifentanil group.

Thus further work is required, especially in small and unwell children, whose physiology is that much more brittle, in other surgical areas.

6. OTHER COMMENTS OR POINTS ARISING FROM THE STUDY THAT MERIT FURTHER CONSIDERATION

1. The study looked at children of all ages receiving a shunt. Although the overall numbers in the remifentanil and control group afford good power to the study and credible statistical analysis has been made, it is not possible to group neonates and older children together as they represent disparate groups. Thus the individual age groups were looked at to see if conclusions could be applied equally to different age groups. The sample sizes for each age group were quite small, however, particularly in the neonate and x-premie groups. This means that the chances of making sound statistically

significant conclusions are less good for individual age groups as for conclusions for all children overall. When all ages are combined, the numbers are sufficient to reveal very obvious and significant differences between remifentanil and control groups, with very real implications for clinical practise. There are strong scientific reasons to suspect that the very young may react differently to older children and it is therefore of import to view each group as separate, even if this diminishes sample sizes. In spite of the small numbers, trends were evident and perhaps further work is necessary within each age group, particularly the x-premies and neonates. In addition, further work could look at a comparison of one age group with another; again, larger numbers of patients are required.

2.If tunnelling is prolonged (i.e.. > 3 - 5 minutes) or complicated, then a further bolus dose of remifentanil may be required, due to the short half life of remifentanil. This may be of relevance if an inexperienced surgeon is operating, or in older children when longer conduits are required.

3.Remifentanil patients generally had a bimodal haemodynamic response to the bolus dose and the stimulus - initially a depression, followed by a smaller degree of stimulation. This knowledge means that timing and dosage of remifentanil may need adapting to the individual clinical situation.

4. What about the ethics of doing such a trial with some patients being provided with no "cover" for the tunnelling phase? Most authorities would usually recommend an increase the level of isoflurane to cover the cardiovascular surge associated with tunnelling. However, several units make no attempt to cover this phase, and therefore it was considered ethical to take this course. There was, also, no way of standardising an increase in volatile partial pressure in the control group and thus it was deemed acceptable by the involved parties and the ethics committee to use saline only as a control group. Perhaps patients receiving higher inspired concentrations throughout would have responded quite differently in both remifentanil and control groups. Further work may be indicated, comparing remifentanil or control with differing levels of baseline anaesthesia. This trial, however, compared responses in patients receiving remifentanil and control only at this particular baseline depth of anaesthesia, which was standardized and equal in each group.

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addendum-raw data

Heart Rate Changes for Neonates

		base hr	HR post Drg	Max HR	dur hr
Control		130	136	141	3
		104	103	116	2
		110	113	133	5
		115	120	131	5
		142	137	145	0
		120.2	121.8	133.2	3.0
		15.5	14.7	11.2	2.1
Remifentanil	Ex-Prem	118	106	96	0
		160	144	146	0
		114	117	131	3
		113	107	107	0
		114	111	126	2
		102	106	107	0
		120	117	114	0
		110	101	95	0
		118.9	113.6	115.2	0.6
		17.5	13.5	17.8	1.2

Heart Rate Changes for Infants

Control	Ex-Prem	115	111	127	3
	Ex-Prem	106	105	117	33
	Ex-Prem	118	121	131	1
	Ex-Prem	139	143	167	5
		107	109	112	5
		107	110	146	6
		115	108	159	3
		115	113	130	1
		122	123	166	5
		123	127	138	9
		129	132	164	35
		117.82	118.359636	141.523	9.6364
		10.078	11.9328885	20.0275	12.266
Remifentanil	Ex-Prem	124	103	100	0
	Ex-Prem	122	106	102	0
	Ex-Prem	117	113	105	0
		151	131	127	0
		115	103	109	0
		128	118	114	0
		141	129	132	0
		135	130	147	2
		123	129	135	35
		115	113	150	15
		130	126	123	0
		88	82	78	0
		124.1	115.3	118.5	4.3
		15.7	15.0	21.1	10.6

Heart Rate Changes for Children > 1 yr

	base hr	HR post Drg	Max HR	dur hr
Control	69	60	87	7
	103	107	119	11
	116	112	139	3
	104	100	126	5
	106	125	119	3
	98	103	144	16
	103	100	110	2
	59	69	108	111
	92	108	114	7
	132	139	162	5
	61	68	106	129
	72	71	107	2
	81	94	146	49
	92.0	96.6	122.1	26.9
	22.2	23.7	20.6	43.3
Remifentar	82	78	89	2
	77	65	66	0
	90	88	110	1
	72	70	63	0
	123	117	132	1
	65	59	61	0
	122	119	136	5
	105	97	101	0
	93	84	110	4
	135	130	129	0
	122	116	151	3
	69	61	58	0
	139	147	161	2
	99.5	94.7	105.2	1.4
	26.2	28.7	35.7	1.7

Mean Arterial Pressure Changes for Neonates

	Ex-Prem	base map	MAP post DG	Max MAP	dur map
Control		47	51	56	3
		57	61	74	6
		49	35	84	5
		39	50	50	4
		38	51	55	7
		46.0	49.9	64.1	5.0
		7.8	9.0	14.4	1.6
Remifentanil	Ex-Prem	43	59	43	55
		65	30	72	2
		39	34	44	2
		49	45	52	1
		54	46	56	0
		51	49	48	0
		48	52	56	2
		51	45	37	0
		50.0	45.0	51.1	7.8
		7.7	9.5	10.8	19.1

Mean Arterial Pressure Changes for Infants

Control	Ex-Prem	44	43	51	4
	Ex-Prem	38	40	49	8
	Ex-Prem	34	43	59	15
	Ex-Prem	33	27	42	1
		49	59	69	4
		47	49	79	9
		56	56	72	8
		83	81	97	4
		64	73	97	35
		62	87	93	8
		65	62	83	3
		52.3	56.4	72.0	9.0
		15.4	18.2	19.5	9.4
Remifentanil	Ex-Prem	38	39	35	0
	Ex-Prem	35	37	31	0
	Ex-Prem	34	37	31	0
		61	53	60	0
		48	37	36	0
		44	27	26	0
		65	60	51	0
		68	75	61	0
		44	36	53	2
		56	53	65	2
		53	44	45	0
		87	95	104	2
		52.8	49.4	49.9	0.5
		15.7	19.2	21.3	0.9

Mean Arterial Pressure Changes for Children >1 yr

	Ex-Prem	base map	MAP post DG	Max MAP	dur map
Control		65	88	100	11
		93	90	97	0
		90	92	91	32
		56	54	82	6
		65	77	80	6
		46	52	73	39
		71	74	111	34
		70	86	105	20
		86	86	120	6
		98	92	131	8
		70	76	112	15
		69	90	116	20
		59	64	98	15
		72.2	78.3	101.0	16.3
		15.4	14.0	16.9	12.2
Remifentanil		72	68	79	2
		81	62	66	0
		58	54	73	1
		88	70	68	0
		76	67	84	3
		69	67	55	0
		103	78	79	0
		86	83	102	5
		66	75	82	7
		80	75	63	0
		49	54	71	9
		60	57	57	0
		75	78	103	2
		74.1	68.1	75.3	2.2
		14.3	9.4	15.0	3.0