Study of Efficacy of Ketamine Analgesia for Surgical Management of Incomplete Miscarriages

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DECLARATION BY CANDIDATE

I, Dr Daniela Krick, hereby declare that the work contained in this dissertation is my original work and work by others has been acknowledged as such.

This study was carried out while a registrar in the Department of Obstetrics and Gynaecology at the University of Cape Town as required by the College of Obstetricians and Gynaecologists of South Africa for the qualification of FCOG (SA).

Name of Applicant : Daniela Krick

Signature of Applicant : _____

Date : _____

DECLARATION BY SUPERVISORS

The research which Dr Daniela Krick has undertaken and the presentation of this dissertation was supervised by Drs Gregory Petro and Anthony Reed.

We are satisfied that this was Dr Krick's original work and that this dissertation should be submitted in part fulfilment of the requirements of the FCOG (SA) examination.

Supervisor: Dr Gregory Petro

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Abstract

Objective: To compare the analgesic efficacy of ketamine with Fentanyl/Midazolam in women requiring uterine evacuation for incomplete miscarriage as measured by the patients' perceived pain.

Study design: An efficacy trial with a naturally occurring control group who received what is currently standard practice. The study ran over two 4-week periods (25/06/2012 to 19/08/2012).

Setting: Groote Schuur Hospital (a tertiary hospital) situated in Cape Town, South Africa.

Population: All women between the ages of 18 and 55 years admitted to Groote Schuur Hospital for uterine evacuation following a spontaneous incomplete miscarriage or missed miscarriage that were not excluded by any of the exclusion criteria.

Methods: Over a 2 month period (two 4-week periods), all patients meeting the inclusion criteria were allocated to either the control group (month 1) or the study group (month 2). Data was collected from all these evacuations during the study period at Groote Schuur Hospital.

Main outcome measures: Patients' perceived pain during and after the procedure (10 minutes, 2 hours) as scored by the patient on a numerical pain scale. Secondary outcomes were a sedation score, complications or side effects and the surgeons' satisfaction with the analgesia.

Results: During the study period 110 of 148 evacuations performed at Groote Schuur Hospital met the study criteria. Pain scores were lower in the Ketamine group compared to the Fentanyl/Midazolam group at all 3 time points. Average pain scores during the procedure were significantly lower in the Ketamine group (3.28 (2.41-4.16) vs. 5.93 (5.26-6.60) , $p<0.0001$). The 10 minute and 2 hour average pain scores were 2.6 (2.01-3.18) and 0.75 (0.49-1.02) for the Fentanyl/Midazolam arm, and 1.68 (1.33-2.02) and 0.43 (0.30-0.57) for the Ketamine arm respectively.

Conclusion: Analgesic doses of ketamine are an effective and safe alternative for the use in procedural sedation for uterine evacuations following 1st and 2nd trimester miscarriages. There is a

significant reduction in patients' pain perception during the procedure. Ketamine's half life is such that patients are sufficiently recovered after a shorter period of time when compared to Fentanyl/Midazolam sedation which would make earlier discharge after the procedure feasible.

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Introduction and literature review

Incomplete miscarriages are the reason for presentation in a major proportion of patients seen in the gynaecological emergency setting. Despite medical or expectant management being a viable option internationally, in South Africa most patients are admitted to gynaecological wards for surgical management.[1,2]

Uterine evacuations are arguably the most common surgical procedures performed in gynaecology. After incomplete miscarriage, retained products of conception are removed by curettage of the uterine cavity. Over the past 20 years sharp curettage has been replaced by vacuum aspiration with suction curettage, or manual vacuum aspiration using a Karman's cannula due to their proven efficacy and safety.[3,4]

These procedures are however associated with varying degrees of pain experienced by the patient necessitating some form of analgesia/anaesthesia. Various methods are available, ranging from simple oral non-steroidal anti-inflammatory (NSAID) administration, paracervical injection with local anaesthetic or intravenous/inhalational conscious sedation to general anaesthesia. The World Health Organization (WHO) 2002 guideline recommends that for uncomplicated evacuations general anaesthesia be avoided.[5] This is to minimize the potential morbidity/mortality associated with general anaesthesia. There are a number of possible complications of general anaesthesia, most importantly the loss of airway control leading to pulmonary aspiration, hypoxia or asphyxia. Procedural sedation should not compromise the patient's airway reflexes.

Procedural sedation also reduces cost and shortens hospital stay due to the cost of drugs used, less anaesthetic equipment/expertise needed and a shorter recovery period.

In South African public health care facilities conscious sedation (better termed procedural sedation) is frequently employed as form of "anaesthesia" under which uterine evacuations are performed.[6] There is no gold standard as to what drug or combination of drugs is administered. The focus rather is on identifying uncomplicated miscarriages which can be safely performed under procedural sedation and then applying local protocols when choosing between different types of analgesia. Commonly, procedural sedation is achieved by intravenous administration of an opioid and benzodiazepine mixture. Fentanyl and midazolam are the drugs currently used in our setting. The use of an opioid together with a benzodiazepine has the potential for complications such as respiratory depression, bradycardia and hypotension. The analgesic requirements for different individuals can be different and it is therefore best to titrate the amount of medication according to the patient's pain response. However, uterine evacuation is a minor procedure with a short operative time. Combined with a high patient load often results in a "standard maximum" dosage being administered with the plan to deal with possible side effects as they may arise. This necessitates close intra-procedural monitoring as well as a monitored recovery period, therefore confining evacuations to being performed in theatre with recovery area in most centres.

The result of this: long delays until a theatre is available with the following consequences:

(1) risk of sepsis secondary to retained products of conception (RPOC) increases,

(2) pre-procedural blood loss increases, possibly leading to haemodynamic instability and an increased need for blood transfusion and

(3) it compromises patient care in other areas. For example at our sister hospital (New Somerset Hospital, Cape Town) this results in one of the 3 labour ward doctors (registrar, medical officer and intern) going to perform the evacuations in main theatre after hours, effectively leaving the labour ward with only 2 doctors and a medical student. Should an emergency Caesarean section need to be performed during that time labour ward is left in the hands of the intern. This is a local issue but may also be relevant to other institutions.

Different drugs and drug combinations have been used for the sedation and analgesia for uterine evacuations.[7] Ketamine, although extensively studied for procedural sedation in the emergency department setting, dental and paediatric oncology procedures, has not been well studied for the use in uterine evacuations.[6,8-14] Only 2 studies were found on the specific subject, both published in the 1970s.[15,16]

Ketamine hydrochloride is a phencyclidine derivative that causes dissociation between the cortical and the limbic systems, preventing the higher centres from perceiving visual, auditory, or painful stimuli.[9] Muscle tone is maintained; therefore airway protective reflexes are preserved.[6] It produces analgesia and sedation in a dose-related manner. Analgesic (sub-anaesthetic) doses are quoted between 0.25-0.5mg/kg which would be equivalent to a plasma concentration of 0.9-2.5µmol/L.[8,17,18]

Ketamine effectively provides anaesthesia for procedural sedation and protects patient safety.[8,10,13,19] It is superior to fentanyl/midazolam in that its intravenous effects are very predictable with onset of action being 1-2 minutes and duration 10-15 minutes.[9,20] Another benefit of ketamine, especially in patients where post-operative pain is anticipated is that the analgesic effects far outlast the sedation.[21]

Ketamine use has been extensively studied in children in the emergency department setting, mainly for analgesia and sedation for painful procedures such as fracture reduction, with several studies supporting its efficacy and safety.[10-12,22-24]

Ketamine is less frequently used in the adult population, as it is believed to have a more extensive side-effect profile. The most likely complication when ketamine is used for procedural sedation is the occurrence of a dissociative state or psychological emergence phenomenon. This is the

experience of dreams, hallucinations and extracorporeal experiences which may be associated with significant distress.[13,18,25] Literature on the subject is more limited, however, a recent literature review concluded that airway and cardio-respiratory adverse events are rare.[25] Dysphoric emergence phenomena occurred in 10-20% of cases, being dose-dependent and effectively managed by addition of sedative medication at time of occurrence or pre-emptively by benzodiazepine pre-medication.[13,25,26]

The ideal agent for facilitating out-of-theatre evacuation of the uterus would provide anxiolytic, analgesic, and amnesic properties without being overly sedating. It would have a rapid onset and a short duration of action, while preserving reflexes and cardio-respiratory function, and have minimal adverse effects.

The currently used fentanyl/midazolam cocktail does provide anxiolysis, analgesia and amnesia but has a comparatively delayed peak effect and prolonged duration of action with narrow therapeutic index which hinders effective titration and prolongs recovery time.

Due to its cost-effectiveness (especially when compared to "more advanced" anaesthetic agents) ketamine is extensively used in under-resourced settings, often by a single operator with minimal monitoring.[19]

Hypothesis and aims of this investigation

Analgesic doses of ketamine are an effective alternative to fentanyl/midazolam for procedural sedation of women requiring surgical evacuation of the uterus following miscarriage.

Aims:

Primary:

To assess and document the efficacy of intravenous ketamine at sub-anaesthetic doses to achieve adequate analgesia for surgical evacuation of the uterus as scored by the patient on a pain scale during the procedure and at 2 intervals after the procedure, namely 10 minutes and 2 hours.

Secondary:

To assess and document and compare the patient's sedation score during and at the 2 intervals after the procedure.

To compare complications and side effects of the different medications.

To assess the surgeon's satisfaction with the analgesia.

This study hoped to show efficacy and safety of ketamine, which would improve the patients' experience during an already traumatic life event by decreasing physical pain experienced and shortening hospital stay.

It would also help lessen the burden on our over-stretched health facilities by perhaps making evacuation an outpatient/short-stay procedure due to the elimination of the need for theatre and an intensely monitored recovery period.

Methods

This was an efficacy trial with a naturally occurring control group who received what was currently "standard medication".

The sample size calculation was based on a two-sided significance level of 95%, with a power of 80%. Based on clinical experience and evidence from the literature, significant pain is experienced by approximately 40% of patients receiving current "standard medication" in the form of procedural sedation with Fentanyl and midazolam. It was anticipated that the proportion of patients experiencing significant pain in the Ketamine group will be reduced to 15%.
Based on these assumptions the sample size would be 50 in each group (total=100). From our knowledge of the service at Groote Schuur Hospital we therefore decided to allocate one month of data collection to each group.

We followed a group of patients while testing a new treatment (analgesic option). The cohort (study group) being all women requiring surgical management (uterine evacuation) following a miscarriage. In two consecutive 4 week periods (25/06/2012 to 22/07/2012 and 23/07/2012 to 19/08/2012) patients were allocated to the control group (group 1) and the intervention group (group 2). Data was collected from all evacuations performed during these periods at Groote Schuur Hospital.

Inclusion Criteria

Patients eligible for the study included all women between the ages of 18 and 55 years admitted to Groote Schuur Hospital for uterine evacuation following:

- a spontaneous incomplete miscarriage,
- a missed miscarriage.

Patients with a missed miscarriage received a prostaglandin E1 analogue (Misoprostol®) as a cervical ripening agent before curettage.

Exclusion Criteria

Patients with the following findings were excluded from the study:

- Signs of haemodynamic instability (BP <80/40 or P>120)
- ward haemoglobin concentration of 8g/dl or less (done using a Haemacue® machine), or
- signs of sepsis (temperature >37.5, foul-smelling vaginal discharge)
- any contraindications for the use of ketamine (chronic hypertension, thyrotoxicosis etc)
- evacuation required after termination of pregnancy. (Termination of pregnancy was excluded for logistical reasons. In our facility these patients are induced in the ward and return to their ward bed after the evacuation. For the purpose of the study only patients which could be followed-up easily at the 2-hour mark (i.e. those that remained in the minor ops recovery area after evacuation) were included.)

Also any woman declining informed consent was not included in the study, received standard procedural sedation and no data was collected.

Ethics approval was obtained prior to the start of the study.

All eligible patients were invited to join the study. They received an information sheet in English, Afrikaans or Xhosa (the 3 main languages spoken by our patients). The outline of the study was described to the patient by the admitting doctor and/or a trained interpreter. Once the patient agreed to be included in the study written informed consent was obtained.

Before the procedure all patients were weighed using the same standard analogue scale and the verbal pain scale was explained.

In theatre, standard protocol for monitoring of patients undergoing procedural sedation was followed. This included the measurement of blood pressure before (base line), as well as after the completion of the procedure. Patients also had pulse and oxygen saturation monitored continuously throughout the procedure through the use of a pulse oximeter.
This basic monitoring was continued during the study period.
Values of blood pressure, maximum pulse and lowest oxygen saturation levels were recorded on a data collection sheet.

During the first month of data collection the fentanyl/midazolam cocktail was administered (100mcg fentanyl and 5mg midazolam intravenous injection) as is current standard practice.

In the second month of data collection (intervention group) all eligible study patients received a pre-operative dose of 1mg midazolam intravenously as pre-medication. This was followed by ketamine in doses of 0.25-0.5mg/kg intravenously as per sedation guideline by the SA Society of Anaesthesiologists.[17] Further back-up sedation with midazolam or fentanyl at set dosages (1mg midazolam or 50mcg fentanyl) for analgesia was available if deemed necessary by the surgeon.

The "surgeon" performing the evacuation was either a registrar or medical officer in gynaecology or an intern under supervision. We included all levels of medical staff as surgeons because evacuations are simple procedures that should be safely performed by any suitably-trained doctor. By including different levels of medical staff the study reflects actual clinical practice and is therefore more reproducible.

The patient was positioned in Lithotomy position after which the sedative/analgesic agents were injected intravenously. After injection, the surgeon cleaned the perineum with lukewarm diluted iodine solution and draped the patient in routine fashion.

Of note here is that doctors were instructed to let a 3-5 minutes pass between injection of the fentanyl/midazolam cocktail and starting the procedure. This was to allow for these drugs to take effect, keeping in mind their delayed onset of action. In the Ketamine group the doctors were instructed to commence the procedure after 1 minute of drug administration, owing to the quick onset of action and relatively short half-life of the drug.

The patient's bladder was emptied by means of a Rotunda catheter.

The size of the uterus was evaluated by bimanual palpation and the dilatation of the uterine cervix assessed. If dilation of the cervix was necessary, this was performed using Hegar dilators in the standard fashion.

The evacuation then continued in a standard fashion using a Karman's cannula attached to low pressure (-50mmHg) wall suction or with the use of a sharp metal curette, depending on the surgeon's training, experience and preference.

During the procedure the attending nurse asked the patient to score her perceived pain on an 11-point numerical rating scale (0-10) (Addendum 1). The member of the medical team also subjectively graded the patient's level of sedation using the University of Michigan Sedation Scale (UMSS) (Addendum 2).

The pain score and sedation level were repeated at 10 minutes as well as 2 hours after the procedure by the nurse in the recovery area. At the 2 hour mark the patient was also asked if she had any recollection of the actual evacuation procedure.

Additional data recorded on the data collection sheet included:

- time of administration of intravenous drugs and time of start of the surgical procedure,
- length of procedure,
- ease of procedure,
- surgeon's satisfaction with analgesia/sedation i.e. patient co-operation,
- perceived completeness of surgical procedure,
- perceived blood loss,
- need for additional analgesia over and above the primary agent, and what was administered,
- dissociative state symptoms,
- need for sedation to alleviate dissociative symptoms,
- any adverse events.

Safety considerations

Safety of the patient is always of utmost importance, during the duration of the study as well as at all other times.

All uterine evacuations of unstable patients in our institution are performed in a formal theatre setting under general anaesthesia.

Uterine evacuations of stable patients at Groote Schuur Hospital are performed in a special evacuation theatre in the gynaecology triage area in casualty. Personnel present are the surgeon who also administers the sedative agent pre-operatively, a trained theatre sister and a nurse. Standard monitoring of the patient includes blood pressure and pulse checks before administration of any medication and patients are monitored throughout the procedure by pulse oximetry. All necessary facilities exist in theatre should a cardiovascular or respiratory emergency occur and an anaesthetist can be summoned for assistance if necessary.

In addition all doctors performing evacuations were thoroughly informed about the possible side-effects of ketamine and their management at the beginning of the study by means of a staff training session and information sheets.

Monitoring post-operatively was continued by a registered nurse in a dedicated recovery area in the gynaecology triage area. Monitoring included pulse oximetry for 30 minutes, as well as heart rate and blood pressure recordings every 30 minutes for 4 hours.

Follow-up of patient

Prior to discharge all patients were reviewed by a medical/ nursing practitioner.

The patient's Rhesus status and rapid plasma reagin (syphilis) result was checked and managed appropriately.

Vital signs and severity of per vaginal bleeding were checked.

The patient was discharged by an intern or registrar if deemed stable.

Education was provided regarding warning signs of infection or prolonged bleeding.

Routine discharge medication included simple analgesia (Paracetamol and Ibuprofen) and oral antibiotics (Doxycycline and Metronidazole).

All women were offered a variety of contraceptive options which were discussed before the evacuation procedure. The patient may have chosen to have an intrauterine contraceptive device (IUCD) inserted after completion of the evacuation (in the absence of contra-indications), alternatively she may choose to receive an intramuscular injection of progestogen before discharge or an oral contraceptive.

Our patients were not followed up after discharge from hospital (this is routine in our setting) except those that had an IUCD inserted. These patients return after 2 weeks to confirm correct positioning of the device and trimming of the threads.

Data were collected on Data Collection Sheets (Appendix 3), captured on an Excel spreadsheet and then analysed using the Stata software package. Categorical data were compared across groups using the χ^2-test of association. Normally distributed data were compared across groups using the Student *t*-test, while non-parametric data were analysed using the Mann-Whitney U Test. Within group comparisons of pre and post procedure variables were compared using the Paired t-test. A *p*-value of <0.05 was regarded as statistically significant.

The primary outcome of this study was pain measured on an 11-point, 0-to-10 verbal rating pain scale during the evacuation, as well as at intervals 10 minutes and 2 hours after the procedure. This 11-point verbal rating scale has been validated by various studies to be an effective way to measure acute pain intensity and has been widely used in literature dealing with analgesia.[27,28] Other outcomes included patient sedation levels (intra-operative, 10-minutes, 2-hours), changes in blood pressure pre- and postoperatively, measures of heart rate and oxygen saturation, patient co-operation, the need for additional analgesia and the patient's recollection of the procedure

Results

During the recruitment period a total of 148 evacuations were performed at Groote Schuur Hospital. 110 of these were included in the study. Of these participants 51.82% (n=57) were in the Fentanyl/Midazolam arm and 48.18% (n=52) were in the Ketamine arm. 38 women were excluded from the study for the following reasons: evacuation required after termination of

pregnancy (n=26), declining participation (n=7), haemodynamic instability (n=2), evidence of sepsis (n=2) and requiring evacuation after a term pregnancy (n=1). [see figure 1]

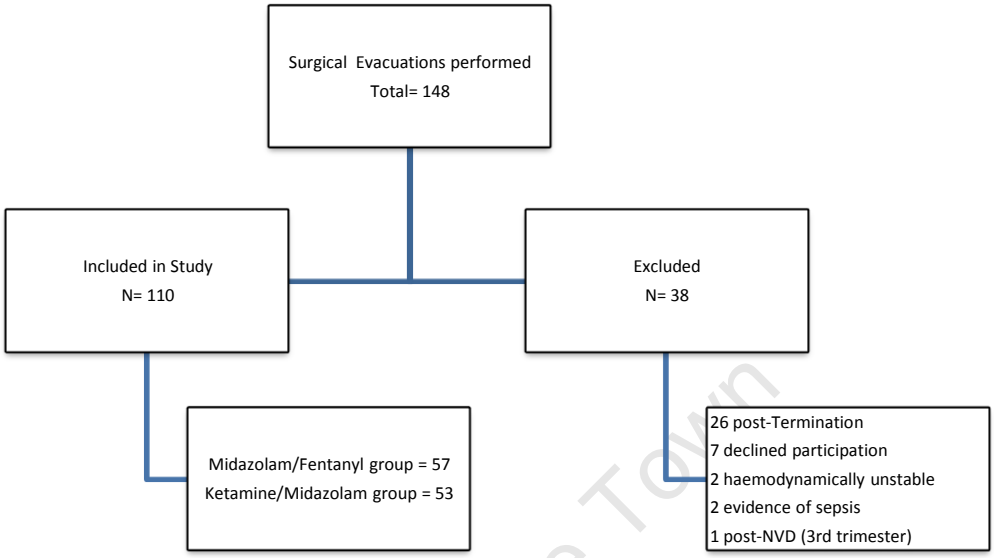


Figure 1 Flow diagram of study participants

The patients in the Ketamine arm received a mean dosage of 0.48mg/kg (CI 0.47-0.49).

There were 2 protocol violations in the Ketamine group. In the first an un-cooperative patient received an additional 5mg Midazolam plus 100mcg Fentanyl. She subsequently had a considerable decrease in oxygen saturation which was corrected upon vigorous manoeuvres to "wake up" the patient. The second violation was that of an additional 4mg Midazolam being administered to a patient in the Ketamine group, this without adverse outcome. Interestingly this patient also had a sedation score of 0 at both the 10-minute and 2-hour marks after the evacuation.

Of the women participating in the study there were no statistically significant differences in their demographic profile except that in the Ketamine group a greater percentage of evacuations was performed by registrars than interns (χ^2(1 d.f.) =5.0003, p=0.025). Characteristics are detailed in Table 1.

Table 1 Characteristics of participants by pain management regimen

	Fentanyl/Midazolam	Ketamine	P-value (Chi-

		(n= 57)	(n=53)	squared test of association/Fisher's exact for small numbers)
Diagnosis				
	Spontaneous miscarriage	29	36	
	Missed miscarriage	28	17	0.069
Trimester				
	1st	47	36	
	2nd	10	17	0.077
Surgeon				
	Intern	28	15	
	Registrar/Medical Officer	29	38	0.025
Misoprostol ripening				
	yes	35	25	
	no	22	28	0.134
mechanical cervical dilation required				
	yes	8	5	
	no	49	48	0.56
Procedure time				
	<10min	37	44	
	10-15min	16	6	
	>15min	4	3	0.062
Ease of procedure				
	Easy	53	50	
	Difficult	4	3	1
Curettage				
	Sharp	21	17	
	Suction	36	36	0.599
Blood loss				
	Mild	49	41	
	Moderate	8	12	
	Severe	0	0	0.324

Average pain scores during the procedure were significantly lower in the Ketamine group (3.28 (2.41-4.16) vs. 5.93 (5.26-6.60) , Mann Whitney U test p<0.0001). The 10 and 2 hour average pain scores were 2.6 (2.01-3.18) and 0.75 (0.49-1.02) for the Fentanyl/midazolam arm, and 1.68 (1.33-2.02) and 0.43 (0.30-0.57) for the Ketamine arm respectively.

Average sedation levels at 10 minutes were also significantly lower in the Ketamine group, (0.77 vs. 1.37, Mann Whitney U test p=0.0006), and again at 2 hours (0.04 vs. 0.51, Mann Whitney U test p<0.0001). Average sedation levels during the procedure were similar between groups (1.72 and 1.94 for Ketamine and Fentanyl/midazolam groups respectively).

Table 2 Pain and Sedation scores at 3 Intervals (intra-procedural, 10 minutes & 2 hours post-procedure)

Variable	Group	Obs	Mean	[95% Conf. Interval]		Median (IQR)
Pain during	Ketamine	53	3.28	2.41	4.16	2 (0-5)
	Midaz	57	5.93	5.26	6.60	6 (4-8)
Sedation during	Ketamine	53	1.94	1.70	2.19	2 (1-2)
	Midaz	57	1.72	1.50	1.94	2 (1-2)
10 min pain	Ketamine	53	1.68	1.33	2.02	1 (1-3)
	Midaz	57	2.60	2.01	3.18	2 (1-4)
10 min sedation	Ketamine	53	0.77	0.62	0.92	1 (0-1)
	Midaz	57	1.37	1.11	1.62	1 (1-2)
2 hr pain	Ketamine	53	0.43	0.30	0.57	0 (0-1)
	Midaz	57	0.75	0.49	1.02	1 (0-1)
2 hr sedation	Ketamine	53	0.04	-0.02	0.09	0 (0-0)
	Midaz	57	0.51	0.30	0.72	0 (0-1)

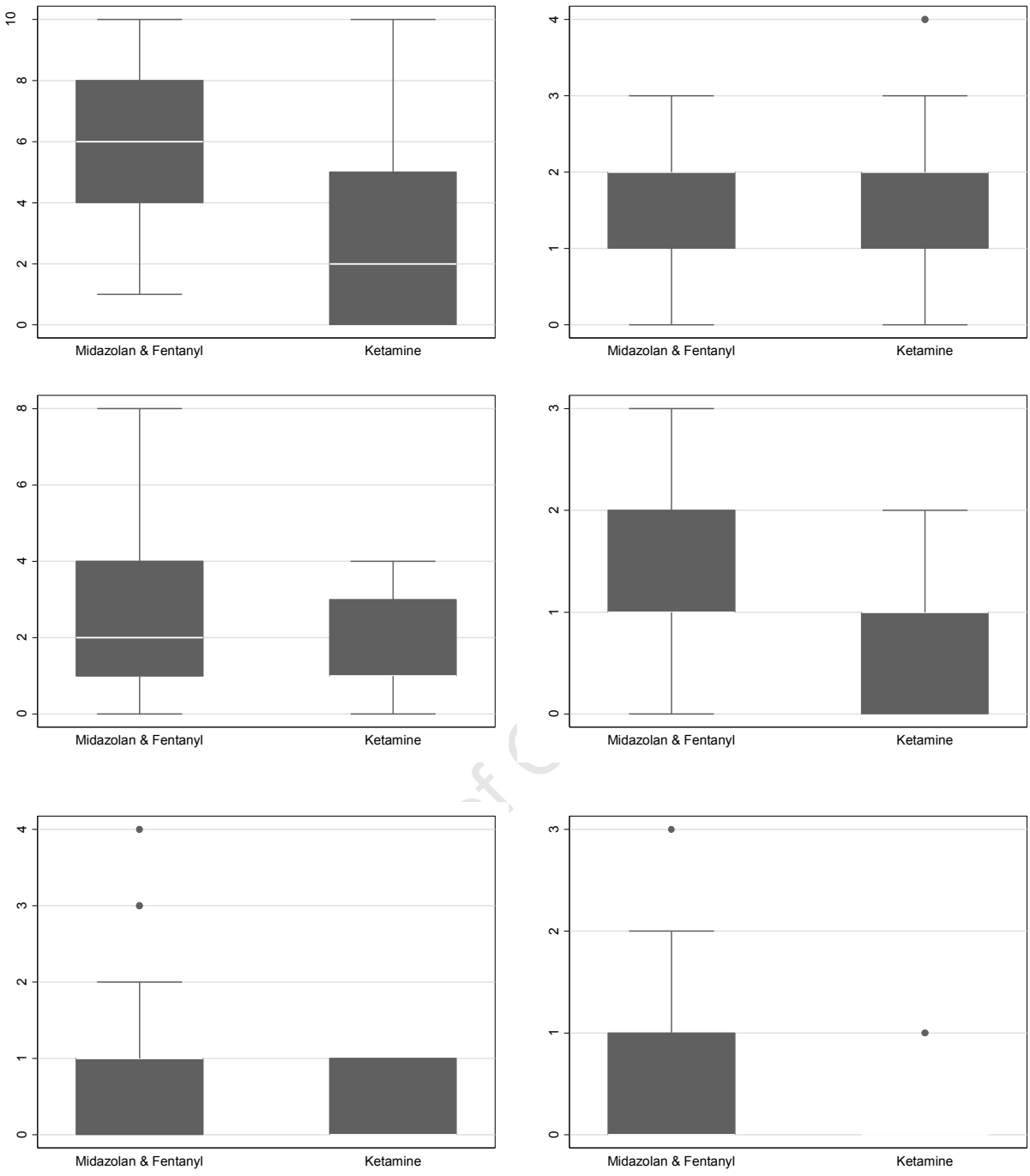


Figure 2 Boxplots showing median and inter-quartile ranges of pain and sedation scores at time: 0, 10 minutes and 2 hours

Systolic and diastolic blood pressures (in mmHg) were approximately equal in both groups before commencement of the procedure (Mann Whitney U test p=0.9024 and T-test p=0.8035).

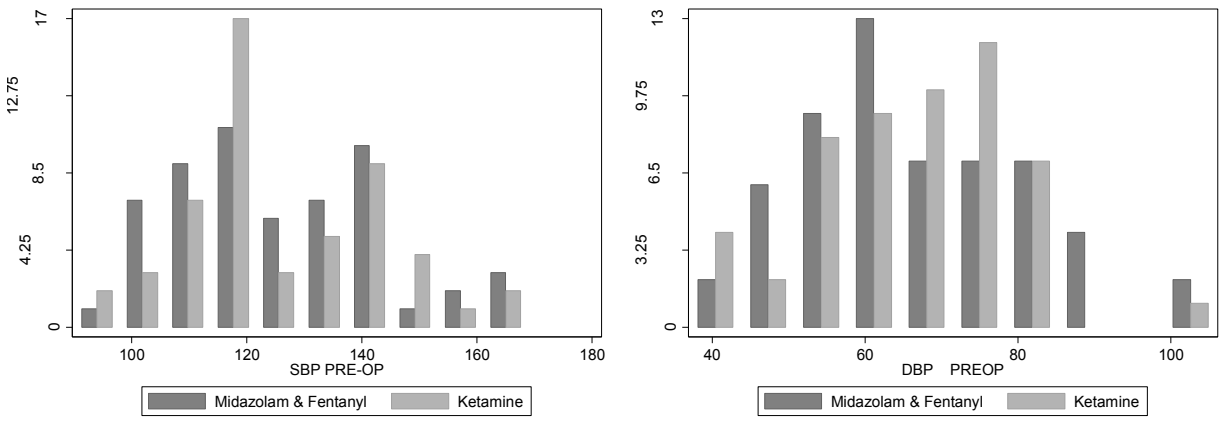
In the Ketamine group, the mean SBP rose from 125 (121-130) pre-op to 130 (125-136) post-op (-Paired t-test t=2.2919, p=0.026). The mean DBP for this group also increased, from 66 (62-69) pre- to 74 (70-79) post-procedure (Paired t-test t=-4.1609, p=0.0001).

The Fentanyl/midazolam group saw a drop in mean pre-op SBP from 126 (121-130) pre-procedure to 122 (116-127) post-procedure, (Paired t-test t=1.6191, p=0.1110), although the DBP increased from 66 (63-70) pre- to 68 (64-72) post-procedure, (Paired t-test t=-0.8974, p=0.3733).

The mean SBP and DBP values post-procedure, were significantly higher in the Ketamine group when compared to the Fentanyl/midazolam group, (T-test p=0.0285 and p=.0524).

Table 3 Comparison of Systolic and Diastolic Blood Pressure pre- and post-procedure for Ketamine and Fentanyl/Midazolam groups

Variable	Group	Obs	Mean	[95% Conf. Interval]		Median (IQR)
SBP Pre	Ketamine	53	125.45	120.65	130.26	121 (114-139)
	Midaz	57	125.51	120.72	130.29	123 (112-138)
DBP Pre	Ketamine	53	65.74	62.09	69.38	64 (54-78)
	Midaz	57	66.40	62.50	70.31	66 (57-76)
SBP Post	Ketamine	53	130.25	124.80	135.69	132 (118-139)
	Midaz	57	121.67	116.18	127.16	119 (106-136)
DBP Post	Ketamine	53	74.28	69.68	78.89	73 (62-86)
	Midaz	57	68.19	63.99	72.40	70 (56-78)
Pulse	Ketamine	53	100.21	95.70	104.72	98 (88-110)
	Midaz	57	94.81	90.67	98.94	96 (85-105)
SATS Low	Ketamine	53	98.17	97.28	99.06	99 (98-99)
	Midaz	57	95.61	94.60	96.63	97 (94-98)



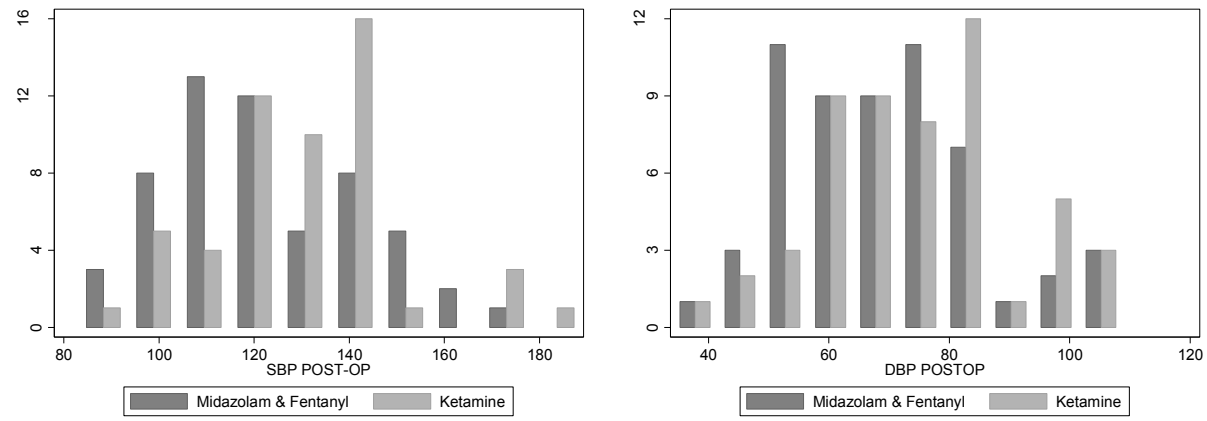


Fig 3 Comparison of Systolic and Diastolic Blood Pressure between groups

There were no statistically significant differences in heart rates between the 2 groups although it was noted that the maximum pulse recorded in the Ketamine group was 140bpm.

Oxygen saturation levels differed significantly with a mean of 95.6% (±3.83) in the Fentanyl/Midazolam group compared to 98.2 (±3.22) in the Ketamine group (Mann Whitney U test $p<0.0001$).

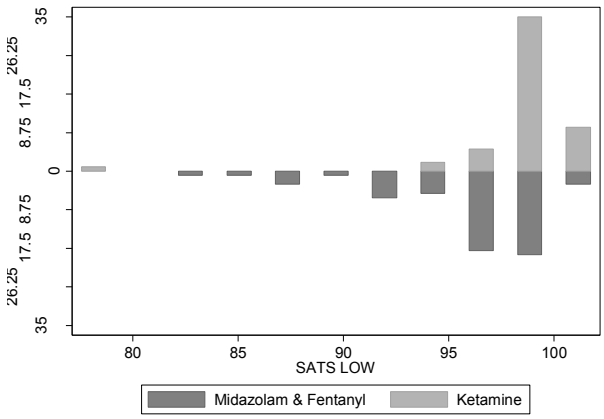


Figure 4 Comparison of Oxygen Saturation between groups

In the Fentanyl/Midazolam group there was one case of the patient's saturation dropping precipitously to 77%. This was quickly corrected by the surgeon interrupting the evacuation and performing a head tilt-jaw thrust manoeuvre to open the obstructed airway. The remainder of the evacuation was uneventful.

The need for additional analgesia was recorded as 3.51% (n=2/57) in the Fentanyl/Midazolam group and 39.62% (n=21/53) in the Ketamine group. In the Fentanyl/Midazolam arm 2 patients received an additional dose of 50mcg fentanyl. In the Ketamine arm, the patients that were given additional analgesia, received the following medications: 38.1% (n=8/21) 50mcg fentanyl, 33.3% (n=7/21) 1mg midazolam, 19.0% (n=4/21) 50mcg fentanyl+ 1mg midazolam, 0.05% (n=1/21) ketamine (0.25mg/kg) and 0.05% (n=1/21) 50mcg fentanyl+ 1mg midazolam+ 0.25mg/kg ketamine.

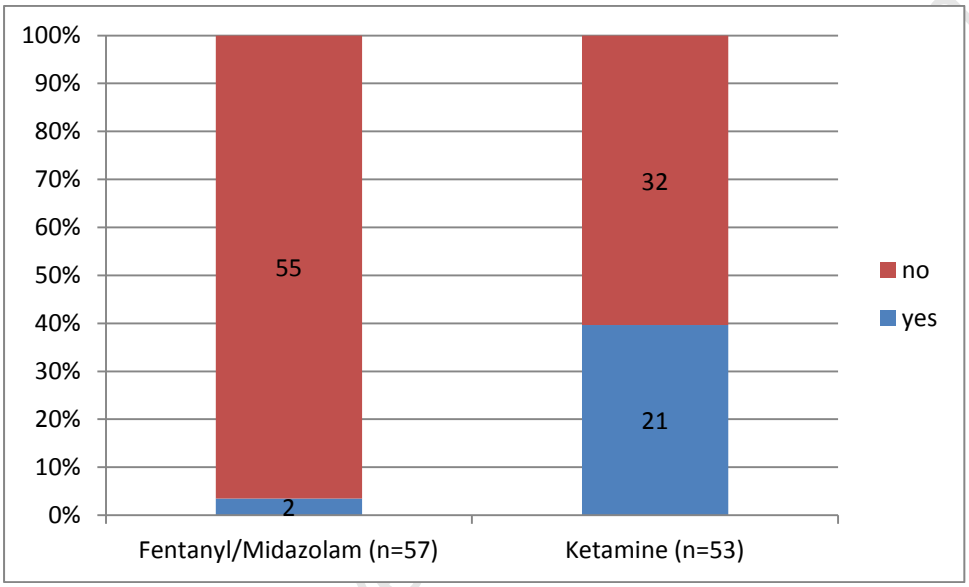


Figure 5 Comparison of requirements for additional analgesia between groups

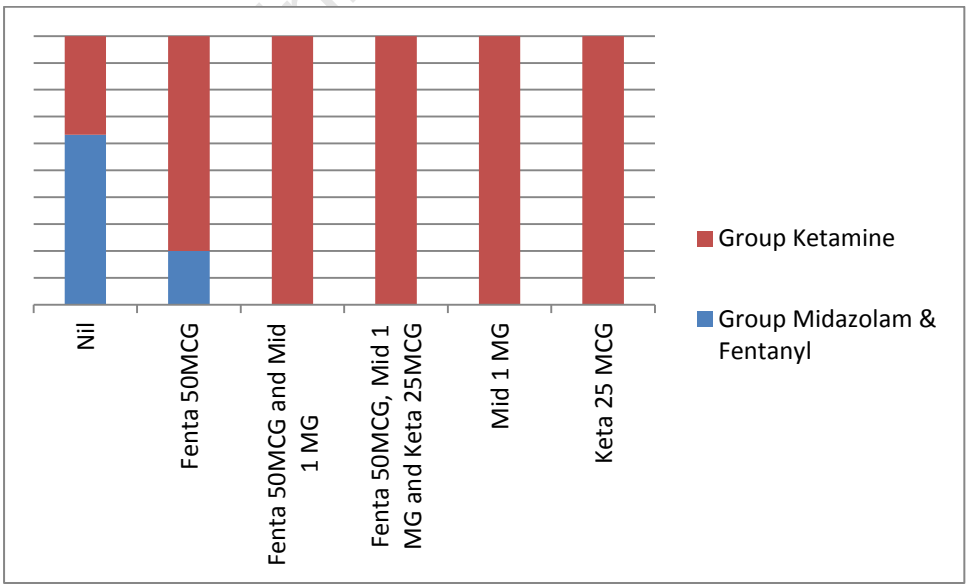


Figure 6 Types of additional analgesia given

Ketamine-specific side effects were recorded on the Data Sheets, with 3/53 (6%) patients objectively hallucinating, 4/53 (8%) exhibiting increased talkativeness, 3/53 (6%) displaying visible distress and 2/53 demonstrating increased salivation/sweating. Only 1 of the patients was given additional benzodiazepine specifically to alleviate these symptoms.

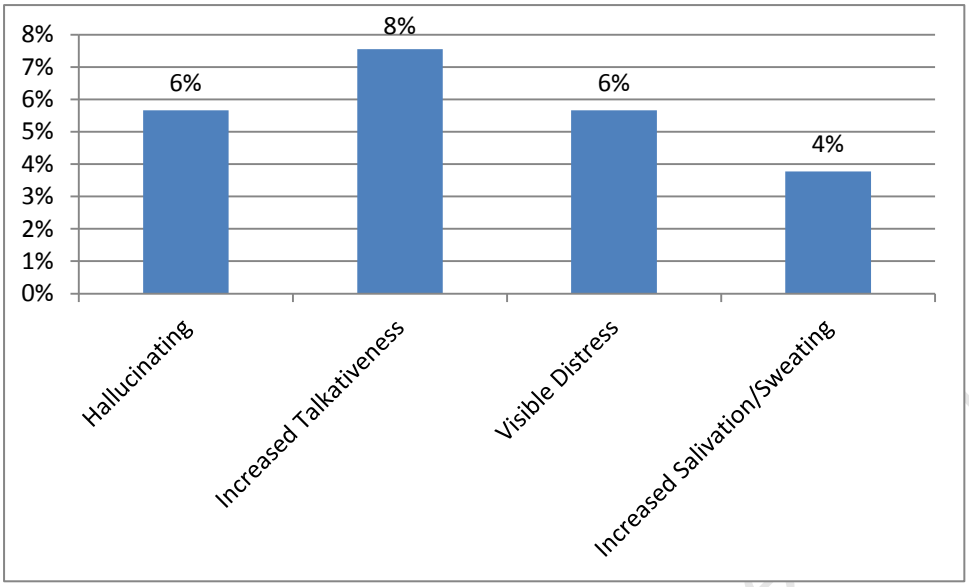


Figure 7 Incidence of ketamine side effects

Recollection differed significantly (χ^2(1 d.f.) =17.28, p<0.0001) in that 42.1 % (n=24/57) of patients who received fentanyl/midazolam could remember the procedure while this number was 0.08% (n=4/53) in the Ketamine group.

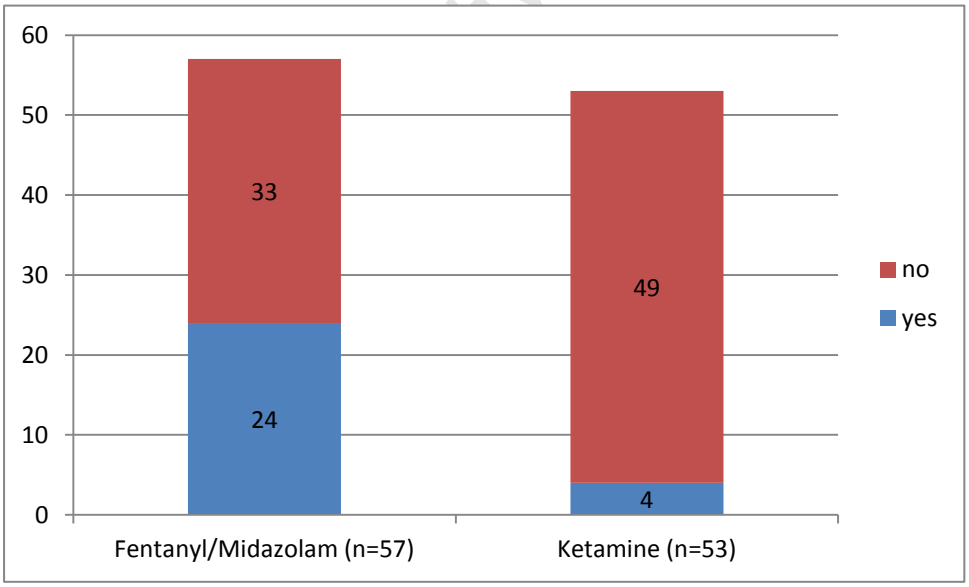


Figure 8 Incidence of recollection of procedure between groups

Discussion

The safe use of procedural sedation over general anaesthesia for pain relief during uterine evacuation was demonstrated in previous studies and is advocated by the World Health Organization.[5] Our study agreed with previous studies in terms of safety, with adverse events (respiratory depression in 2 cases) being quickly and easily managed.

There was adequate pain control, such that all procedures were completed under procedural sedation and none had to be abandoned and converted to general anaesthesia. Patients in the Ketamine arm had significantly lower pain scores (Mann Whitney U test $p<0.0001$). However, they received significantly more additional analgesia as deemed necessary by the attending surgeon. Here an interesting and important observation was made when analysing the data in more detail. We assigned pain scores of 7-10 the umbrella term "severe" and looked at patients that fell into this category in both the Fentanyl/Midazolam and Ketamine groups. In the Fentanyl/Midazolam group 42.1% (n=24) had severe pain. Of these 24 patients only 2 (8%) received additional analgesia. In the Ketamine group 20.7% (n=11) had severe pain. All 11 of these received additional analgesia. We are not sure why severe pain was not more aggressively managed in the Fentanyl/Midazolam group? Secondly, the 11 Ketamine patients received various drugs or combinations of drugs to manage their pain, the various options having been outlined in the protocol and at the discretion of the surgeon. 4 patients received additional fentanyl, 4 received additional midazolam, 2 fentanyl plus midazolam and 1 fentanyl plus midazolam plus ketamine. Since midazolam on its own is a sedative rather than an analgesic the question is whether its use alone was appropriate and effective in relieving the patient's discomfort.

The excellent amnesic effects displayed especially in the Ketamine group are very likely to improve overall patient satisfaction.

There was no significant difference in affect on heart rate by the different drugs, however both systolic and diastolic blood pressures increased in the Ketamine group whereas they decreased in

the Fentanyl/Midazolam group. This effect of ketamine may provide and advantage in patients with compensated haemodynamic instability where Fentanyl/Midazolam may in fact precipitate breakdown in compensation. However, it also means ketamine should be used with caution in patients with an underlying hypertensive disorder, especially those at risk for cerebrovascular events.

In terms of maintenance of respiratory mechanisms ketamine proved superior with mean oxygen saturation levels remaining significantly higher in the Ketamine group.

Using ketamine, uterine evacuations of stable patients could be safely performed as an out-of-theatre procedure with a shortened period of recovery required, owing to the evidence for quick recovery time from sedation. These characteristics of ketamine may make it possible to decrease the need for ward admission while awaiting formal theatre facilities and fast-track discharge patients after the procedure. This would decrease the cost to and burden on health facilities also improve patient satisfaction.

Limitations

Factors affecting the patients' pain scores were not adequately explored. These would include : patient characteristics and history, preparation and counselling, atmosphere, procedure time, provider characteristics, misoprostol for cervical ripening and IUCD insertion. It may be useful to include this data in future research.

The results may have been affected by various forms of bias. From the side of the patient these would include attention bias due to the patient being aware of being involved in a study and therefore being more attentive to perceived pain and possible side effects, for instance hallucinations ("the power of suggestion"). This could be addressed by a double-blind, randomised study.

Medical staff may have been influenced by expectation bias. This could apply to nursing staff when recording sedation levels, and may be suggested by the more aggressive management of pain by surgeons treating an expected failure of adequate analgesia in the Ketamine group.

Proficiency bias may have crept in, suggested by the evacuations in the Ketamine group being performed predominantly by registrars. Interns may have not felt comfortable using ketamine analgesia as its use is currently uncommon in adult procedural sedation. Registrars may have also decided to perform the procedure themselves, knowing that the half-life of ketamine is much shorter and therefore evacuations would need to be completed more quickly, which is achievable the more experienced one is.

These biases may be reduced by blinding the patients to the drugs used, and pain/sedation scores being recorded consistently by an independent blinded observer. However surgeons would need to be aware of the type of medication used as it influences the time allowed between administration of drug and start of surgery due to the differences in onset of action.

Further research should focus finding the most suitable dosage of ketamine to minimize pain while minimizing dissociative symptoms. Another option to explore would be the administration of additional pre-operative analgesia such as oral paracetamol and a non-steroidal anti-inflammatory drug (NSAID) given 1-2 hours before the procedure. Also, it would be of benefit to collect data on factors that may influence the patient's perceived pain and formally evaluate the patient's satisfaction with analgesia and/or sedation provided.

Conclusion

This study suggests that ketamine provides a potential superior alternative to the current fentanyl/midazolam technique. However the supplementation rate was higher in the Ketamine group and the use of adjunctive oral analgesics may be an approach to be considered. This data supports the performance of a multi-centre, randomised and double-blinded trial.

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Appendices:

1: Verbal Pain Score system

2: University of Michigan Sedation Scale (UMSS)

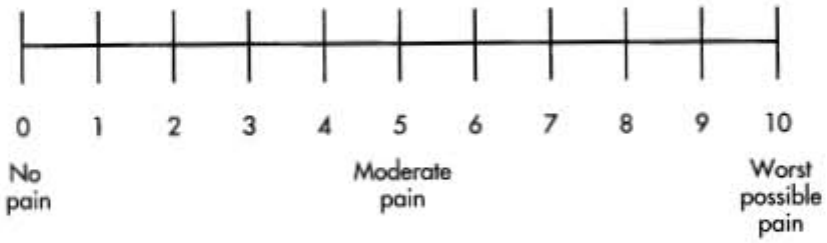
3: Data Collection Sheet

4: Patient Information Sheet

5: Consent Form

6: Tables and Figures

Verbal Pain Scoring Scale



University of Michigan Sedation Scale:

0 Awake and Alert

1 Minimally sedated, tired/sleepy
Appropriate response to verbal conversation/ sound

2 Moderately sedated, sleeping
Easily aroused by light touch or verbal command

3 Deeply sedated, deep sleep
Arousable only with significant physical stimulation

4 Unarousable

DATA COLLECTION FORM – Analgesia for Evacuations

Study ID _____ **DATE** _____

TYPE OF ABORTION	**SPONATEOUS**	**MISSED**		
TRIMESTER	**1ST**	**2ND**		
SURGEON	**INTERN (supervised)**	**REGISTRAR**		
PATIENT WEIGHT	**kg**			
PRE-OP MISOPROSTOL	**YES**	**NO**		
PRIMARY MEDICATION & DOSE USED	**FENTANYL**	**100MCG**		
	MIDAZOLAM	**5MG**		
	KETAMINE (MG)			
TIME OF ADMINISTRATION	**H**			
TIME OF START OF SURGERY	**H**			
VITAL SIGNS	**PRE-OP BP**	**/**		
	POST-OP BP	**/**		
	HIGHEST PULSE			
	LOWEST O2 SATS			
SURGERY	**CERVICAL DILATION NEEDED**	**YES**	**NO**	
	LENGTH OF PROCEDURE	**<10MIN**	**10-15MIN**	**>15MIN**
	EASE OF PROCEDURE	**EASY**	**DIFFICULT**	
	BLOOD LOSS	**MILD**	**MODERATE**	**SEVERE**
	CURETTAGE	**SHARP**	**SUCTION**	
SATISFACTION WITH ANALGESIA:				
PT CO-OPERATIVE	**YES**	**NO**		
COMPLETENESS OF PROCEDURE	**YES**	**NO**		
NEED FOR ADDITIONAL ANALGESIA	**YES**	**NO**		
	IF YES	**MIDAZOLAM 1MG**		
		FENTANYL 50MCG		
		KETAMINE 0,25MG/KG		
DISSOCIATIVE SYMPTOMS	**YES**	**NO**		
	IF YES SPECIFY	**HALLUCINATIONS**		
		TALKATIVENESS		
		VISIBLE DISTRESS		
		OTHER		
	SEDATION TO ALLEVIATE SX		**YES**	**NO**

ADVERSE EVENTS _____

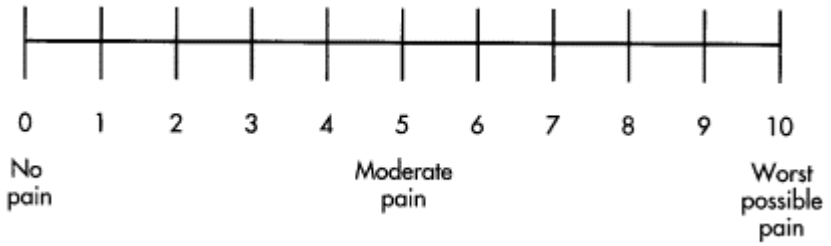
Intra-procedural: **Verbal Pain Score 0 1 2 3 4 5 6 7 8 9 10**
Sedation Scale 0 1 2 3 4

10 minutes post-op: **Verbal Pain Score 0 1 2 3 4 5 6 7 8 9 10**
Sedation Scale 0 1 2 3 4

2 hours post-op: **Verbal Pain Score 0 1 2 3 4 5 6 7 8 9 10**
Time:_____ **Sedation Scale 0 1 2 3 4**

Recollection of the procedure? YES NO

Verbal Pain Score:



Sedation Scale:

0 **Awake and Alert**
1 **Minimally sedated, tired/sleepy**
Appropriate response to verbal conversation/ sound
2 **Moderately sedated, sleeping**
Easily aroused by light touch or verbal command
3 **Deeply sedated, deep sleep**
Arousable only with significant physical stimulation
4 **Unarousable**

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This Informed Consent Form is for women who are admitted to Groote Schuur Hospital for evacuation of the uterus, and who we are inviting to participate in research on pain relief and sedation. The title of our research project is "Study of Efficacy of Ketamine Analgesia for Surgical Management of Incomplete Miscarriages".

This Informed Consent Form has two parts:

- Information Sheet (to share information about the research with you)
- Certificate of Consent (for signatures if you agree to take part)

You will be given a copy of the full Informed Consent Form

PART I: Patient Information Sheet

Introduction
We are doing research uterine evacuations, which you may have heard of as "womb scrape" or "womb cleaning".
Our research is aimed at trying to find the best medication to relieve the discomfort or pain of a womb scrape.

I am going to give you information and invite you to be part of this research.

If there is something that you do not understand please ask me to stop as we go through the information and I will take time to explain.

Who is doing the research?
The research is being conducted by:

Dr Daniela Krick
Registrar
UCT Department of Obstetrics and Gynaecology
Tel: 021 402 6464 / Cell: 082 568 5435

Supervisors:
Dr GA Petro
Chief Specialist and Head of Obstetrics & Gynaecology
Metro West
New Somerset Hospital, Greenpoint
Tel: 021 402 6324

Dr A Reed
Chief Specialist Anaesthesiologist
Metro West Anaesthetic Service
New Somerset Hospital, Greenpoint
Tel: 021 402 6418

Why are we doing this research?
Miscarriages are very common. Often there are products or pieces of pregnancy tissue left inside the uterus (womb). This is then called an incomplete miscarriage. If these tissues are left inside the womb they can cause you to bleed a lot or to suffer from infection. To prevent these problems doctors do a uterine evacuation which you may have heard of as a "womb scrape" or "womb cleaning". This is a procedure done in the operating theatre where these pieces of tissue removed from your womb either by cleaning with a metal instrument or by sucking with something that looks like a plastic straw.

This procedure is painful and to make the pain as little as possible you are sedated. This means that we give you 2 medications through a drip into your vein. The medications that we use at the moment are called Fentanyl and Midazolam.

Fentanyl is a very strong pain killer.
Midazolam sedates you (you get very sleepy and forgetful).
The problems with Midazolam and Fentanyl are that they may not start working quickly enough after they have been given to you in the drip. For example Midazolam usually only works best after 5 to 10 minutes. This is called the onset of action and is different in different people. Therefore it may be possible that by the time your doctor starts the evacuation the medicine may not have started working fully and you could still feel some pain.

The other problem is that both Midazolam and Fentanyl can suppress that part of your brain that controls your breathing. You breathe too slowly and this causes you to have too little oxygen in your blood. This can be dangerous. Because we know that this is a problem that can easily occur we are very careful to monitor your breathing and oxygen saturation (level of oxygen in your blood) and make sure we keep your oxygen saturation at safe levels. However, Midazolam and Fentanyl work for quite a few hours, even after the evacuation is over. It is therefore necessary to keep you in hospital for a few hours to make sure the medications have fully worn off before we can discharge you safely.

There is a medication that may work better. This medication is called Ketamine.
Ketamine has been used for many years as a pain killer and sedative. It is a registered drug that is safe for human use. It has been safely used in both children and adults with great success. Doctors use it quite regularly as pain killer and sedative in cases other than uterine evacuations (for example when realigning a broken bone) and are therefore familiar with it.
It works very well as a pain killer and causes the patient to forget the trauma of the procedure.

Ketamine is different from Midazolam and Fentanyl in that:

- it does not depress your respiratory centre. You continue to breathe normally and therefore your oxygen saturation does not decrease.

- its onset of action is fast (about 1 minute) and nearly the same for every patient.
- it works for a shorter time (10-15minutes) which is enough time for the evacuation but you would awake sooner and therefore be able to be discharged home earlier.

You should know that Ketamine has a few side effects. One of the side effects, or problems, is that you may have strange dreams while asleep or have hallucinations (see or hear things that are not real) when you are in the process of waking up. This can happen in up to 15% of people but mainly if the medication is used in amounts that are much more than we plan to use in this study. We want to use a dosage that is just enough to keep you pain free but not put you to sleep. Then the chance of side effects is much lower.

These side-effects only occur while the Ketamine is still in your body. Once the Ketamine wears off completely any side effects disappear.

The reason we are doing this study is to see if Ketamine works just as well for uterine evacuations as it has been shown to work for other procedures.

What are we doing?
This research will involve giving you Ketamine in the drip, rather than Midazolam and Fentanyl. We will collect information about your womb scrape (for example how easy it was, how much you bled and what your oxygen saturation was).
We will also ask you about how much pain you are feeling during and after the procedure.
Someone will also check how sedated (sleepy) you are after the procedure.

All the findings will be recorded and at the end of the study scientifically analysed to see if Ketamine works as well and safely for evacuations as for other procedures.

Why are we asking you to be part of this study?
We are asking all patients that need a "womb scrape" at Groote Schuur Hospital to take part. This includes 50-80 patients each month.

Do you HAVE TO take part?
No. It is your choice whether to take part or not. Your decision will in no way change the way we treat you in our hospital. If you do not agree to take part you will receive the same medication that we give to all patients needing a "womb scrape" at the moment.
If you agree to participate but change your mind later, you may do so.

This is how the study will happen:
The doctor attending to you has already explained to you that you need your womb evacuated (cleaned). You will be admitted to the ward while waiting for a theatre to become available to do the procedure.

When you get to the operating room, medication will be given to you in your drip. This may be either Fentanyl+Midazolam (the routine medication that we have been giving to all patients) or it may be Ketamine (the research medication). The medication given depends on whether you have chosen to be part of the study and in which group of patients you fall in the study. The first month of the study patients will receive Fentanyl+Midazolam, and in the second month the study patients will receive Ketamine. Should you decide not to be part of the study you will receive the routine Fentanyl+Midazolam mixture.

You are then put into a position that makes it easier for the doctor to do the evacuation. The "womb scrape" is done either by something that looks a little like a thin metal spoon or by suctioning through something like a plastic straw. The procedure usually only takes about 5-10 minutes.

During the procedure a nurse will make sure you are not too sleepy and breathing well. She will also ask you how much pain you are feeling. If the pain killer is not strong enough for you, the doctor may give you some more medication to make you more comfortable. After the evacuation is finished you will again be checked and asked about the pain. This will happen while you are recovering in theatre and later (after about 2 hours) in the ward.

You will then be observed in the ward and discharged by the doctor. This usually happens the next morning.
This ends your participation in the research.

The risks are those of the side-effects of the medication, which as I have explained are very small at the dosages (amount of medication) we are using. The other complication may be that the pain killing effect is not strong enough. This can occur with either the routine Fentayl+Midazolam mixture or the Ketamine. If you are in pain during the procedure the doctor will give you a different or more pain medication to make you more comfortable.

There are no immediate benefits for you during this study. The possible benefit in the future is if we prove that Ketamine is safe and works well, it could be used for all evacuations making it possible for patients to go home much earlier (in 2-4 hours).

Will my identity or personal information be known to others?
The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key. It will not be shared with or given to anyone.

The results of the research may also be made public in a medical journal. No confidential information (anything that may identify you) will be published though.

Will you get paid?
No. No patient participating in this study will receive any form of compensation.

Do you want to take part?
You have the right to choose to take part or not. All your rights will still be respected and you will receive the same standard of care as every patient. We strive to provide excellent care to all our patients and your medical care will in no way suffer if you do not want to participate in the study. We expect that approximately 50-80 women eligible for this study will participate.

PART II: Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant_____

Signature of Participant _____

Date _____

Print name of witness_____

Signature of witness _____

Date _____

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

Clinical Data will be collected for research purposes.
Ketamine may be given for procedural sedation for uterine evacuation.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.
A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____

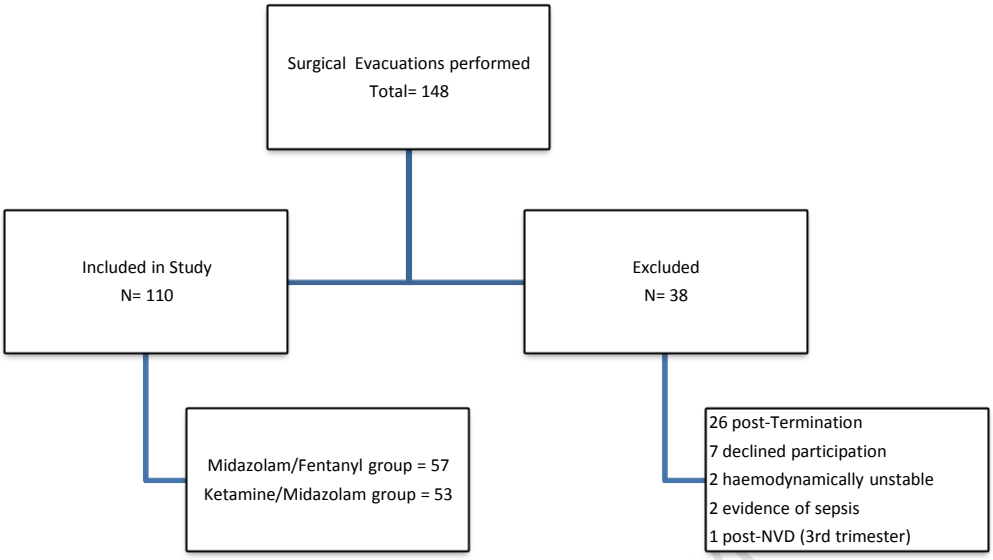

Figure 1 Flow diagram of study participants

Table 1 Characteristics of participants by pain management regimen

		Fentanyl/Midazolam (n= 57)	Ketamine /Midazolam (n=53)	P-value (Chi-squared test of association/Fisher's exact for small numbers)
Diagnosis				
	Spontaneous miscarriage	29	36	
	Missed miscarriage	28	17	0.069
Trimester				
	1st	47	36	
	2nd	10	17	0.077
Surgeon				
	Intern	28	15	
	Registrar/Medical Officer	29	38	0.025
Misoprostol ripening				
	yes	35	25	
	no	22	28	0.134
mechanical cervical dilation required				
	yes	8	5	
	no	49	48	0.56
Procedure time				
	<10min	37	44	
	10-15min	16	6	
	>15min	4	3	0.062
Ease of procedure				
	Easy	53	50	
	Difficult	4	3	1
Curettage				
	Sharp	21	17	
	Suction	36	36	0.599
Blood loss				
	Mild	49	41	
	Moderate	8	12	
	Severe	0	0	0.324

Table 2 Pain and Sedation scores at 3 Intervals (intra-procedural, 10 minutes & 2 hours post-procedure)

Variable	Group	Obs	Mean	[95% Conf. Interval]		Median (IQR)
Pain during	Ketamine	53	3.28	2.41	4.16	2 (0-5)
	Midaz	57	5.93	5.26	6.60	6 (4-8)
Sedation during	Ketamine	53	1.94	1.70	2.19	2 (1-2)
	Midaz	57	1.72	1.50	1.94	2 (1-2)
10 min pain	Ketamine	53	1.68	1.33	2.02	1 (1-3)
	Midaz	57	2.60	2.01	3.18	2 (1-4)
10 min sedation	Ketamine	53	0.77	0.62	0.92	1 (0-1)
	Midaz	57	1.37	1.11	1.62	1 (1-2)
2 hr pain	Ketamine	53	0.43	0.30	0.57	0 (0-1)
	Midaz	57	0.75	0.49	1.02	1 (0-1)
2 hr sedation	Ketamine	53	0.04	-0.02	0.09	0 (0-0)
	Midaz	57	0.51	0.30	0.72	0 (0-1)

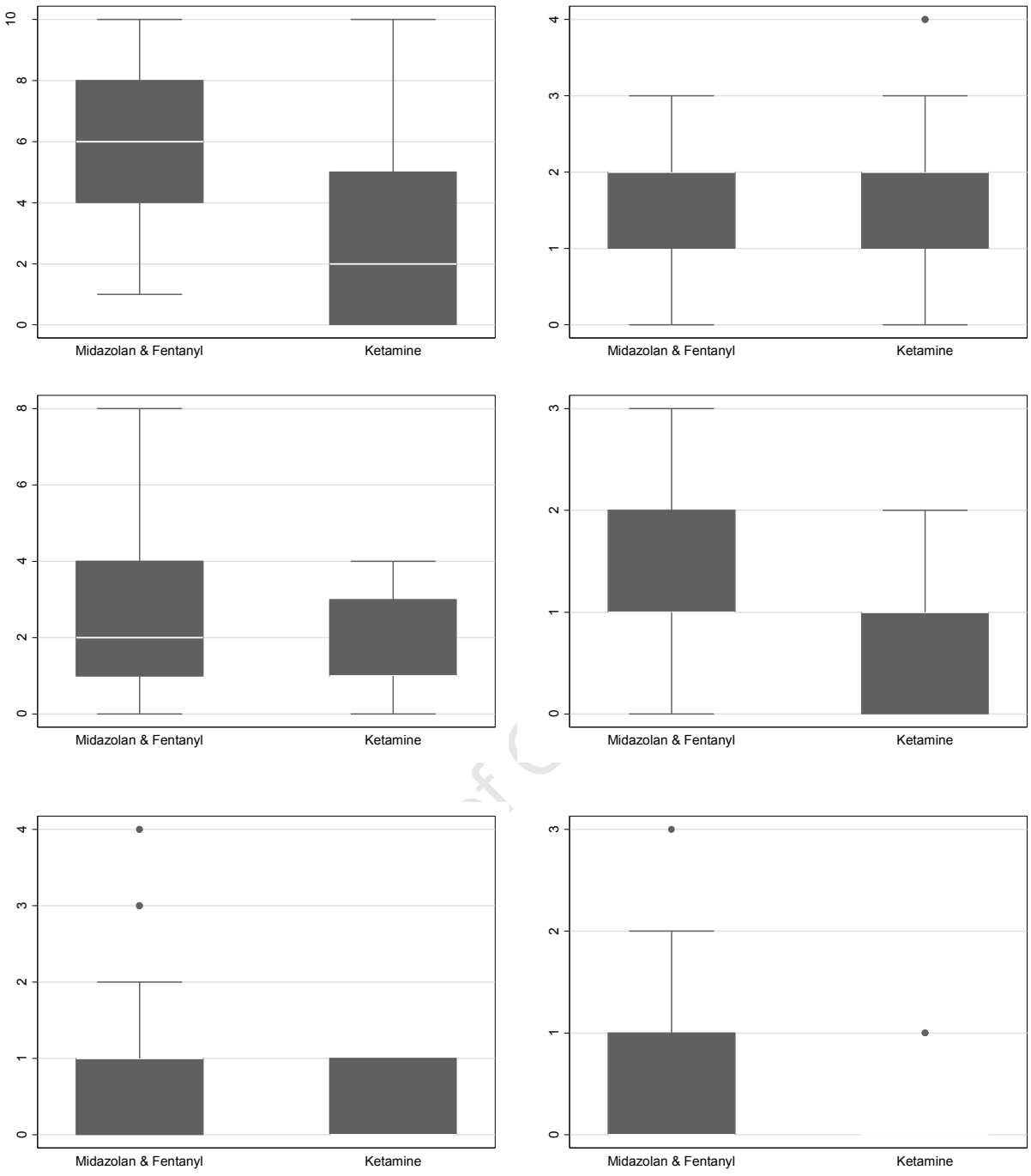

Figure 2 Pain and Sedation scores at time: 0, 10 minutes and 2 hours

Table 3 Comparison of Systolic and Diastolic Blood Pressure pre- and post-procedure for Ketamine and Fentanyl/Midazolam groups

Variable	Group	Obs	Mean	[95% Conf. Interval]		Median (IQR)
SBP Pre	Ketamine	53	125.45	120.65	130.26	121 (114-139)
	Midaz	57	125.51	120.72	130.29	123 (112-138)
DBP Pre	Ketamine	53	65.74	62.09	69.38	64 (54-78)
	Midaz	57	66.40	62.50	70.31	66 (57-76)
SBP Post	Ketamine	53	130.25	124.80	135.69	132 (118-139)
	Midaz	57	121.67	116.18	127.16	119 (106-136)
DBP Post	Ketamine	53	74.28	69.68	78.89	73 (62-86)
	Midaz	57	68.19	63.99	72.40	70 (56-78)
Pulse	Ketamine	53	100.21	95.70	104.72	98 (88-110)
	Midaz	57	94.81	90.67	98.94	96 (85-105)
SATS Low	Ketamine	53	98.17	97.28	99.06	99 (98-99)
	Midaz	57	95.61	94.60	96.63	97 (94-98)

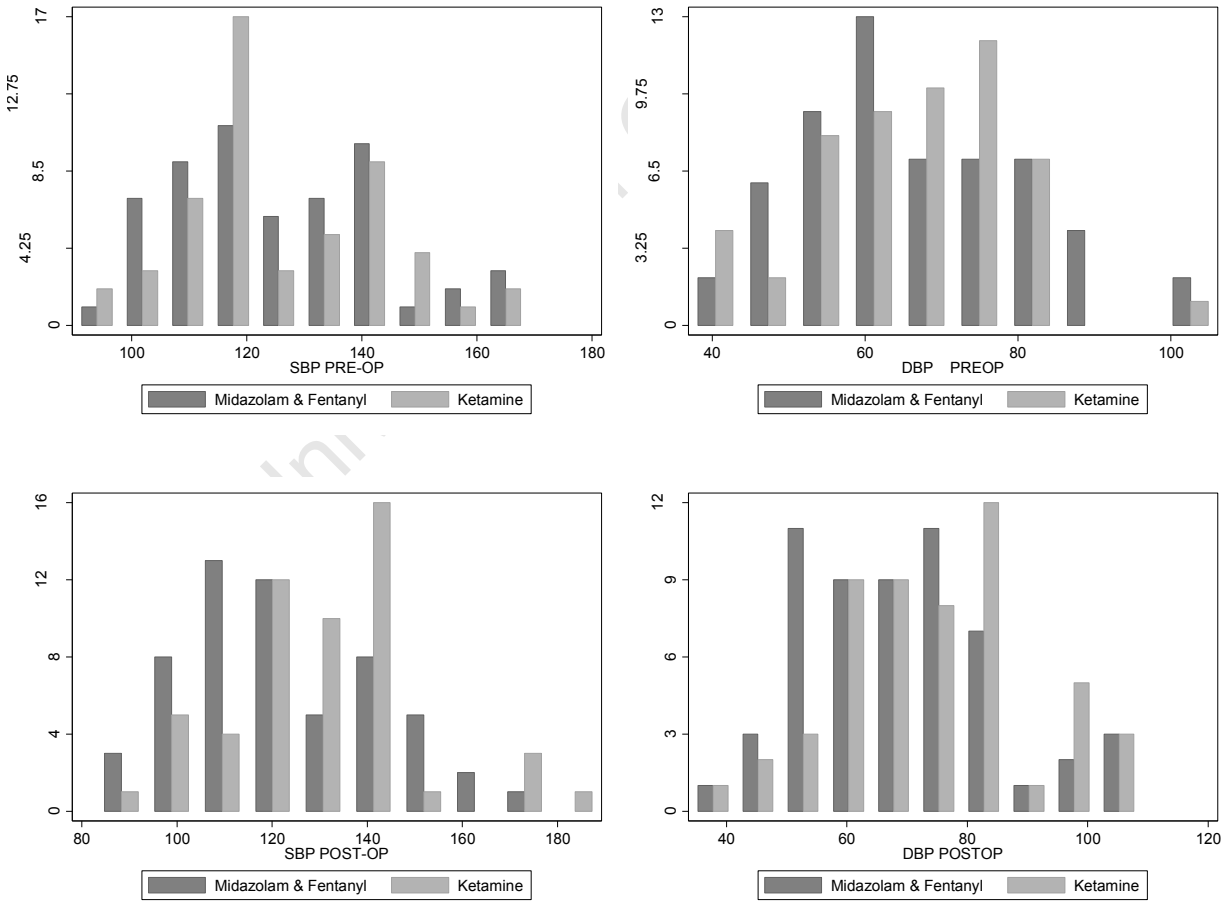

Fig 3 Comparison of Systolic and Diastolic Blood Pressure between groups

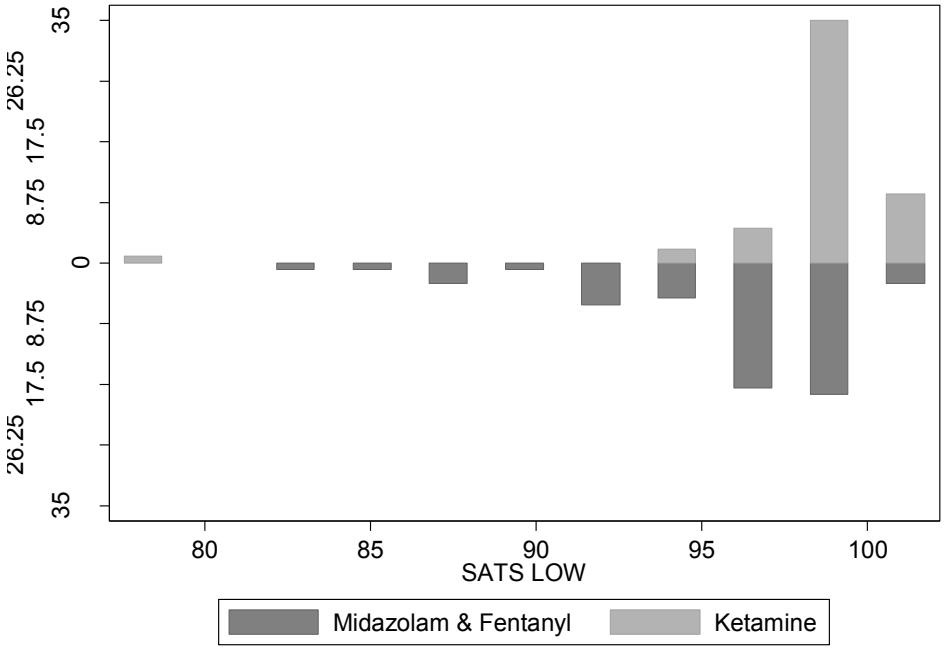

Figure 4 Comparison of Oxygen Saturation between groups

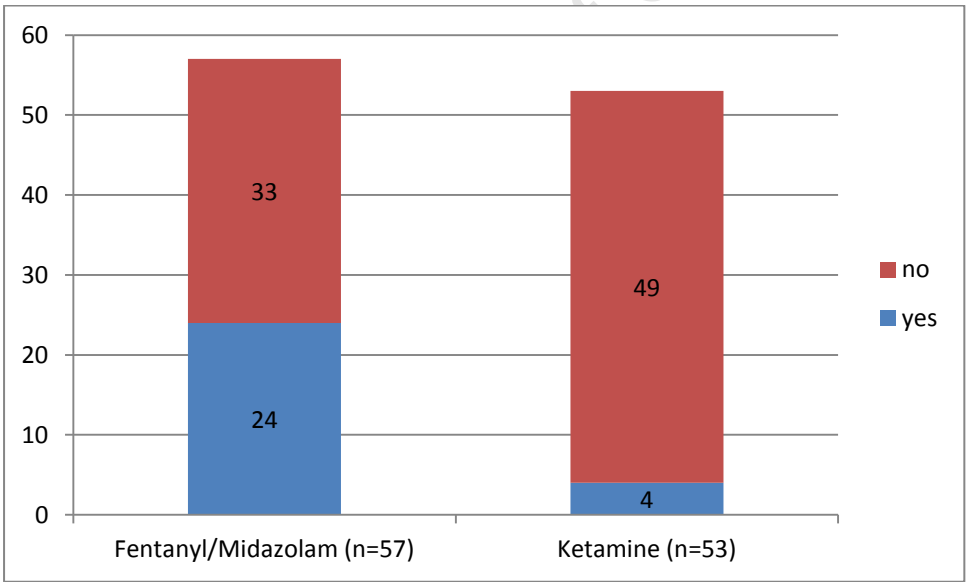

Figure 5 Comparison of requirements for additional analgesia between groups

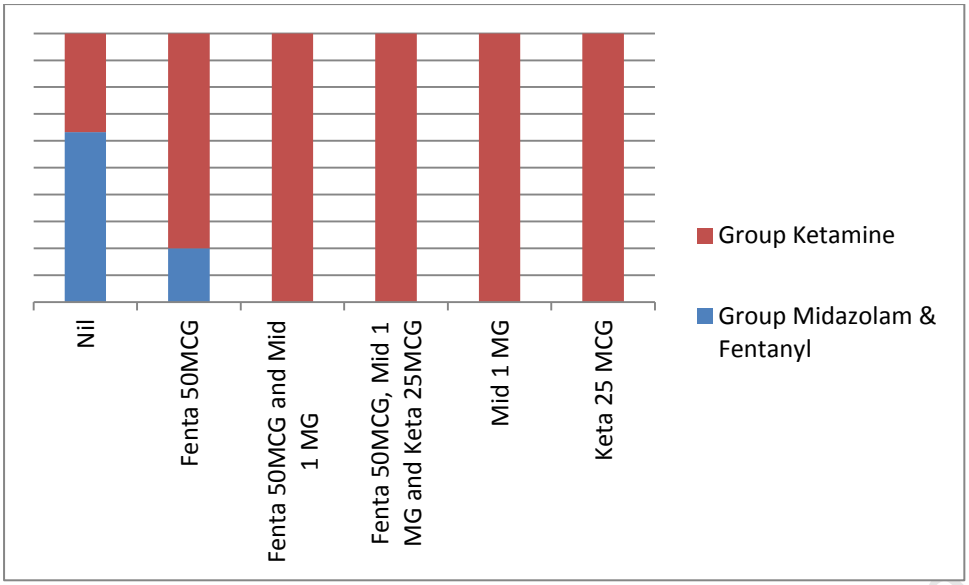

Figure 6 Types of additional analgesia given

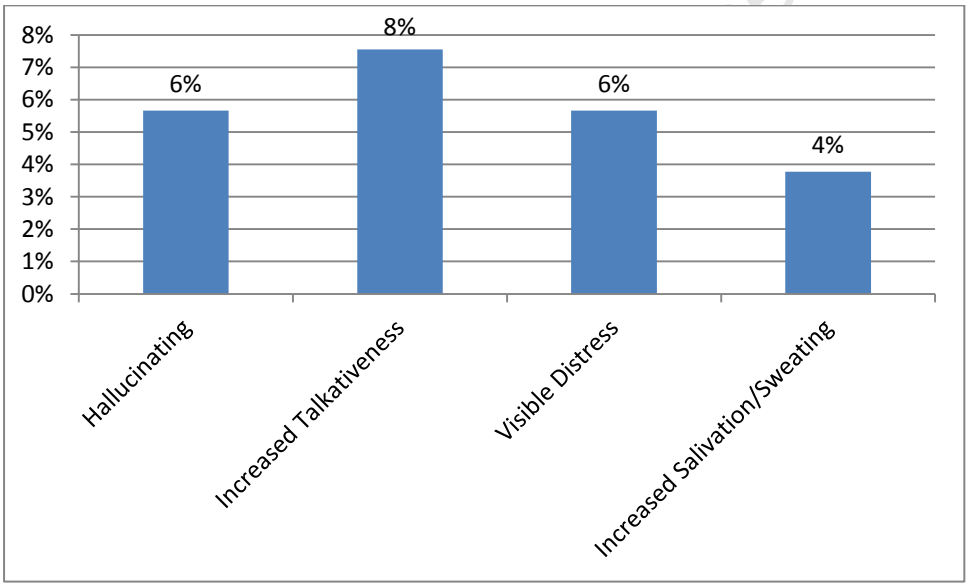

Figure 7 Incidence of ketamine side effects

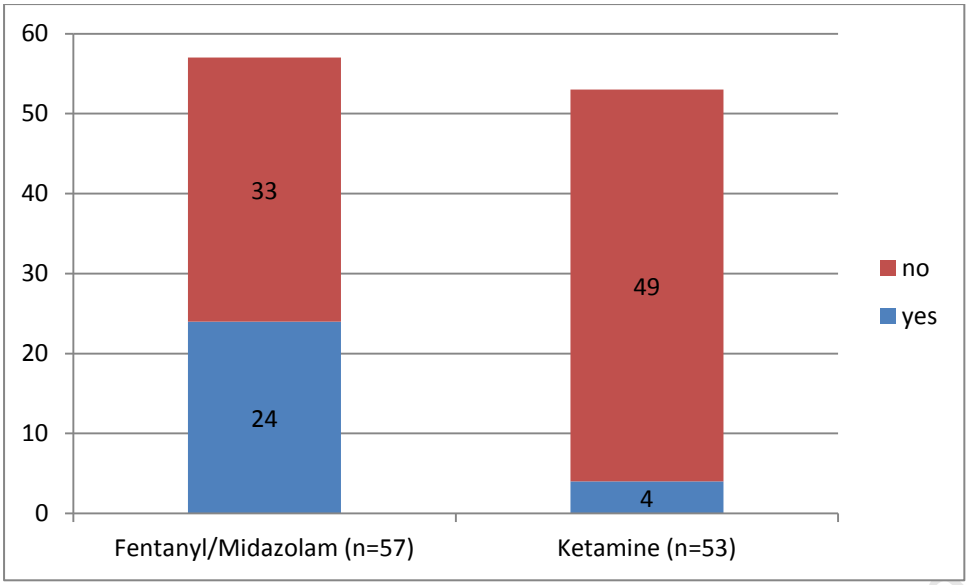

Figure 8 Incidence of recollection of procedure between groups