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**SPINAL ANAESTHESIA FOR BRACHYTHERAPY  
FOR CARCINOMA OF THE CERVIX:  
A COMPARISON OF TWO DOSE REGIMENS OF  
HYPERBARIC BUPIVACAINE**

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## **DECLARATION**

I, Dr Nikolas Jason Haus, hereby declare that the work on which this dissertation is based is my own original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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## **ABSTRACT**

### **Background**

The main purpose of the study was to help establish the best dose regimen of hyperbaric bupivacaine, when combined with intrathecal fentanyl, for spinal anaesthesia for brachytherapy for carcinoma of the cervix. This procedure is performed as a day case at Groote Schuur Hospital.

It was therefore decided to compare what may be considered as a conventional dose of hyperbaric bupivacaine with a lower dose, both combined with fentanyl 15 ug for spinal anaesthesia. The lower dose would hopefully allow for adequate anaesthesia, with less motor block and a shorter time to complete recovery, the latter being the primary outcome measure. This would have a significant advantage for ambulatory surgery.

### **Patients and methods**

The study was a prospective, randomised, double-blinded trial. Ethics approval was sought and granted from the University of Cape Town Human Research Ethics Committee prior to patient enrolment for the study. Written, informed patient consent was given in every case. All patients attending the oncology clinic for brachytherapy for carcinoma of the cervix were assessed for inclusion in the study. Exclusion criteria were a contra-indication to spinal anaesthesia or an unwillingness to take part in the study.

Forty patients were randomized by sealed envelope to receive a dose of either 1 ml of hyperbaric bupivacaine 0.5% (5 mg) vs 1.8 ml hyperbaric bupivacaine (9 mg) both with fentanyl 15 ug, via the L3/4 interspace. Both the patients as well as the anaesthetist recording and collecting the clinical data were blinded to the group allocation.

## Results

The time to achieve hospital discharge criteria was significantly shorter in the Low Dose (LD) group (mean time of 235 [206-264] minutes) versus the High Dose (HD) group (mean time of 280 [263-297] minutes) ( $p < 0.01$ ). Patients in the LD group were also eligible for discharge from the recovery area in a shorter time ( $p < 0.01$ ). Although there was significantly less motor block in the LD group ( $p < 0.001$ ), patient satisfaction regarding motor block was the same in the two groups ( $p = 0.96$ ). There was a trend towards more inadequate (unsatisfactory) spinal blocks in the low dose group ( $p = 0.34$ ).

## Discussion

The trend towards a larger number of patients with failed spinal anaesthesia in the low dose group was a concern, and in an adequately powered study examining quality of analgesia, this could have achieved statistical significance. This trend towards more failed spinal anaesthesia in the low dose group was despite an acceptable median peak sensory level (to cold ethyl chloride spray) of T8 for the required surgery (IQR of T8-T10). This suggests that the quality of surgical anaesthesia for any given procedure cannot be predicted entirely by the dermatomal spread of local anaesthetic (or peak sensory level achieved) as assessed by cold sensitivity.

## Conclusions

Our study suggests that a dose closer to- or equivalent to that of the high dose group may be preferable, to ensure consistent and reliable spinal anaesthesia in this patient population presenting for ambulatory surgery. More studies are needed to find the best dose regimen for spinal anaesthesia for this specific group of patients.

## **DISSERTATION IN PUBLICATION-READY FORMAT**

### **Part A: The Research Protocol**

Spinal anaesthesia for brachytherapy for carcinoma of the cervix: a comparison of two dose regimens of hyperbaric bupivacaine

**N Haus, RA Dyer**

#### **Introduction**

Spinal anaesthesia (SA) can be suitably performed for a variety of outpatient procedures. Time taken for fitness to discharge home from hospital is an important consideration, as it impacts not only on patient satisfaction, but also on human and financial resource constraints within a hospital. The main goal is to use the lowest dose of local anaesthetic for adequate anaesthesia. This allows for the shortest recovery time for ambulatory surgery. [1] This study was undertaken to establish the best regimen for spinal anaesthesia for brachytherapy in carcinoma of the cervix. Patients undergo insertion of an intra-cervical stent which is 8 mm in diameter. This stent facilitates the subsequent introduction of an applicator necessary to perform brachytherapy (immediate-proximity radiotherapy). The insertion of the intra-cervical stent is especially painful as the cervical anatomy is distorted to varying degrees by malignant tumour. The procedure also involves probing (“sounding”) of the fundus of the uterus. Therefore the height of the spinal block should extend at least to the T10 level and include all the lumbar and sacral dermatomes.

The duration of the procedure (and hence required duration of anaesthesia) may be greater than 1 hour and even as long as 80 minutes in some cases, so that the short duration of action of lidocaine makes it unsuitable. Furthermore, concerns regarding a significant incidence of transient neurological deficits after lidocaine spinal anaesthesia have resulted in a preference for bupivacaine, despite its long duration of action.[2] Hyperbaric bupivacaine, administered at the L3-4 level, was considered more appropriate than dextrose - free bupivacaine as it allows for more reliable spread

within the cerebro-spinal fluid (CSF) in the supine position, in order to block the required dermatomal levels (T10-S4).[3-5] In addition, plain bupivacaine may be associated with a greater duration of motor block than the hyperbaric formulation. [6]

When combined with a small dose of short-acting lipophilic opioid such as fentanyl, sensory block is intensified without a significant increase in side-effects. This allows a reduction in bupivacaine dose and hence less motor blockade. [7] Although fentanyl may cause a minor increase in the time taken for regression of sensory block, a small dose does not cause urinary retention or significantly prolong the time taken to achieve discharge criteria. [8]

It was therefore decided to compare a conventional dose of bupivacaine and fentanyl for SA, with a lower dose regimen, the composition of which would allow for adequate anaesthesia and a shorter time to complete recovery. The primary outcome variable will be the time taken to achieve criteria for hospital discharge. Secondary outcomes will include patient satisfaction scores, based upon quality of anaesthesia and motor block (appendix C). The findings should contribute to the establishment of an anaesthesia management protocol for this specific procedure.

### **Patients and methods**

This proposed study is a prospective, randomized, double-blinded trial. After approval from the Faculty of Health Sciences Human Ethics Committee of the University of Cape Town, informed consent will be obtained in the patient's first language, inside a quiet, private clinic room during the consultation with the consultant radiotherapist Dr van Wyk on the day prior to the brachytherapy (see appendix D for the English version, compiled according to the Standard Operating Procedures published by the UCT HREC). All patients attending the radiotherapy clinic scheduled for brachytherapy for carcinoma of the cervix will be included in the enrolment process. The only exclusion criteria will be a contra-indication to spinal anaesthesia, or unwillingness from the patient to take part in the study.

Regarding the informed consent process, an interpreter will be available to assist with any difficulties of interpretation or technical medical terms. Once signed, 2 copies of



the original document will be made. The original will be placed in the trial records and one copy placed in the patient's medical records. The other copy will be given to the patient for reference. The "Consort Statement (2010) Flow Diagram" (see appendices) will be used in order to help lend credibility to the study and allow us to reflect on the processes of enrolment, allocation, study intervention and analysis.

Forty patients will be randomised by sealed envelope to receive a subarachnoid dose of either 1 ml of hyperbaric bupivacaine 0.5% (5mg) plus 15 µg fentanyl (Group LD, n=20), or 1.8 ml hyperbaric bupivacaine 0.5% (9 mg) plus 15 µg fentanyl (Group SD, n=20), via the L3/4 interspace, for brachytherapy for carcinoma of the cervix. The anaesthetist collecting the data during the procedure will not be the anaesthetist who performed the spinal anaesthetic, so that blinding is ensured.

On the day of surgery, patients will receive no pre-medication. An 18 gauge cannula will be inserted for intravenous (IV) access. Standard monitoring (pulse oximeter, non-invasive blood pressure and ECG) will be applied, prior to sitting the patient upright for SA. Baseline blood pressure will be calculated as the mean of two systolic blood pressures measured at rest during the 5 minutes prior to spinal anaesthesia. SA will be administered in the sitting position, via the L3/4 interspace, using a 25 gauge Whitacre spinal needle. The dose will be injected over 10-15 seconds. The patient will remain sitting for 2 minutes after the injection is complete and then be re-positioned to lie supine at first, followed by the lithotomy position for the duration of the procedure. The anaesthetist performing the postoperative assessment will be blinded to the group allocation. Intravenous midazolam 0.025 mg/kg (maximum of 2 mg) will be administered, unless the patient is over 65 years of age. The investigators believe that this relatively small dose of midazolam is unlikely to have a significant effect on memory recall and therefore not bias the results of the patient questionnaire.

Lactated Ringer's solution 500 ml will be used for co-loading. Blood pressure will be measured every 3 minutes after induction of anaesthesia. A decrease in systolic blood pressure to less than 80% of the baseline value will be treated with 5 mg ephedrine IV.

The dermatomal level of the sensory block will be measured using cold sensitivity to ethyl chloride spray, but not assessed using light touch. In order to reduce possible inter-observer variability and increase clinical precision (or reproducibility) when assessing dermatomal level of block, the following method will be employed by every clinician collecting the data. The level of the block will be assessed starting from the dermatomes above the level of the block. The level at which any decrease in cold sensitivity is first reported will be regarded as the dermatomal level of sensory block. The level of sensory block will initially be assessed every 5 minutes until the height of the block has remained the same for 3 consecutive readings, i.e. until the sensory block is fully established. It will then be measured every 10 minutes until there has been a regression in sensory block of 2 dermatomes, and then every 15 minutes until all of the hospital discharge criteria are met. Time taken to eligibility for discharge from the theatre recovery area (sensory level T10 or lower, together with cardiovascular stability) will be noted.

Planned management in the case of failed or inadequate SA: if no sensory block is achieved, the patient will receive general anaesthesia. If there is evidence that an adequate sensory block has been achieved, the patient will be asked to grade their level of discomfort after initiation of the surgical procedure. The sensation experienced by the patient during the procedure will be assessed and categorized into one of 4 groups (appendix A). If the patient falls into group 1-3, the quality of pain control will be deemed adequate and the surgical procedure will continue without giving any supplemental analgesia or converting to a general anaesthetic.

If, however, the patient is experiencing pain and requests additional pain relief upon being offered it, or is in obvious need of additional analgesia, the patient will be allocated to group 4 and the SA regarded as inadequate for the planned surgical procedure. The attending anaesthetist will then give additional analgesia to supplement SA. This will consist either of intravenous fentanyl or conversion to general anaesthesia.

### **Data collection and entry**

We will initially use Microsoft Excel to record the data we have collected in a simple

format. EpiData Analysis and/or *Stata* (Stata/IC 12.1, StataCorp, LP, 4905 Lakeway Drive, College Station, TX 77845, USA) statistical programs will then be used to further analyse the data.

### **Statistical analysis**

The Null hypothesis is that there is no difference in time to eligibility for hospital discharge following injection of either of the spinal solutions.

#### *Calculating sample size*

The following time sequences are expected, based upon literature review. [1, 7, 8] Time taken for eligibility for hospital discharge in the lower dose (LD) group (Mean [SD]) = 195 [50] minutes, and in the higher dose group 275 [50] minutes.

Using the means calculated from clinical data collected before the study (called our “pilot study”), which were 195 and 250 minutes for the 2 groups respectively, with a standard deviation of 50 minutes, the statistical program *Stata* (Stata/IC 12.1, StataCorp, LP, 4905 Lakeway Drive, College Station, TX 77845, USA) calculated that 18 patients would be needed in each group for a power of 90%. This was confirmed by a sample size and analysis statement from *PASS (Power analysis and sample size 2008)* which suggests that Group sample sizes of 18 and 18 achieve 91% power to detect a difference of -55.0 between the null hypothesis that both group means are 195 minutes and the alternative hypothesis that the mean of group 2 is 250 minutes, with known group standard deviations of 50 minutes and with a significance level (alpha) of 0.05 using a two-sided Mann-Whitney test. We have therefore decided to enrol 20 patients in each group, to decrease the possibility of a beta-error.

#### *Data analysis*

Histograms and/or box-and-whisker plots will be used to depict numerical data, and frequency tables for categorical data. The “Shapiro-Wilk” test will indicate whether the numerical data are normally distributed or not.

The following statistical tests will be employed:

i) For numerical data

- Statistical analysis of the primary outcome variable, namely time taken to achieve criteria for hospital discharge, will employ the Student's t-test, or otherwise Mann-Whitney U-test if appropriate. All other time comparisons will employ ANOVA for repeated measures
- Group demographic data will be analysed separately using the Student's t-test, except for the ASA rating which will employ the Mann-Whitney U-test
- Inter-group differences in dermatomal levels of sensory block (including peak dermatomal level achieved) will be analysed using the Mann-Whitney U-test, as this data does not follow a normal distribution

ii) For categorical data:

- Quality of analgesia (appendix A) will be grouped into either satisfactory anaesthesia (scores 1-3) or unsatisfactory anaesthesia (a score of 4). A Fisher's exact test will then be employed to detect any inter-group differences
- The degree of motor block (according to the modified Bromage scale, appendix B) will be compared using the Chi-squared test
- To detect any possible differences between the 2 groups regarding the 3 questions being asked in the patient satisfaction questionnaire (appendix C), we will employ the Mann-Whitney U-test to compare each variable separately

## **Results**

The primary outcome variable will be the time taken to achieve criteria for discharge from hospital, i.e. all of the following to be achieved:

- 1) Regression of sensory block to S2 sensory level
- 2) Ability to walk unaided
- 3) Ability to void unaided

Secondary outcomes will include a patient satisfaction score. A visual analogue score will be used to assess satisfaction with quality of anaesthesia and motor block. The following data will be collected for comparison:

- The highest (peak) dermatomal level of sensory blockade achieved
- Time taken to reach this peak sensory level
- Sensation felt by the patient during the procedure (appendix A)
- Modified Bromage Scale of motor blockade at the time of peak sensory blockade (appendix B)
- Time to eligibility for discharge from theatre recovery area
- Time to 2-segment regression of sensory block
- Time taken for sensory block to regress to dermatomal level S2
- Time taken to walk unaided
- Time taken to void unaided
- Side effects:
  - nausea and/or vomiting
  - pruritus
  - light-headedness or dizziness
- Blood pressure (baseline, immediately prior to spinal anaesthesia, then at 2 minutes, at 5 minutes, and every 5 minutes thereafter until 60 minutes after induction of spinal anaesthesia)
- Vasopressor requirement

Follow up will be done after one week by the radiotherapist, who will inquire about post-operative headache or radicular pain (i.e. pain not related to the operative site, but in the buttocks, thighs or lower limbs) which may be as a result of the spinal anaesthetic given. Patients will be encouraged to report any symptoms experienced in the interim to the radiotherapist or the anaesthetist.

### **Addendum: “Pilot study”**

During 2008 – 2009 the principal investigator undertook a small pilot study, as part of routine clinical practice, to assess the feasibility of the study. In summary, data was collected on 16 female patients between 23-78 years of age, ASA grades 1-3. Clinical outcomes were assessed using doses of between 0.5-1.8 ml of hyperbaric bupivacaine 0.5%, combined with either 15 or 20 µg of fentanyl. No patients required conversion to general anaesthesia, and none required IV supplementation of analgesia. Some patients who received less than 1.0 ml of hyperbaric bupivacaine 0.5% with fentanyl 15 µg experienced some discomfort, but declined supplementary analgesia when offered. Time taken for regression of sensory block to level S2 varied between 190 – 200 min for 1 ml of hyperbaric bupivacaine 0.5% and between 240 – 250 min for patients receiving 1.8 ml of hyperbaric bupivacaine 0.5%.

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## **Appendices**

### **A: Quality of analgesia**

- 1- Complete absence of any sensation
- 2- Sensation of motion only
- 3- Mild discomfort, but declining offer for additional analgesia
- 4- Patient requests additional analgesia / in obvious need of additional analgesia

### **B: Modified Bromage scale [9]**

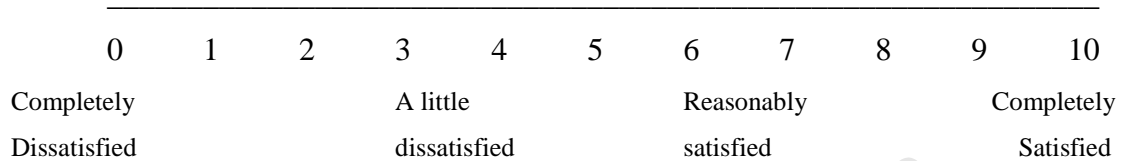
- 0 = Full leg movement (full flexion of knees and ankles)
- 1 = Inability to raise extended legs, just able to flex knees, full ankle flexion
- 2 = Inability to flex knees, some flexion of ankles possible
- 3 = No movement possible (unable to move legs or feet)

**C: Patient questionnaire**

**(VAS - completed on the day of surgery, once eligible for hospital discharge)**

1) How satisfied are you, overall, with the spinal anaesthetic you received for your surgical procedure?

(Mark the spot on the line below that best describes your experience)



If you marked a value below 5, please say why: \_\_\_\_\_

2) How satisfied are you with the amount of pain/discomfort you felt during the surgical procedure?

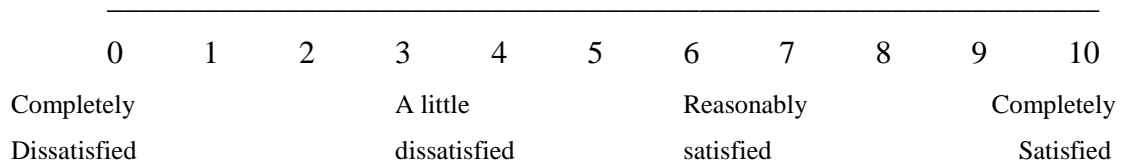
(Mark the spot on the line below that best describes your experience)



If you marked a value below 5, please say why: \_\_\_\_\_

3) How satisfied are you with the amount of weakness in your legs experienced during and after the procedure?

(Mark the spot on the line below that best describes your experience)



If you marked a value below 5, please say why: \_\_\_\_\_



## **Appendix D: Patient Information and Informed Consent**

**Study Title:** Spinal anaesthesia for brachytherapy for carcinoma of the cervix: a comparison of two dose regimens of hyperbaric bupivacaine

Principal Investigators: N Haus, RA Dyer (Contact no. 021 404 5001/3)

UCT Human Research Ethics Committee (HREC) Ref no: 421/2010

Patient Folder no: Patient Study no:

### **Introduction**

You are invited to take part in this study. Before you decide whether or not to take part in the study, you should fully understand what is involved. After reading and having had this information properly explained to you, if you have anything you would like to know or questions you would like to ask, please feel free to discuss these with either the doctor taking you through this consent process, or the main researchers mentioned above.

### **Why is this study being performed?**

We have decided to compare 2 different doses of a local anaesthetic called bupivacaine. This local anaesthetic is given to you when the anaesthetic doctor gives you a spinal anaesthetic. We want to see if the one dose is better than the other dose, for patients who are having the same surgical procedure as you are under spinal anaesthetic.

### **Why are you being asked to take part?**

We are asking all women who are attending this clinic, who are having the same surgical procedure as you are under spinal anaesthetic, to take part. Every woman who agrees to take part in the study will receive either the one dose, or the other dose of local anaesthetic that is part of the spinal injection. If you agree to take part in the study, the dose that you receive will be randomly decided based on what appears in a

sealed envelope, which will be opened immediately before your anaesthetic. Only the doctor who is doing the spinal anaesthetic will know which dose was given.

### **How long will I personally be involved?**

Almost all of the information that we need for our study will be collected on the day of your surgical procedure, both during the procedure and for a few hours immediately after your procedure until you are ready to go home. During your next follow up clinic visit, we will ask you about any possible side effects of the spinal anaesthetic, which are very uncommon.

### **What anaesthetic management will I receive?**

If it is safe to do so, you will have a spinal anaesthetic, which is our routine for this procedure. The anaesthetic doctor doing your anaesthetic will inform you about the actual anaesthetic. He/she will explain to you how the anaesthetic is performed. Then you will be able to give your consent for the spinal anaesthetic. This is part of normal medical practice and will take place anyway, whether you take part in the study or not.

What is specific to the study is that we are collecting information during the time that you are under the effects of the spinal anaesthetic. For example, we will measure your blood pressure, assess how good your level of pain control is, the amount of weakness you have in your legs, as well as how long it takes for you to recover from the effects of the spinal anaesthetic.

### **What will happen if I decide not to take part in the study?**

You do not have to take part in the study. If you decide not to take part, you will still get the same quality of care for your specific illness, both now and in the future. You will still get a spinal anaesthetic if safe to do so. You may decide to stop being involved at any time during the study.

**What are the risks to you?**

The risks to you are the same as for any spinal anaesthetic and will be explained to you by the doctor doing the anaesthetic. Should you have any discomfort during the surgical procedure, the anaesthetic doctor will offer you additional medicine. In the very unlikely event that you have severe discomfort, you may have to have a general anaesthetic for the procedure in addition to having the spinal anaesthetic.

**Are there benefits to you for being in this study?**

There are no extra benefits to you for being involved in this study. The care and attention you will receive whilst having the surgical procedure are part of routine medical practice. There are no financial benefits to you for being involved in this study.

**Privacy/confidentiality**

The personal information we collect from those who take part in the study will only be shared among the doctors who are involved in the study. The study may be published in a medical journal and the results of the group as a whole shared with those who read it. However, there will be no way for the general public to know the identity of those who took part in the study. These few doctors who will be responsible for looking at the results are the “principal investigators” mentioned at the start of this information document. It is also important that the Human Research Ethics Committee (HREC) of the University of Cape Town is able to have access to the results of the study. They do so in relation to their regulatory duties which seek to act in your favour. Be assured that no blood samples will be taken from you during the study for the purposes of tests.

I hereby confirm that the doctor who has signed below has informed me about the nature, conduct, benefits and risks of this clinical trial. I have also received, read and understood this written “**PATIENT INFORMATION AND INFORMED CONSENT**” form. I have had enough opportunity to ask questions and I agree to take part in this study.

\_\_\_\_\_

Name and Signature of Adult Participant

\_\_\_\_\_

Date

\_\_\_\_\_

Name and Signature of Person Obtaining Consent

\_\_\_\_\_

Date

\_\_\_\_\_

Name and Signature of Witness/Interpreter  
(Only necessary if an interpreter was used)

\_\_\_\_\_

Date

University of Cape Town

## **Part B:        STRUCTURED LITERATURE REVIEW**

### **a) Objectives of Literature Review**

The purpose of this literature review, conducted before drafting the research proposal, was to educate and hence guide myself regarding the rationale for and conduct of the study. My overall aim was to find the most suitable dose regimen for spinal anaesthesia for day-stay brachytherapy for carcinoma of the cervix at Groote Schuur Hospital.

### **b) Literature search strategy**

The initial search was done during the second half of 2008 using 'PubMed', a recognized search portal for medical journal articles. Medical subject headings (key words) used were "low" and "dose" and "spinal" and "anaesthesia". Together they found 514 results. Adding the search terms "ambulatory" or "day case" to the above four terms separately yielded a total of only 42 and 14 results respectively. To avoid missing important references on the subject, I manually filtered through all 514 initial results by reading their titles and occasionally the abstracts as well, choosing 66 articles thought to be potentially relevant to the subject. After reading the abstracts of these 66 articles, it was only the 33 articles referenced below that were thought to be applicable to our study.

I was most interested in studies comparing the various types and doses of local anaesthetics available for spinal anaesthesia, as well as the variety of drugs used as additives in spinal solutions. Literature relevant to design methodology was also viewed in order to give necessary guidance regarding the conduct of the study.

Studies that were excluded were those involving children and those not exclusively related to spinal anaesthesia, i.e. either epidural or combined spinal-epidural anaesthesia. Those involving pregnant patients, for either labour analgesia or spinal anaesthesia for Caesarean section, were largely disregarded because the conclusions thereof cannot logically be applied to the non-pregnant patient due to the physiological changes that accompany pregnancy. Other studies that were not thought

suitable were those describing selective, unilateral spinal anaesthesia, a technique not applicable to our study.

### **c) Quality criteria**

Those articles found to be most useful were good reviews on the subject of low dose spinal anaesthesia and well-designed prospective, randomised controlled trials comparing different local anaesthetics, their doses and additives for spinal anaesthesia for day-stay (ambulatory) surgery.

### **d) Summary and interpretation of literature (implications for research)**

Spinal Anaesthesia (SA) can be suitably performed for a variety of day-stay (ambulatory) surgical procedures. [1-2] The time taken for recovery to allow discharge home from hospital is an important consideration, as it impacts not only on patient satisfaction, but also on human and financial resource constraints within a hospital. As a reasonable alternative to general anaesthesia, spinal anaesthesia should provide reliable anaesthesia and there should be rapid recovery with few side effects. This necessitates the rational use of local anaesthetics and appropriate use of additives for spinal solutions, tailored specifically to the nature (site) and duration of the intended surgery. [1-3] It is therefore vital to understand the factors that influence the intrathecal spread of local anaesthetics, in order to choose the most appropriate drug combination and dose regimen for the required surgery. [2]

#### Choice of local anaesthetic

Many local anaesthetics have been successfully used for day case surgery, each with their respective advantages and disadvantages. Lidocaine was widely used for spinal anaesthesia from 1948 until the mid – 1990's. However, in the mid – 1990's serious concerns were raised regarding its safety for sub-arachnoid administration due to various case reports of transient neurological symptoms (TNS) and even permanent neurological injury on occasion. Although the short duration of action makes it rather suitable for ambulatory surgery, concerns regarding its safety have meant that alternative local anaesthetic agents are being preferred for use in this setting. [4-8]

Certainly, studies showed that there was a much higher incidence of transient radicular symptoms after use of lidocaine, when compared to bupivacaine, for spinal anaesthesia. It was found that this statistically significant difference was not dependent on the baricity of the lidocaine either and was a problem even at the lowest possible concentrations used in clinical practice i.e. it was a specific drug effect. [4-8]

Recently there has been renewed interest in using the “older” local anaesthetics (first used intrathecally in the 1950-1970’s), for spinal anaesthesia in the day case setting. The short-acting drugs articaine and chlorprocaine, as well as prilocaine with its intermediate duration of action, have all been used successfully and are all thought to cause less TNS than lidocaine. [5-6] Mepivacaine has also been associated with TNS following intrathecal use. [9]

Prilocaine may have significant advantages over bupivacaine for ambulatory surgery. In a recent study published in 2011 low dose prilocaine (20 mg) was compared to low dose plain bupivacaine (7.5 mg), both combined with fentanyl 20 ug, for spinal anaesthesia for ambulatory arthroscopic surgery of the knee. The prilocaine group had a shorter duration of motor block, faster regression of sensory block and less clinically significant decreases in arterial blood pressure, all of these outcomes reaching statistical significance. [10]

Various studies have investigated the use of ropivacaine for spinal anaesthesia and its potential advantage over bupivacaine for ambulatory surgery in terms of the amount of motor blockade encountered. Some authors initially thought that ropivacaine had a similar analgesic efficacy and yet a lesser degree of motor block when compared to the same concentration of bupivacaine. [11] In a well-conducted study designed to evaluate the relative potency and dose-response characteristics of ropivacaine, it was shown to have about half the analgesic potency of bupivacaine and at equipotent doses a similar degree of motor block. [12] Ropivacaine holds no significant advantage over bupivacaine for spinal anaesthesia for day-stay surgery. [12-13]

Levobupivacaine is a suitable alternative to bupivacaine when used for low dose spinal anaesthesia for day-stay surgery, being associated with less motor block as well as a longer duration of sensory block. [14]

The use of drugs at any given institution depends on various organisational and local traditional factors. At Groote Schuur Hospital the local anaesthetics lidocaine and bupivacaine are freely available. We favoured bupivacaine for spinal anaesthesia over lidocaine, due to the procedural requirement for at least an hour of anaesthesia, as well as the known better risk profile of bupivacaine in terms of transient neurological symptoms.

#### Baricity of chosen local anaesthetic

Hyperbaric bupivacaine was preferred to plain bupivacaine, due to its more consistent and reliable subarachnoid spread, as well as having a relatively shorter duration of complete motor blockade. [15-18] When considering the spread of bupivacaine in the sub-arachnoid space, the addition of dextrose to the local anaesthetic makes the solution more dense as well as more viscous, which leads to a more definite and consistently reliable spread (as compared to the dextrose-free solution) when the patient is in the supine position. [15]

Knowledge of the fact that the spread of hyperbaric bupivacaine in the cerebro-spinal fluid (CSF) is affected by patient positioning during the first 20 – 30 minutes after injection (as the solution tends to “fall” under the influence of gravity) means that the clinician is able to use this to their advantage by intentional patient positioning immediately after injection of the solution. In our study, for example, by keeping the patient sitting for a duration of 2 minutes after the injection of hyperbaric bupivacaine into the sub-arachnoid space, the clinician will ensure that the bupivacaine will at first descend into and “bathe” the lower lumbar and sacral nerve roots. Thereafter, placing the patient supine and then almost immediately in the lithotomy position (for the remaining duration of the procedure), the hyperbaric bupivacaine will spread (in a more reliable and consistent manner than “plain” bupivacaine) under the influence of gravity, from the point of injection to include not only the sacral, but also the lumbar and lower thoracic nerve roots.

A study examining the effect of baricity on spinal anaesthesia using bupivacaine showed that the hyperbaric solutions produced a greater cephalad spread and yet the baricity did not impact the duration of the block, i.e. adding dextrose had the



beneficial effect of increasing the “height” (dermatomal level of anaesthesia) of the sensory block without increasing its duration. [16] Another study designed to investigate the effect of glucose concentration on the intrathecal spread of 0.5% bupivacaine confirmed these findings and showed that the average maximum extent (or height) of sensory block was significantly higher with 8% glucose as compared to either 0.83% or 0.33% glucose. [17]

Furthermore, in a double-blind study of motor blockade in the lower limbs, comparing the same dose of either hyperbaric or glucose-free bupivacaine 0.5%, it was found that the glucose-free solution caused complete motor block of significantly longer duration. [18] This would be an unwanted effect in our study as it would supposedly lead to decreased patient satisfaction.

It is for these reasons that hyperbaric bupivacaine was considered a better choice than plain or dextrose-free bupivacaine (the latter in fact becomes hypobaric at body temperature, when injected intrathecally) for our study population undergoing this specific procedure.

The minimum effective anaesthetic concentration (MEAC) of bupivacaine for spinal anaesthesia has been calculated. MEAC is defined as the median effective concentration at which a spinal anaesthetic produces surgically equivalent anaesthesia within 20 minutes of administration in 50% of human subjects. In healthy volunteers the MEAC of hyperbaric bupivacaine for spinal anaesthesia up to dermatomal level T12 using pin-prick sensation, was 0.43% (95% confidence interval 0.24-0.62) when 10 mg was administered. [19]

#### Additives to the local anaesthetic

Many drugs have been investigated as additives to local anaesthetics for intrathecal use, with the aim of intensifying analgesia without causing any unwanted effects like prolonging recovery. This allows a lower dose of local anaesthetic to be used and hence hasten complete recovery from spinal anaesthesia, an advantage in ambulatory surgery. It also lends itself towards more cardiovascular stability.

Although adding clonidine 15-30 ug to hyperbaric bupivacaine 5 mg for intrathecal use improved analgesic quality, it was also associated with an increase in duration for complete regression of motor block as well as time to spontaneous voiding. [20]

Another study compared the effects of low dose clonidine and dexmedetomidine on bupivacaine-induced spinal anaesthesia. Dexmedetomidine 3 ug and clonidine 30 ug caused a similar increase in the duration of both sensory and motor block. [21]

Adding magnesium sulphate 50 mg to intrathecal bupivacaine and fentanyl for spinal anaesthesia for ambulatory knee arthroscopy was not advantageous either because it also prolongs time to ambulation without significantly decreasing analgesic consumption in the first 24 hours after surgery. [22]

Ketamine has also been successfully used as an additive to bupivacaine for spinal anaesthesia. In a study comparing bupivacaine 10 mg to bupivacaine 7.5 mg with S(+) ketamine 0.1 mg for spinal anaesthesia for prostate surgery in the elderly, this combination of S(+) ketamine and low dose bupivacaine resulted in a shorter onset time for both motor and sensory block, a shorter duration of action and less motor blockade. [23] In this regard the S(+) isomer of ketamine acts as a potent analgesic and has a similar clinical effect as the opiates. A benefit to using ketamine as an additive to local anaesthetics for spinal anaesthesia is that it has the ability to maintain cardiovascular stability relatively well. [24]

The use of intrathecal opioids can enhance analgesia allowing for a lower dose of local anaesthetic to be used. Amongst the short-acting opiates that have been investigated for intrathecal use, fentanyl is perhaps the most widely studied and most commonly used clinically. A study looking at the value of adding fentanyl 25 ug to a low dose of bupivacaine (4 mg) for spinal anaesthesia for trans-urethral prostatectomy compared this group of patients to those receiving a conventional dose of plain bupivacaine 7.5 mg alone. The fentanyl-bupivacaine combination resulted in satisfactory analgesia as well as having the benefits of a lesser degree and duration of motor block, less hypotension and shivering. [25]

Some clinicians believe that sufentanil is just as good, if not better than fentanyl in terms of quality of sensory block produced. The two short-acting opiates were

compared to each other, when combined with low dose bupivacaine (4 mg) for spinal anaesthesia for trans-urethral prostatectomy. Those who received sufentanil 5 ug had a higher peak level of sensory block and less requirement for perioperative analgesics than those who received fentanyl 25 ug, with no difference between the groups for the degree of motor block. [26]

A study compared the use of intrathecal bupivacaine alone with bupivacaine combined with either sufentanil 10 ug or butorphanol 25 ug for spinal anaesthesia for endoscopic urology surgery. Both sufentanil and butorphanol increased the duration of sensory block without increasing the duration of motor block. The benefit of butorphanol over sufentanil was that it had less tendency to cause pruritus. [27]

The synergistic effect of a small dose of intrathecal fentanyl with bupivacaine improves the quality of anaesthesia without the drug prolonging recovery from spinal anaesthesia. [3] This has allowed very small doses of bupivacaine to be used effectively for ambulatory surgery. Low dose hyperbaric bupivacaine (5 mg), when combined with fentanyl 25 ug for spinal anaesthesia for endoscopic urological procedures, resulted in a shorter duration of sensory and motor block, with less use of ephedrine as vasopressor when compared to higher doses of hyperbaric bupivacaine. [28]

In summary, a lower dose of bupivacaine combined with fentanyl, may provide adequate sensory blockade (and analgesia) but have the advantage of a shorter duration of action with less motor blockade. Although adding fentanyl to bupivacaine injected intrathecally has been shown to prolong the time taken for sensory block regression, this does not translate into a significantly longer time for the patient to start mobilizing and walk unaided, or the time taken to urinate, or the time taken to be eligible for discharge from the hospital. [29]

The amount of fentanyl added is another factor to be considered, because the higher the dose the greater the risk of unwanted side effects. Doses of intrathecal fentanyl greater than 15 ug cause clinically significant pruritus. [30-31] Intrathecal opiates are also known to inhibit bladder function, which could delay the patient's ability to void spontaneously and hence prolong the time taken for discharge from hospital.

However, Ben-David et al. found that intrathecal opiates did not in fact delay the return of bladder function or the time to discharge. [29]

When considering the evidence from the literature, 15 ug fentanyl was considered the optimal dose when used as an additive to hyperbaric bupivacaine for spinal anaesthesia in ambulatory surgery. Our study was undertaken to help establish the best dose of hyperbaric bupivacaine, when combined with intrathecal fentanyl 15 ug, for spinal anaesthesia for brachytherapy (immediate-proximity radiotherapy) for carcinoma of the cervix. There are no other studies investigating the use of low dose spinal anaesthesia in this group of patients and the results of our study will be useful in the generation of specific guidelines for spinal anaesthesia for this specific procedure.

The primary outcome variable in our study was the time taken for complete recovery from spinal anaesthesia, i.e. for all of the discharge criteria to be fulfilled. In order to calculate an appropriate sample size for the patient groups to adequately power the study, we relied on clinical data previously collected on the same group of patients at Groote Schuur Hospital as well as the results of previous dose-response studies. From these we expected a mean duration to full recovery from spinal anaesthesia of 195 (full range: 170-220) and 275 (full range: 250-300) minutes for our low dose (hyperbaric bupivacaine 5 mg + fentanyl 15 ug) and high dose (hyperbaric bupivacaine 9 mg + fentanyl 15 ug) groups respectively. [3,15-18,29]

The dermatome level of the sensory block was measured using cold sensitivity to ethyl chloride spray. The sensory (dermatomal) level measured can vary greatly between clinicians unless a recognized, standardized method is used. In our study protocol we prescribed the method as follows: assessment started from above the level of sensory block achieved and the dermatome level at which the patient first noticed any decrease in cold sensitivity was regarded as the level of sensory block. [32]

To record the degree of motor block we used the modified Bromage scale as published in the literature: [18,33]

0 = Full leg movement (full flexion of knees and ankles)

1 = Inability to raise extended legs, just able to flex knees, full ankle flexion

2 = Inability to flex knees, some flexion of ankles possible

3 = No movement possible (unable to move legs or feet)

#### **e) Need for further research**

Further studies on SA for brachytherapy would help to establish the optimal dose regimen. In particular, a larger sample size would give a better indication of differences in quality of analgesia. In ideal circumstances without any resource or time constraints, an ED 50 / ED 95 dose-response study for hyperbaric bupivacaine (when combined with fentanyl 15 ug) for this specific procedure would possibly give the most valuable information.

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**Part C: PUBLICATION-READY MANUSCRIPT**

*(For submission to Anaesthesia, the journal of the Association of Anaesthetists of Great Britain and Ireland)*

**Spinal anaesthesia for brachytherapy for carcinoma of the cervix: a comparison of two dose regimens of hyperbaric bupivacaine**

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**Summary**

The purpose of this study was to help establish the most suitable dose of hyperbaric bupivacaine for spinal anaesthesia for day-stay brachytherapy for carcinoma of the cervix. The study was a prospective, randomised, double-blind trial. Forty patients were randomised to receive either 1 ml of hyperbaric bupivacaine 0.5% (5 mg) plus 15 µg fentanyl (Low Dose, n=20), or 1.8 ml of hyperbaric bupivacaine 0.5% (9 mg) plus 15 µg fentanyl (High Dose, n=20), via the L3/4 interspace. The time to achieve hospital discharge criteria was significantly shorter in the Low Dose (LD) group (mean time of 235 [206-264] minutes) versus the High Dose (HD) group (mean time of 280 [263-297] minutes) ( $p < 0.01$ ). Patients in the LD group were also eligible for discharge from the recovery area in a shorter time ( $p < 0.01$ ). Although there was significantly less motor block in the LD group ( $p < 0.001$ ), patient satisfaction regarding motor block was the same in the two groups ( $p = 0.96$ ). There was a trend towards more inadequate (unsatisfactory) spinal blocks in the low dose group ( $p = 0.34$ ).

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Spinal anaesthesia (SA) can be suitably performed for a variety of day-stay (ambulatory) surgical procedures. [1] The time taken for adequate recovery to allow

discharge home from hospital is an important consideration, as it impacts not only on patient satisfaction, but also on human and financial resource constraints within a hospital. The dose and type of local anaesthetic used needs to be specifically tailored to the nature (site) and duration of the intended surgery. [1-2]

This study was undertaken to help establish the best dose of hyperbaric bupivacaine, when combined with intrathecal fentanyl, for spinal anaesthesia for brachytherapy (immediate-proximity radiotherapy) for carcinoma of the cervix. These day-stay surgical patients undergo insertion of an intra-cervical ('Smit sleeve') stent which is 8 mm in diameter, the stent facilitating subsequent introduction of an applicator necessary to perform brachytherapy. The procedure also involves probing (sounding) the fundus of the uterus which requires a spinal block up to- and including the T10 dermatome level.

During 2008 – 2009 data were retrospectively analysed after varying clinical practice by several anaesthetists performing spinal anaesthesia for brachytherapy at Groote Schuur Hospital (unpublished). Sixteen patients received doses of between 0.5-1.8 ml of hyperbaric bupivacaine 0.5%, combined with either 15 or 20 µg of fentanyl. None of the patients required conversion to general anaesthesia and none required IV supplementary analgesia. Time taken for regression of sensory block to dermatome level S2 in this sample patient population varied between 190 – 200 minutes for a dose of 1 ml of hyperbaric bupivacaine 0.5% (5 mg) and 240 – 250 minutes for patients receiving a dose of 1.8 ml of hyperbaric bupivacaine 0.5% (9 mg).

It was therefore decided to conduct a prospective study comparing what may be considered a relatively standard or conventional dose of heavy bupivacaine, with a lower dose, both combined with fentanyl 15 µg, for spinal anaesthesia. The aim was to provide adequate anaesthesia using the lower dose, as well as allowing for a shorter time to complete recovery. The study findings could then be used to contribute to a guideline for spinal anaesthesia for brachytherapy for carcinoma of the cervix.

## Methods

This prospective, randomized study was approved by the Human Research Ethics Committee (HREC) of the University of Cape Town. Patients attending the radiotherapy clinic scheduled for brachytherapy for carcinoma of the cervix were included in the enrolment process, the only exclusion criteria being either a contra-indication to spinal anaesthesia or unwillingness on the part of the patient to take part in the study. Written informed consent for the study was obtained in the patient's first language, at least 12 hours before the procedure, and a copy given to the patient for their reference.

A literature review suggested similar times for eligibility for hospital discharge as in the Groote Schuur pilot data, namely a mean of 195 (full range: 170-220) minutes for the low dose group and 275 (full range: 250-300) minutes for the high dose group.[2,4-7] Using this information, power analysis using the statistical package Stata (Stata/IC 12.1, StataCorp, LP, 4905 Lakeway Drive, College Station, TX 77845, USA) calculated that 18 patients would be needed in each group at an alpha level of 0.05 and a beta value of 0.90 to detect this difference. We decided to enrol 20 patients into each group to minimise the possibility of a beta-error in the study.

Patients were randomised by a sealed envelope technique and allocated to either the Low Dose (LD) or High Dose (HD) group in the following manner: 20 LD labels and 20 HD labels were each placed into 40 separate envelopes which were then sealed, shuffled extensively and then labelled as "patient number 1" through to "patient number 40". During the study these envelopes were opened in order from patient number 1 – 40 by the anaesthetists performing each spinal anaesthetic, but then put back into the same envelope and closed again. The group allocation of each envelope was only made known to the data collector and primary investigator after recruitment was complete and data ready to be analysed.

Patients received a subarachnoid dose of either 1 ml of hyperbaric bupivacaine 0.5% (5 mg) plus 15 µg fentanyl (Group Low Dose [LD], n=20), or 1.8 ml hyperbaric bupivacaine 0.5% (9 mg) plus 15 µg fentanyl (Group High Dose [HD], n=20).

Prior to performing spinal anaesthesia, an 18 gauge cannula was inserted for intravenous (IV) access and standard monitoring (pulse oximeter, non-invasive blood pressure and ECG) applied. IV midazolam  $0.025 \text{ mg.kg}^{-1}$  (maximum of 2 mg) was given to all patients younger than 65 years of age ( $n=38$ , 19 from each group). Baseline systolic blood pressure was calculated as the mean of two systolic blood pressures measured at rest during the five minutes prior to spinal anaesthesia.

Spinal anaesthesia was administered using an aseptic technique with the patient in the sitting position. A 25 gauge Whitacre spinal needle was introduced via the L3/4 interspace and once free flow of clear cerebro-spinal fluid (CSF) was demonstrated, the solution was injected over 10-15 seconds. The patient remained sitting for two minutes after completion of the injection and was then re-positioned in the lithotomy position for surgery.

A different anaesthetist who was blinded to the treatment group of the patient was responsible for patient monitoring and clinical data collection for the study. Therefore, both the patient and the attending anaesthetist for the duration of the study were blinded (double-blinded study). Lactated Ringer's solution 500 – 1000 ml was administered as a co-load. Blood pressure was measured every three minutes after induction of anaesthesia. A decrease in systolic blood pressure to less than 80% of the mean baseline value was treated with 5 mg ephedrine IV and the dose repeated as necessary.

The dermatomal level of the sensory block was measured using cold sensitivity to ethyl chloride spray. The level of sensory block was assessed every five minutes until the height of the block had remained constant for three consecutive readings, i.e. until the sensory block was fully established. Thereafter the level was assessed every 10 minutes until there had been a regression in sensory block of at least two dermatomes, thereafter every 15 minutes until all of the hospital discharge criteria had been met. Time taken to eligibility for discharge from the theatre recovery area (sensory level T10 or lower, together with cardiovascular stability) was noted.

Planned management in the case of failed or inadequate spinal anaesthesia was as follows: if no sensory block was achieved, the patient received general anaesthesia.

Once there was evidence that a sensory block to a particular dermatomal level had been achieved, the patient was asked to grade their quality of anaesthesia (sensation) and their description at the start of the procedure was categorized into one of four groups (appendix A). If the patient fell into groups 1-3, the quality of pain control was deemed adequate and the surgical procedure continued without giving any supplemental analgesia or converting to a general anaesthetic. If, however, the patient was experiencing discomfort or pain and either requested or agreed to additional pain relief upon being offered it, or was in obvious need of additional analgesia, the patient was allocated to group 4 and the spinal anaesthetic regarded as inadequate for the planned surgical procedure. The attending anaesthetist then explained to the patient that general anaesthesia would be required for the surgery.

The primary outcome variable was the time taken to achieve the clinical criteria for discharge from the hospital, i.e. all of the following to be achieved:

- Regression of sensory block to the S2 dermatome
- Ability to walk unaided
- Ability to void urine

Secondary outcomes included the following information and comparisons:

- Time to eligibility for discharge from theatre recovery area (sensory level at or below the T10 dermatome, with cardiovascular stability)
- Quality of analgesia: sensation felt by the patient during the procedure (appendix A)
- Degree of motor blockade at the time of peak sensory blockade (appendix B)
- Patient satisfaction, rated on a visual analogue scale (VAS) from 0 – 10, regarding both the quality of anaesthesia and degree of motor block experienced (appendix C)
- The peak sensory dermatomal level and the time taken to reach this level
- Side effects (nausea and/or vomiting, pruritus, light-headedness or dizziness)
- The dose of ephedrine required

At the next clinic visit patients were specifically asked if they had had any pain not related to the operative site, but specifically in the buttocks, thighs or lower limbs (transient neurological symptoms) or those of post-dural puncture headache. Patients were encouraged to report these or any other symptoms experienced in the interim to the radiotherapist or the anaesthetist, whose contact telephone numbers were given. For statistical analysis, the Shapiro-Wilk test was used to establish whether data was normally distributed. For between-group comparisons of normally distributed numerical data, a two-sample Student's T-test was used. This was the case for the primary outcome variable of the study. For non-normally distributed numerical data, the Wilcoxon rank sum (Mann-Whitney U) test was used. For categorical data the Fisher's exact test was employed for between-group comparisons, since there were less than five observations in multiple categories. All statistical analyses were performed using the statistical package Stata (Stata/IC 12.1, StataCorp, LP, 4905 Lakeway Drive, College Station, TX 77845, USA).

## Results

Forty one patients were assessed for inclusion in the study, since one patient had to be excluded due to a contra-indication to spinal anaesthesia (idiopathic thrombocytopenic purpura, with a platelet count of  $74 \times 10^9/L$ ). Forty patients were randomised to either the LD (n=20) or the HD (n=20) group. There were no significant between-group differences in demographic data (Table I). The median duration (interquartile range [IQR]) for the surgical procedure for the 40 patients, measured from the time of intrathecal injection of the spinal solution to the transfer of the patient to the recovery area, was 60 (52-70) minutes.

The data relating to discharge ability from the hospital was found to be normally distributed (Shapiro-Wilk test value 0.56 [ $p > 0.05$ ]). Between-group comparisons of eligibility criteria for discharge ability from recovery room to the ward, and from the hospital, are shown in Table II. The LD group demonstrated statistically significantly shorter discharge ability times from recovery room and the hospital, overall and as regards each individual criterion for hospital discharge ability. In one patient in the LD group, there was no spinal block established after injection. This patient was thus excluded from the analysis of the individual criteria for hospital discharge ability.

In terms of quality of anaesthesia, five of the 40 patients were assessed as having inadequate spinal anaesthesia. These patients had their quality of analgesia graded as a “4” (Appendix A) and general anaesthesia was appropriately administered, according to the protocol. Four of these patients were from the LD group and one from the HD group. Comparing the two groups specifically for this category of “inadequate” spinal anaesthesia, the Fisher’s exact test was used. There was a trend towards more failures in the LD group. (Table III). Comparing the two groups for quality of analgesia within their original categories of 1-4, the results were also not statistically significant (Table IV).

The degree of motor block was assessed using the modified Bromage scale – see appendix B. [8-9] The LD group had significantly less motor block than the HD group (Table V). There was no statistically significant difference between the two groups in terms of patient satisfaction (Table VI). Amongst the other results, the LD group had a lower peak sensory dermatome level (Table VII).

There were no symptoms of nausea, vomiting or pruritus in any of the patients. On direct questioning only two of the 40 patients admitted experiencing dizziness, one patient from each group. None of the patients had any symptoms consistent with transient neurological symptoms on follow up. One patient had symptoms suggestive of a post-dural puncture headache which improved with conservative management (bed rest) and resolved over a few days.

## **Discussion**

The purpose of our study was to compare a conventional dose of hyperbaric bupivacaine for spinal anaesthesia for day stay brachytherapy for carcinoma of the cervix, with a lower dose, with a view to shortening the time to full recovery without compromising quality of analgesia during the procedure. The study showed statistically significantly shorter time to readiness for hospital discharge in the LD group, with less motor block. Both groups had minimal side effects. There was a trend towards a higher incidence of failed spinal anaesthesia in the LD group.



We favoured bupivacaine for spinal anaesthesia over lidocaine, due to the procedural requirement for at least an hour of anaesthesia, as well as the known better risk profile of bupivacaine in terms of transient neurological symptoms. [1,10-12] Hyperbaric bupivacaine was preferred to isobaric bupivacaine, due to its more consistent and reliable subarachnoid spread, as well as having a relatively shorter duration of complete motor blockade. [6,8,13] The synergistic effect of a small dose of intrathecal fentanyl with bupivacaine improves the quality of anaesthesia, without the drug prolonging recovery from spinal anaesthesia. [5] This allows for a smaller total dose of bupivacaine to be used, potentially shortening the time to complete recovery.

In choosing our dose regimen of hyperbaric bupivacaine for the two groups, we were guided by clinical information collected before the study began, as well as a review of the published literature on the subject. In a dose-response study of hyperbaric bupivacaine for spinal anaesthesia in volunteers, bupivacaine 3.75 mg and 7.5 mg achieved a median peak dermatomal block to pinprick of T9 (IQR=5 dermatomes) and T7 (IQR=5 dermatomes) respectively. [2]

In another dose-response study using different doses, volumes and concentrations of glucose-free bupivacaine for spinal anaesthesia in patients undergoing trans-urethral surgery, bupivacaine 10 mg achieved a peak sensory level of T5-T8. [4] It seems that the intrathecal spread of a local anaesthetic is primarily determined by the dose given rather than depending on its volume or concentration. [4,14]

Our study analysed the clinical response to two different doses of hyperbaric bupivacaine, when combined with fentanyl 15 µg, for spinal anaesthesia in the ambulatory setting. It must be remembered, however, that our conclusions apply to a specific surgical procedure in a particular patient population, and cannot be loosely extrapolated to other groups of patients.

An analysis of the primary outcome variable of our study, showed that patients in the LD group benefitted by being eligible for home discharge sooner than those in the HD group. Patients in the LD group were also eligible for discharge from the recovery area in a shorter time. Although there was significantly less motor block in the LD group, patient satisfaction regarding motor block was the same in the two groups.

The trend towards more patients with inadequate spinal anaesthesia in the LD group was a concern. In an adequately powered study examining quality of analgesia, this may have achieved statistical significance. Power analysis using the statistical package Stata (Stata/IC 12.1, StataCorp, LP, 4905 Lakeway Drive, College Station, TX 77845, USA) calculated that for an alpha level of 0.05 and a beta value of 0.90 we would need 114 patients in each group to prove that the LD provided unsatisfactory spinal anaesthesia compared to the HD. However, it was not possible to conduct such a large study as we were limited by human resources and time constraints.

Interestingly, the trend towards more inadequate spinal anaesthesia in the LD group was despite an acceptable median (IQR) peak sensory level, using ethyl chloride cold spray, of T8 (8-10) for the required surgery. This suggests that the quality of surgical anaesthesia for any given procedure cannot be predicted entirely by the dermatomal spread of local anaesthetic (or peak sensory level achieved) as assessed by cold sensitivity.

The strength of this study is that prior to this, there have been no published prospective, randomised, double-blinded, controlled trials in this specific group of patients undergoing this specific procedure. Previously published data investigating the use of low dose spinal anaesthesia in patients undergoing trans-urethral resection of the prostate (TURP), for example, cannot reliably be extrapolated to our group of patients. The procedure our patients had is different and the physiology related to their underlying malignancy (of the cervix) may affect the pharmacokinetic and/or pharmacodynamics profile of the intrathecal solution.

Our study suggests that a dose closer to- or equivalent to that of the HD group may be preferable, to ensure consistent and reliable spinal anaesthesia in this patient population. This may be more important than a statistically significantly shorter hospital discharge time and less motor block. Similar conclusions were drawn from a recent meta-analysis examining the use of low-dose spinal anaesthesia for caesarean delivery, which cautioned against the use of low dose bupivacaine for single shot spinal anaesthesia, since anaesthetic efficacy is compromised. [15]

A considerable weakness of our study, related to the human resource and time constraints we faced, was that we only compared two different doses of hyperbaric bupivacaine. Ideally we would have liked to conduct a dose-response study for hyperbaric bupivacaine, when combined with intrathecal fentanyl 15 ug, to determine the ED 50 and ED 95 for our specific group of patients. Alternatively, an ED 50 dose-finding study using the minimum local anaesthetic concentration (MLAC) for hyperbaric bupivacaine would have been extremely valuable. Further studies investigating the use of low dose spinal anaesthesia in this group of patients is needed.

### **Acknowledgements**

The authors wish to thank the following colleagues: Dr L van Wyk, gynaecology oncologist and treating radiotherapist, for his cooperation and enthusiasm, and Professor MF James for his support in the protocol design.

### **Competing Interests**

No external funding was received and no competing interests declared.

### **Appendices**

#### Appendix A: Quality of anaesthesia (sensory block)

- 1- Complete absence of any sensation
- 2- Sensation of motion only
- 3- Mild discomfort, but declining offer for additional analgesia
- 4- Patient requests additional analgesia / in obvious need of additional analgesia

#### Appendix B: Modified Bromage scale [8-9]

- 0 = Full leg movement (full flexion of knees and ankles).
- 1 = Inability to raise extended legs, just able to flex knees, full ankle flexion.
- 2 = Inability to flex knees, some flexion of ankles possible.
- 3 = No movement possible (unable to move legs or feet).

Appendix C: Patient questionnaire

(Mark the spot on the line below that best describes your experience)

- 1) How satisfied are you, overall, with the spinal anaesthetic you received for your surgical procedure?

---

0	1	2	3	4	5	6	7	8	9	10
Completely			A little			Reasonably				Completely
Dissatisfied			dissatisfied			satisfied				Satisfied

If you marked a value below 5, please say why: \_\_\_\_\_

- 2) How satisfied are you with the amount of pain/discomfort you felt during the surgical procedure?

---

0	1	2	3	4	5	6	7	8	9	10
Completely			A little			Reasonably				Completely
Dissatisfied			dissatisfied			satisfied				Satisfied

If you marked a value below 5, please say why: \_\_\_\_\_

- 3) How satisfied are you with the amount of weakness in your legs experienced during and after the procedure?

---

0	1	2	3	4	5	6	7	8	9	10
Completely			A little			Reasonably				Completely
Dissatisfied			dissatisfied			satisfied				Satisfied

If you marked a value below 5, please say why: \_\_\_\_\_

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**Table I: Patient characteristics – no difference between the 2 groups**

	<u>Low Dose</u>	<u>High Dose</u>	<u>p-value</u>
Mean Age (SD) in years:	49.9 (45.7-54.1)	51.55 (46.95-56.15)	0.58*
Mean BMI (kg.m-2):	27.5	26.9	0.84**
ASA rating:	2, 3 (n=11, 9)	2, 3 (n=15, 5)	0.19***

\* Two-sided Student's T-test

\*\* Two-sample Wilcoxon rank-sum (Mann-Whitney U) test

\*\*\* Chi-squared test

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**Table II: Primary outcome variable (minutes) –  
Shorter mean time (SD) to discharge home and from recovery area  
in the low dose group**

	<u>Low Dose</u>	<u>High Dose</u>	<u>p -value</u>
Discharge recovery (n=40):	72 (64-81)	90 (82-97)	< 0.01*
Hospital discharge (n=40):	235 (206-264)	280 (263-297)	< 0.01*
Hospital discharge (n=39):	241 (214-268)	280 (263-297)	0.01*
Time to walk (n=39):	219 (193-246)	268 (251-285)	< 0.01*
Time to void (n=39):	235 (208-263)	271 (255-287)	0.02*
Regression to S2 (n=39):	233 (208-258)	278 (256-301)	< 0.01*

\*Two-sided Student's T-test



**Table III: Number of adequate versus inadequate spinal anaesthetics - actual number of patients (percentages) in each category**

	<u>Low Dose</u>	<u>High Dose</u>
Adequate (category 1-3):	16 (80%)	19 (95%)
Inadequate (category 4):	4 (20%)	1 (5%)

Fisher's exact test:  $p$  -value = 0.34

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**Table IV: Quality of anaesthesia (sensory block) – actual number of patients (percentages) in each category**

	<u>Low Dose</u>	<u>High Dose</u>
Category 1:	5 (25%)	12 (60%)
Category 2:	8 (40%)	5 (25%)
Category 3:	3 (15%)	2 (10%)
Category 4:	4 (20%)	1 (5%)

Fisher's exact test:  $p$  -value = 0.16

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**Table V: Grouping of patients according to the modified Bromage scale - actual number of patients (percentages) in each category**

<u>Score</u>	<u>Low Dose</u>	<u>High Dose</u>
0:	15 (75%)	3 (15%)
1:	4 (20%)	3 (15%)
2:	0 (0%)	4 (20%)
3:	1 (5%)	10 (50%)

Fisher's exact test:  $p$ -value < 0.001

University of Cape Town

**Table VI: Patient satisfaction – median scores (IQR) are no different between groups**

	<u>Low Dose</u>	<u>High Dose</u>	<u>p-value</u>
Q 1:	10 (IQR 7.5-10)	10 (IQR 10-10)	0.26*
Q 2:	10 (IQR 5.5-10)	10 (IQR 10-10)	0.20*
Q 3:	10 (IQR 8-10)	10 (IQR 9-10)	0.96*

\*Wilcoxon rank sum (Mann-Whitney) test for numerical data not normally distributed

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**Table VII: Other measured variables (secondary outcomes) – higher peak sensory level achieved with the high dose**

	<u>Low Dose</u> (n=19)	<u>High Dose</u> (n=20)	<u>p-value</u>
Median peak sensory level:	8 (IQR 8-10)	8 (IQR 6-8)	< 0.01*
Mean time to reach peak:	20 (15-20)	15 (15-20)	0.14*
Use (need) of ephedrine	1 (5%)	3 (15%)	0.30**

\*Wilcoxon rank-sum (Mann-Whitney U) test

\*\* Fisher's exact test

University of Cape Town

## **Part D: APPENDICES**

### **Acknowledgements**

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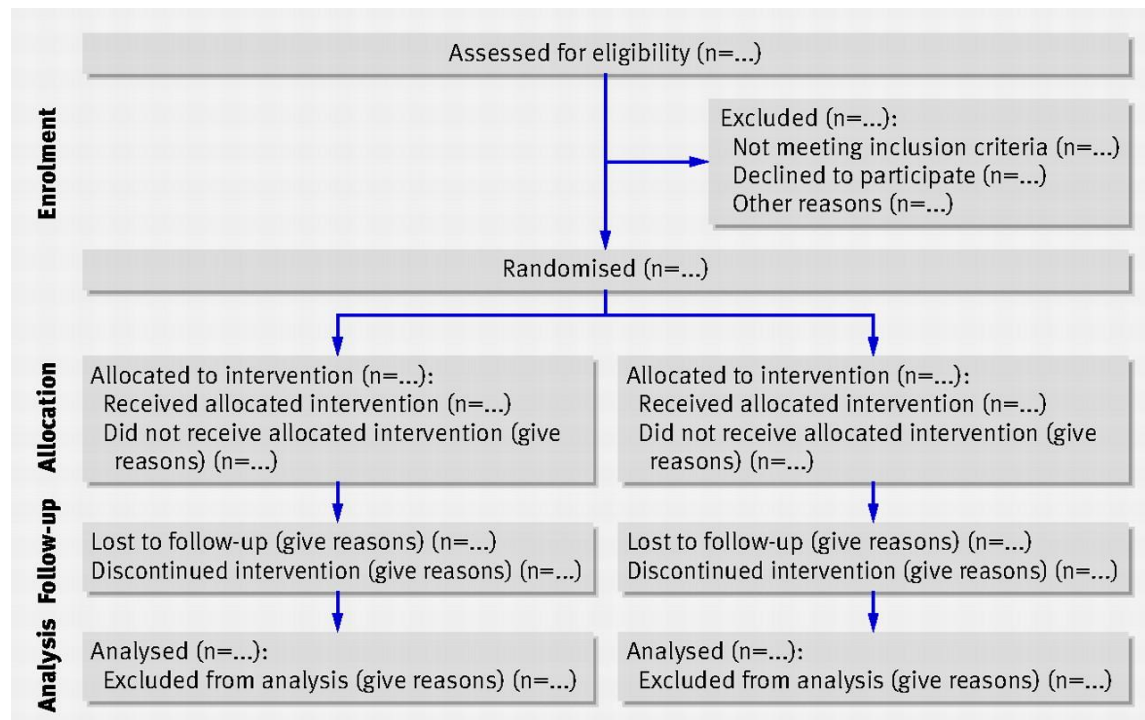
Our anaesthesia colleagues Drs P Diyelela and A de Jager, for translating the informed consent form into the Xhosa and Afrikaans versions respectively.

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Our head of dept Professor MFM James for your support, guidance and continuing interest in this work.

## The Consort Statement (2010) Flow Diagram

(Flow diagram of the progress through the phases of a parallel randomised trial of two groups (that is, enrolment, intervention allocation, follow-up, and data analysis – see [www.consort-statement.org](http://www.consort-statement.org))



### Process of enrolment

Assessed for eligibility: n = 41

Excluded: n = 1: contra-indication to spinal anaesthesia

Randomised: n = 40

### Group allocation

n = 20 in each group

**None were lost to follow-up or had their intervention discontinued**

**20 in each group were analysed for the primary outcome measure**

## **Patient Information and Informed Consent – Xhosa version**

**Study Title:** Spinal anaesthesia for brachytherapy for carcinoma of the cervix: a comparison of two dose regimens of hyperbaric bupivacaine

Principal Investigators: N Haus, RA Dyer (Contact No. 021 404 5001/3)

UCT Human Research Ethics Committee (HREC) Ref no: 421/2010

### **Patient Folder no:**

(Place hospital sticker here)

Patient Study no:

### **Introduction**

Uyamenywa ukuthabatha inxaxheba koluphando. Phambi kokuba ugqibe ukuba uyafuna na ukuthatha inxaxheba umelwe kukwazi ukuba oluphando lungantoni na. Emva kokuba ufunde eliphepha lengcaciso, wachazelwe ngokupheleleyo ngophando, ukuba unemibuzo okanye okunye onqwenela ukukuqonda, nceda ubuze ugqirha ozakube ekucacisela ngophando.

### **Lwenzelwa ntoni oluphando?**

Sigqibe ekubeni sithlekise imilinganiselo emibini yeyeza elihlatywa emqolo ukwenzela ukubulala intlungu(ukudonywa) ngexesha lonyango. Lendlela yokudonywa yenziwa ngokuhlhatywa iyeza (“Bupivacaine”) emqolo. Sifuna ukuqonda ukuba umlinganiselo othile wokubulawa kwentlungu ungcono na kunomnye umlinganiselo weyeza lokubulala iintlungu.

### **Kutheni ucelwa uthabathe inxaxheba kuphando?**

Sicela bonke abantu abahamba kulekliniki, abaze kunyangwa umhlaza wesibekeko ukuba bathabathe inxaxheba koluphando. Wonke umntu ovumayo ukuthabatha inxaxheba kolu phando ufumana umlinganiselo oqingqiweyo weyeza elihlatywa emqolo. Ukuba uyavuma ukuthabatha inxaxheba kolu phando, umlinganiselo ozakuwufumana uxhomekeke ekubeni kufunyanwa iyeza elingakanani emvulophini ekhethiweyo. Le mvulophu ikhethwa phambi kokuba uhlatywe iyeza lokubulala



iintlungu. Ngugqirha ongumbulali zintlungu owazi umlinganiselo weyeza ozakulifumana.

### **Ndizakubandakanyeka ixesha elingakanani koluphando?**

Zonke inkcukatha esizidingayo ngophando, ziqokelelwa ngemini yonyango, ngexesha lokunyangwa kwakho nangeyure ezimbalwa emva kokusetyenzwa kwakho, ude ube ulungele ukugoduka. Xa ubuya usiza ekliniki, siza kubuza indlela oziva ngayo nangengxaki onokuba uye wazifumana emva kokuhlatywa iyeza emqolo, into kodwa engaxhaphakanga.

### **Ndizakufumana luphi uhlobo lokubulawa kwentlungu (ukudonywa)?**

Ukuba akukho bungozi bulindelekileyo, uzakudonywa ngokuhlatywa emqolo, into eluhlobo oluqhelekileyo lokubulawa kwentlungu kolunyango ulufumanayo. Ugqirha ozakukudoma uzakucacisela kabanzi ngendlela yokubulawa kwentlungu azakuyi-sebenzisa. Uzakucacisela indlela azakukudoma ngayo. Emva koko, wena uzakunikezela ngemvume yokunikwa iyeza ngokuhlatywa inaliti emqolo. Le naliti ihlatywa emqolo yindlela eqhelekileyo yokubulawa kwentlungu kubantu abazele oluhlobo lonyango. Uzakuhlatywa emqolo nokuba awuthabathi nxaxheba kuphando. Into ejamelene ngqo nophando kukuqokelelwa kwenkcukhaca ngexesha umzimba wakho usadonyiwe ngenaliti ehlatywe emqolo. Umzekelo, sizakuthabatha iBlood Pressure yakho, sijonge nokuba iintlungu onazo zingakanani na, sijonge nokutyhafa kwemilenze ukuba kukangakanani na, nokuba kuthabatha ixesha elingakanani ukuphela kobundindisholo okubangelwe liyeza elihlatywe emqolo.

### **Kuzakuthini ukuba andivumi ukuthabatha inxaxheba koluphando?**

Awunyanzelekanga ukuthabatha inxaxheba koluphando. Ukuba awufuni ukuthabatha inxaxheba koluphando, uzakuqhuba ufumane uhoyo olufanelekileyo kwisigulo onaso, na kwixa elizayo. Uzakubulawa intlungu ngokuhlatywa emqolo ukuba kukulungele oko. Unelungelo lokuyeka ukuthabatha inxaxheba nangaliphi ithuba ufuna.

### **Zeziphi izinto ezinokuba yingxaki kuwe ngokuthabatha inxaxheba koluphando?**

Ingxaki kuwe zifana nengxaki ezibakhona xa umntu ebulewe intlungu ngokuhlatywa iyeza emqolo. Ugqirha obulala intlungu uzakucacisela ngazo zonke iingxaki ezinokubela. Ukuba kunokwenzeka uvakalelwe ziintlungu ngexesha lonyango, ugqirha obulala iintlungu unakho ukunika amayeza awongeziweyo ukuphelisa iintlungu. Ukuba kunokwenzeka okungaqhelekanga, okufana nokuqaqanjelwa kakhulu ngexesha lonyango, ugqirha obulala iintlungu uyakwazi ukukulalisa wonke ngaphezu kokuba uzakube ufumene iyeza elihlatywa emqolo elenza ndindisholo amazantsi omzimba kuphela.

### **Kukhona okuzuzayo ngokuthabatha inxaxheba koluphando?**

Akukho nzuzo engaphezulu oyifumanayo ngokuthabatha inxaxheba koluphando. Uhoyo nenkathalo oyifumanayo ngexesha ufumana unyango, ziyinxalenye yohoyo obufanele ukulufumana esibhedlele. Akukho mali nantlawulo uzakuyifumana ngokuthabatha inxaxheba koluphando.

### **Imfihlo**

Inkcukacha zakho ezifihlakeleyo, eziqokelelwe kwabo bathabatha inxaxheba koluphando zaziwa ngoogqirha ababandakanyeka koluphando kuphela. Iziphumo zophando zingabhalwa kwiincwadi zogqirha, zixoxwe zaziwe ngoogqirha abafunda ezoncwadi kuphela. Akukho ndlela yokuba abanye abantu ngokubanzi bangayazi ukuba ngobani abathabathe inxaxheba koluphando. Oogqirha abambalwa abazakuzazi iziphumo ngabo babandakanyekayo koluphando kuphela. Kubalulekile ukuba icandelo lezobuntloli neengcali zeyunivesi yase Kapa zikwazi ukuzifumana iziphumo zoluphando. Bazijonga eziziphumo ukwenzela ukukhusela wena nje ngomguli. Baqinisekisa ukuba konke okenziwayo akukonzakalisi ngokwasempilweni. Qiniseka ukuba akukho gazi lizakutsalwa kuwe ngexesha koluphando.

Ndiyaqinisekisa ukuba uGqirha obhalwe apha ngezantsi undicacisele ngentlobo yokubulawa kwentlungu nendlela oluzakuqhutywa ngayo oluphando, nazo zonke iinkcukaca zophando. Ndiyifundile ndayiqonda yonke imininingwane ebhalwe kweliphepha lokunikezela ngemvume. Ndifumene iithuba elaneleyo lokubuza imibuzo, nokucaciselwa ngophando, yaye ndiyavuma ukuthabatha inxaxheba koluphando.

_____	_____
Igama notyikityo lomntu othabatha inxaxheba kuphando (Name and Signature of Adult Participant)	Umhla (Date)
_____	_____
Igama notyikityo lomntu othabatha imvume (Name and Signature of Person obtaining Consent)	Umhla (Date)
_____	_____
Igama notyikityo lomntu olingqina (Xa kusetyenziswe itoliki) (Name and Signature of Interpreter/Witness)	Umhla (Date)

## **Patient Information and Informed Consent (Afrikaans version)**

**Study Title:** Spinal anaesthesia for brachytherapy for carcinoma of the cervix: a comparison of two dose regimens of hyperbaric bupivacaine

Principal Investigators: N Haus, RA Dyer (Contact no. 021 404 5001/3)

UCT Human Research Ethics Committee (HREC) Ref no: 421/2010

**Patient Folder no:**  
(Place hospital sticker here)

Patient Study no:

### **Inleiding**

U word uitgenooi om deel te neem aan hierdie studie. Voordat u besluit of u hieraan gaan deelneem, moet u ten volle verstaan wat dit behels. Nadat u hierdie inligting gelees en dit aan u verduidelik is, voel vry om enige vrae wat u het te deel met die dokter wat hierdie inligtingstuk met u deurgaen, of met die navorsers hierbo genoem.

### **Waarom word hierdie studie gedoen?**

Ons het besluit om twee verskillende doserings van lokale verdoving, genaamd Bupivakain, met mekaar te vergelyk. Dit is wat gebruik word wanneer die dokter die spinale narkose op jou doen. Ons wil vasstel of die een dosering beter is as die ander vir pasiente wat dieselfde chirurgiese procedure as u onder spinale narkose gaan ondergaan.

### **Waarom word u gevra om hieraan deel te neem?**

Ons vra al die dames wat hierdie kliniek besoek en dieselfde procedure as u ondergaan, om deel te neem. Elke dame wat instem om aan hierdie studie deel te neem sal dan of die een of die ander dosering van lokale verdoving waarmee die spinale narkose gedoen gaan word, ontvang. Indien u instem om deel te neem, sal die dosering wat u gaan ontvang lukraak gekies word op grond van wat in 'n verseelde koevert verskyn. Die koevert word oopgemaak direk voordat u spinaal gedoen word. Slegs die dokter wat die spinaal doen sal weet watter dosering toegedien is.

### **Hoe lank sal ek persoonlik hierby betrokke wees?**

Feitlik al die inligting wat ons benodig vir ons studie sal gekollekteer word op die dag van u prosedure, beide tydens en vir 'n paar ure na die prosedure totdat u gereed is om huis toe te gaan. Tydens u volgende kliniek besoek sal u gevra word oor enige moontlike nuwe effekte wat u ondervind het. Nuwe effekte is baie ongewoon.

### **Watter tipe narkose sal ek ontvang?**

Indien daar geen teen-indikasies is nie sal u 'n spinale narkose ontvang- wat die roetiene is vir hierdie prosedure. Die narkotiseur wat die spinaal gaan doen sal u volledig daaromtrent inlig. Hy/sy sal aan u verduidelik hoe die prosedure uitgevoer gaan word. Daarna sal u kan toestemming gee vir die uitvoer van die spinale narkose. Hierdie toestemming moet gegee word of u deelneem in die studie of nie- dis deel van normale narkose praktyk.

Wat spesiaal is aan die studie is dat ons inligting insamel terwyl u onder die effek van die spinale narkose is. Ons gaan byvoorbeeld u bloeddruk meet, vasstel hoeveel ongemak of pyn u ondervind, hoeveel swakheid u in u bene ondervind, sowel as hoe lank dit neem vir u om te herstel van die effekte van die spinale narkose.

### **Wat sal gebeur indien ek besluit om nie aan hierdie studie deel te neem nie?**

U hoef glad nie aan hierdie studie deel te neem nie. Indien u besluit om nie hieraan deel te neem nie sal u nog steeds dieselfde kwaliteit sorg vir u spesifieke toestand ontvang, beide nou en in die toekoms. U sal steeds 'n spinale narkose ontvang indien dit geskik is vir u. U mag ook besluit om op enige stadium van die studie te onttrek.

### **Wat is die risiko's vir u?**

Die risiko is vir u dieselfde as vir enige ander pasient wat 'n spinale narkose ondergaan, en dit sal aan u verduidelik word deur die dokter wat die spinale narkose op u gaan doen. Sou u enige ongemak tydens die chirurgiese prosedure ondervind, sal die narkotiseur addisionele medisyne aan u bied. In die onwaarskynlike geval waar u baie ongemak mag ondervind, sal daar met algemene narkose voortgegaan moet word, tesame met die spinaal wat dan reeds uitgevoer is.

### **Is daar enige voordele vir u om deel te neem aan hierdie studie?**

Daar is geen addisionele voordele vir u deur deel te neem aan hierdie studie nie. Die sorg en aandag wat u sal ontvang tydens hierdie prosedure is deel van roetiene mediese praktyk. Daar is geen finansiële voordeel deur aan hierdie studie deel te neem nie.

## Privaatheid/Konfidensialiteit

Die persoonlike inligting wat gekollekteer word van almal wat aan hierdie studie deelneem sal net gedeel word onder die dokters wat aan hierdie studie deelneem. Hierdie studie mag dalk in 'n mediese joernaal gepubliseer word en die resultate van die groep as 'n geheel sal gedeel word met almal wat dit lees. Daar is egter geen manier waarop die publiek sal kan weet wie aan die studie deelgeneem het nie. Die dokters wat na die resultate gaan kyk is die " principal investigators " wat aan die begin van hierdie dokument genoem is. Dit is ook belangrik dat die " Human Research Ethics Committee ( HREC ) of the University of Cape Town " toegang het tot die resultate van hierdie studie. Hulle doen so in gevolge hulle regulatoriese pligte wat in u voordeel optree. Wees verseker dat geen bloed geneem sal word tydens hierdie studie nie.

Hiermee bevestig ek dat die dokter wat hieronder geteken het my volledig ingelig het omtrent die aard, prosedure, voordele en risiko's van hierdie kliniese studie. Ek het ook hierdie " **PATIENT INFORMATION AND INFORMED CONSENT** " vorm ontvang, gelees en verstaan. Ek het genoeg geleentheid gehad om vrae te vra en ek stem in om aan hierdie studie deel te neem.

---

Name and Signature of Adult Participant

---

Date

---

Name and Signature of Person Obtaining Consent

---

Date

---

Name and Signature of Witness/Interpreter  
(Only necessary if an interpreter was used)

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Date



UNIVERSITY OF CAPE TOWN  
FACULTY OF HEALTH SCIENCES

School of Public Health and Family Medicine  
& Primary Health Care Directorate

# *Certificate of Completion*

*This certificate is presented to*

*Nikolas Haus*

*For successfully completing the  
MMed Research Methods for Registrars Workshops  
held on the 22nd & 29<sup>th</sup> May 2010*

*The 29<sup>th</sup> day of May 2010*



Signed by candidate

Signature Removed

## **Instructions to Authors (taken from the *Anaesthesia* journal web page)**

### **Anaesthesia**

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## *Acknowledgments*

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