

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

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Abstract

Objectives: Spinal anaesthesia can be suitably performed for a variety of day-stay (ambulatory) surgical procedures. The time taken for adequate recovery to allow discharge home from hospital is an important consideration. The purpose of this study was to compare the suitability of two different doses of hyperbaric bupivacaine for spinal anaesthesia for day-stay brachytherapy for carcinoma of the cervix.

Design: This was a prospective, randomised, double-blind study.

Setting and subjects: Forty female patients, presenting to Groote Schuur Hospital for brachytherapy for carcinoma of the cervix, were randomised to receive either 5 mg or 9 mg (1 ml or 1.8 ml) of 0.5% hyperbaric bupivacaine, plus 15 µg fentanyl via the L3/L4 interspace.

Results: Patients receiving the lower dose could be discharged from the recovery room in a shorter time (p -value < 0.01). The time taken to achieve hospital discharge criteria was significantly shorter in the group receiving the lower dose [a mean time of 235 (206-264) vs. 280 (263-297) minutes, p -value < 0.01]. There was significantly less motor block in the low-dose group (p -value < 0.001). Patient satisfaction regarding motor block was similar in the two groups (p -value = 0.96). There was a trend towards a higher number of inadequate spinal blocks in the low-dose group (p -value = 0.34).

Conclusion: Our study suggests that a dose that is closer or equivalent to that of the high-dose group (9 mg bupivacaine plus 15 µg fentanyl) is preferable for brachytherapy for carcinoma of the cervix in ensuring consistent and reliable spinal anaesthesia in this patient population.

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Introduction

Spinal anaesthesia 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. This may impact on patient satisfaction, and also on human and financial resource constraints within a hospital. The dose and type of local anaesthetic that is used needs to be specifically tailored to the nature (site) and duration of the intended surgery.¹⁻²

This study was undertaken to establish whether a low dose of hyperbaric bupivacaine, when combined with intrathecal fentanyl, was suitable for spinal anaesthesia

for brachytherapy (immediate proximity radiotherapy) for carcinoma of the cervix. Day-stay surgical patients undergo insertion of an intra-cervical (Smit sleeve) stent which is 8 mm in diameter. The stent facilitates subsequent introduction of an applicator that is 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.

Between 2008 and 2009, data were retrospectively analysed after varied clinical practices by several anaesthetists performing spinal anaesthesia for brachytherapy at Groote Schuur Hospital (unpublished). Sixteen patients received doses of between 0.5 ml and 1.8 ml of hyperbaric bupivacaine 0.5%, combined with either

15 µg or 20 µg of fentanyl. None of the patients required supplementary intravenous (IV) analgesia or conversion to general anaesthesia. The time taken for regression of the sensory block to dermatome level S2 in this sample patient population varied between 190 and 200 minutes for a dose of 1 ml of hyperbaric bupivacaine 0.5% (5 mg), and 240 and 250 minutes in patients receiving a dose of 1.8 ml of hyperbaric bupivacaine 0.5% (9 mg).

Therefore, a decision was made to conduct a prospective study that compared a relatively standard dose of hyperbaric bupivacaine (9 mg), with a lower dose (5 mg), 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.

Method

This prospective, randomised study was approved by the Human Research Ethics Committee of the University of Cape Town. Patients attending the radiotherapy clinic who were scheduled for brachytherapy for carcinoma of the cervix were included in the enrolment process. The only exclusion criteria were a contraindication to spinal anaesthesia or unwillingness on the part of the patient to take part in the study. Written informed consent to participate in the study was obtained in the patient's first language at least 12 hours before the procedure. A copy was given to the patient for reference purposes.

A literature review suggested similar times for eligibility for hospital discharge as those in our pilot data, namely a mean of 195 (a full range of between 170 and 220) minutes for the low-dose group, and 275 (a full range of between 250 and 300) minutes for the high-dose group.²⁻⁶ Using this information, power analysis was calculated using the statistical package Stata[®]/IC 12.1 (StataCorp, USA), 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 in each group to minimise the possibility of a beta error. Patients were randomised by sealed envelope and allocated to either the low-dose or high-dose group in the following manner: 20 low-dose labels and 20 high-dose labels were each placed in 40 separate envelopes which were then sealed, labelled and shuffled. The group allocation of each envelope was only made known to the primary investigator after the recruitment process was complete.

Patients received a subarachnoid dose of either 1 ml of hyperbaric bupivacaine 0.5% (5 mg) plus 15 µg fentanyl (low-dose group, n = 20), or 1.8 ml hyperbaric bupivacaine 0.5% (9 mg) plus 15 µg fentanyl (high-dose group, n = 20).

Prior to performing spinal anaesthesia, an 18 G cannula was inserted for intravenous (IV) access and standard monitoring (pulse oximeter, noninvasive blood pressure and an electrocardiogram) applied. IV midazolam 0.025 mg/kg (a 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 pressure measurements taken 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 G Whitacre spinal needle was introduced via the L3/L4 interspace. Once free flow of clear cerebrospinal fluid 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. An anaesthetist, blinded to the treatment group of the patient, was responsible for patient monitoring and clinical data collection for the study. Therefore, the study was double blind. Lactated Ringer's solution 500-1 000 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, which is standard practice in our institution. The level of sensory block was assessed every five minutes until the height of the block had remained constant for three consecutive readings. Thereafter, the level was assessed every 10 minutes until sensory block had regressed at least two dermatomes, then 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 at least the T10 dermatome had been achieved, the patient was asked to grade her quality of anaesthesia (sensation). Her description at the start of the procedure was categorised into one of four groups (1: complete absence of any sensation; 2: sensation of motion only; 3: mild discomfort, but declines offer of additional analgesia, 4: patient requests additional analgesia, or is in obvious need of it). If the patient fell into groups 1-3, the quality of pain control was deemed to be adequate, and the surgical procedure continued without giving any supplemental analgesia or converting to a general anaesthetic. However, if the patient experienced discomfort or pain, and either requested or agreed to

additional pain relief upon being offered it, or was in obvious need of additional analgesia (group 4), general anaesthesia was administered.

The primary outcome variable was the time taken to achieve the clinical criteria for discharge from the hospital, i.e. all of the following had 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 (1: complete absence of any sensation; 2: sensation of motion only; 3: mild discomfort, but declines offer of additional analgesia, 4: Patient requests additional analgesia or is in obvious need of it).
- *Degree of motor blockade:* Measured at the time of peak sensory blockade [modified Bromage scale: 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, and 3 = no movement possible (unable to move legs or feet)].⁷⁻⁸
- *Patient satisfaction:* Rated on a visual analogue scale from 0-10, regarding both the quality of anaesthesia and the degree of motor block experienced.
- 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 required dose of ephedrine.

At the next clinic visit, patients were specifically asked if they had had any pain that did not relate to the operative site, specifically in the buttocks, thighs or lower limbs (transient neurological symptoms) or pertaining to a postdural puncture headache. Patients were encouraged to report these or any other symptoms experienced in the interim to the radiotherapist or the anaesthetist.

For statistical analysis, the Shapiro-Wilk test was used to establish whether data were normally distributed. A two-sample Student's t-test was used for between-group comparisons of normally distributed numerical data. This was the case for the primary outcome variable of the study. The Mann-Whitney U test was used to determine non-normally distributed numerical data. The Fisher's exact test was employed for between-group comparisons for categorical data, since there were less than five observations in multiple categories. All statistical analyses were performed using the statistical package Stata®/IC 12.1 (StataCorp, USA).

Results

A total of 41 patients were assessed for inclusion in the study, since one patient had to be excluded because of a contraindication to spinal anaesthesia (idiopathic thrombocytopenic purpura, with a platelet count of $74 \times 10^9/l$). Forty patients were randomised to either the low-dose ($n = 20$) or the high-dose ($n = 20$) group. There were no significant between-group differences in demographic data (Table I). The median duration and interquartile range (IQR) for the surgical procedure for the 40 patients, measured

Table I: Patient characteristics

	Low-dose group	High-dose group	p-value
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 ^{***}

There were no differences in patient characteristics between the groups
 ASA: American Society of Anesthesiologists, BMI: body mass index, SD: standard deviation
^{*}: Two-sided Student's t-test
^{**}: Two-sample Wilcoxon rank sum (Mann-Whitney U) test
^{***}: Chi-squared test

Table II: Primary outcome variable (in minutes)

	Low-dose group	High-dose group	p-value
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 [*]

There was a shorter mean time (standard deviation) to discharge home and from the recovery area in the low-dose group
^{*}: Two-sided Student's t-test

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 dischargeability from the hospital were found to be normally distributed [Shapiro-Wilk test value 0.56 (p-value > 0.05)]. Between-group comparisons of eligibility criteria for dischargeability from the recovery room to the ward, and from the hospital, are shown in Table II. The low-dose group had statistically significantly shorter dischargeability times from both the recovery room and the hospital. In addition, this finding applied to each individual criterion for hospital dischargeability. One patient in the low-dose group, in whom there was no demonstrable spinal block, was excluded from this analysis.

In terms of quality of anaesthesia, five of the 40 patients were assessed as having inadequate spinal anaesthesia (grade 4), and general anaesthesia was administered. Four of these patients were from the low-dose group and one was from the high-dose group. Fisher's exact test was used to compare the two groups in this category of "inadequate" spinal anaesthesia. There was a trend towards more failures in the low-dose group (Table III).

Table III: Number of adequate versus inadequate spinal anaesthetics

	Low-dose group	High-dose group
Adequate (Category 1-3)	16 (80%)	19 (95%)
Inadequate (Category 4)	4 (20%)	1 (5%)

The table reflects actual number of patients (percentages) in each category
Fisher's exact test: p-value = 0.34

A comparison of the two groups for quality of analgesia within their original categories of 1-4, showed no significant between-group differences (Table IV).

Table IV: Quality of anaesthesia (sensory block)

	Low-dose group	High-dose group
Category 1	5 (25%)	12 (60%)
Category 2	8 (40%)	5 (35%)
Category 3	3 (15%)	2 (10%)
Category 4	4 (20%)	1 (5%)

The table reflects the actual number of patients (percentages) in each category
Fisher's exact test: p-value = 0.16

The low-dose group had significantly less motor block than the high-dose group (Table V).

There was no significant difference between the two groups in terms of patient satisfaction (Table VI).

The low-dose group had a lower peak sensory dermatome level (Table VII).

Table V: Grouping of patients according to the modified Bromage scale

Score	Low-dose group	High-dose group
0	15 (75%)	3 (15%)
1	4 (20%)	3 (15%)
2	0 (0%)	4 (20%)
3	1 (5%)	10 (50%)

The table reflects the actual number of patients (percentages) in each category
Fisher's exact test: p-value < 0.001

Table VI: Patient satisfaction

	Low-dose group	High-dose group	p-value
Q1	10 (IQR 7.5-10)	10 (IQR 10-10)	0.26*
Q2	10 (IQR 5.5-10)	10 (IQR 10-10)	0.20*
Q3	10 (IQR 8-10)	10 (IQR 9-10)	0.96*

Median scores (interquartile range) were no different between the groups

IQR: interquartile range

*: Wilcoxon rank sum (Mann-Whitney U) test for numerical data that are not normally distributed

Table VII: Other measured variables (secondary outcomes)

	Low-dose group (n = 19)	High-dose group (n = 20)	p-value
Median peak sensory level	T8 (IQR T8-T10)	T8 (IQR T6-T8)	< 0.01*
Mean time to reach peak (minutes)	20 (IQR 15-20)	15 (IQR 15-20)	0.14*
Use (need) of ephedrine	1 (5%)	3 (15%)	0.30**

Higher peak sensory level was achieved with the high dose

IQR: interquartile range

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

** : Fisher's exact test

There were no symptoms of nausea, vomiting or pruritus in any of the patients. On direct questioning, only two of the 40 patients had dizziness, one from each group. No patients had symptoms that were consistent with a transient neurological deficit. One patient had symptoms suggestive of a postdural puncture headache which improved with conservative management.

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 that of a lower dose, with a view to shortening the time to full recovery, without compromising quality of analgesia during the procedure. The study showed a statistically significantly shorter time to readiness for hospital discharge in the low-dose group, with less motor block. Both groups had minimal side-effects. However, there was a trend towards a higher incidence of inadequate spinal anaesthesia in the low-dose group.

We favoured bupivacaine for spinal anaesthesia over lidocaine because of the procedural requirement of at least an hour of anaesthesia, as well as the known-better risk profile of bupivacaine in terms of transient neurological symptoms.^{1,9-11} 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 encountered motor blockade. A well-conducted study evaluated the relative analgesic potency of spinal ropivacaine and bupivacaine. Ropivacaine was shown to have half the analgesic potency of bupivacaine, with a similar side-effect profile, including motor block, when equipotent doses were used.¹² Therefore, ropivacaine seems to hold no advantage over bupivacaine for spinal anaesthesia for day-stay surgery.¹²⁻¹³

Hyperbaric bupivacaine was preferred to isobaric bupivacaine because of its more consistent and reliable subarachnoid spread, as well as its shorter duration of complete motor blockade.^{5,7,14} 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.⁴

In choosing our dose regimen of hyperbaric bupivacaine for the two groups, we were guided by data obtained from varied clinical practices at our institution, 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 transurethral surgery, bupivacaine 10 mg achieved a peak sensory level of T5-T8.³ This suggests that the intrathecal spread of a local anaesthetic is primarily determined by the dose given, rather than the volume or concentration.^{3,15}

Therefore, our study analysed the clinical response to two doses of hyperbaric bupivacaine when combined with fentanyl 15 µg for spinal anaesthesia in the ambulatory setting. 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 low-dose group were eligible for discharge from both the recovery area and the hospital sooner than those in the high-dose group. Although there was significantly less motor block in the low-dose group, there were no significant differences between the groups regarding patient satisfaction.

The trend towards a larger number of patients with inadequate spinal anaesthesia in the low-dose group was a concern. However, based on pilot clinical data, as well as our literature review, we had no reason to believe that the lower

dose of bupivacaine would provide inferior anaesthesia. Therefore, we did not include quality of analgesia as one of our primary outcome variables. The study was only powered to investigate the time taken to meet clinical criteria for home discharge. In an adequately powered study examining quality of analgesia, the trend towards a greater number of inadequate spinal anaesthesia in the low-dose group may have achieved statistical significance. Even though there was no statistically significant difference in terms of adequacy of anaesthesia, the proportion of 4/20 failures in the low-dose group is clearly unacceptable.

A recent study highlights the controversies in the prediction of surgical anaesthesia relating to sensory modality that is tested during Caesarean section.¹⁶ Interestingly, in our study, the trend towards more inadequate spinal anaesthesia in the low-dose group occurred 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 peak sensory level achieved, as assessed by cold sensitivity.

The strength of this study is that there are no previously published, prospective, randomised, double-blind trials on local anaesthetic dosing for spinal anaesthesia in patients undergoing this specific procedure. For example, previously published data that investigated the use of low-dose spinal anaesthesia in patients undergoing transurethral resection of the prostate could not reliably be extrapolated to our group of patients. A weakness of our study was that we only compared two doses of hyperbaric bupivacaine. Ideally, a dose-response study is required for hyperbaric bupivacaine and fentanyl, to determine the effective dose (ED) 50 and ED 95 for this specific procedure.

Our study suggests that a dose closer or equivalent to that of the high-dose group (9 mg bupivacaine plus 15 µg fentanyl) is preferable for brachytherapy for carcinoma of the cervix to ensure consistent and reliable spinal anaesthesia in this patient population. This is clearly of greater importance than a statistically significantly shorter hospital discharge time and less motor block. Similar conclusions were drawn from a recent meta-analysis that examined 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 would be compromised.¹⁷

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Conflict of interest

No external funding was received and no competing interests declared.

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