Chloroprocaine versus prilocaine for spinal anesthesia in ambulatory knee arthroscopy: a double-blind randomized trial

Elsbeth Wesselink,[1] Godelief Janssen-van den Hurk,[2] Rien van der Vegt,[3] Cornelis Slagt,[4] Jan van der Aa,[5] Eric Franssen,[6] Peter van de Ven,[7] Noortje Swart,[8] Christa Boer,[9] Marcel de Leeuw[10]

For numbered affiliations see end of article.

Correspondence to
Mrs Elsbeth Wesselink, Clinical Pharmacy, Zaans Medisch Centrum, Zaandam 1502 DV, The Netherlands; e.wesselink@vumc.nl

Data from this work were presented at the 44th Annual Regional Anesthesiology and Acute Pain Medicine meeting, 11–14 April 2019, Las Vegas, Nevada. The abstract received a Best of Meeting Award for this meeting.

Received 5 May 2019
Revised 5 August 2019
Accepted 12 August 2019

To cite: Wesselink E, Hurk GJ, Vegt Rv, *et al*. *Reg Anesth Pain Med* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/rapm-2019-100673

SUMMARY

Background In ambulatory lower limb surgery, spinal anesthesia with rapid onset and a short duration of block is preferable. We hypothesized that the use of 2-chloroprocaine would be associated with a faster motor block recovery compared with prilocaine in knee arthroscopy. A difference of 15 min was considered clinically relevant.

Methods 150 patients were randomly allocated to receive intrathecally either 40 mg of 2-chloroprocaine or 40 mg of prilocaine. The primary outcome was the time to complete recovery from motor blockade. Secondary outcomes included time to full regression of sensory block, peak sensory block level, urine retention needing catheterization, time until hospital discharge, incidence of transient neurologic symptoms and patient satisfaction.

Results Time to complete recovery from motor blockade was 15 min shorter for 2-chloroprocaine (median: 60 min; IQR: 60–82.5) than for prilocaine (median: 75 min; IQR: 60–90; p=0.004). 2-Chloroprocaine also resulted in faster full regression of sensory block (median: 120 min; IQR: 90–135 compared with median: 165 min; IQR: 135–190, p<0.001) and faster time to hospital discharge (mean difference: 57 min; 95% CI 38 to 77, p<0.001). Peak sensory block was higher in the 2-chloroprocaine group (median: T9; IQR: T6–T12 compared with median: T10; IQR: T8–T12, p<0.008). Patient satisfaction and urine retention needing catheterization were equal in both groups.

Conclusions In knee arthroscopy, spinal anesthesia with 2-chloroprocaine results in a faster recovery of motor and sensory block, leading to quicker hospital discharge compared with prilocaine.

Trial registration number NTR6796.

INTRODUCTION

In day case lower limb surgery, spinal anesthesia with both rapid onset and a short duration of block is a useful option. For spinal anesthesia, a short-acting local anesthetic facilitates rapid recovery of motor function supporting unassisted ambulation compared with general anesthesia or a long-acting local anesthetic.[1–5]

Historically, the drug of choice for short-duration intrathecal blocks has been lidocaine. However, intrathecal lidocaine is limited by concerns related to a high incidence (20%–30%) of unwanted transient neurologic symptoms (TNS).[6–9] In recent years, both preservative-free 2-chloroprocaine and prilocaine have gained interest in Europe as short-acting spinal anesthetics.[10–15] In 2018, preservative-free 2-chloroprocaine (Clorotekal) was approved by the Food and Drug Administration for spinal anesthesia. Intrathecal prilocaine, although not commonly used in the USA, is currently available in Europe as a lidocaine alternative.[10] To the best of our knowledge, 2-chloroprocaine and prilocaine have not been clinically compared as to whether one would be more preferable than the other in an ambulatory surgery setting. The aim of the present study was to determine whether time to complete recovery from motor blockade in patients undergoing an outpatient knee arthroscopy differs between patients receiving 40 mg 2-chloroprocaine 1% and patients receiving 40 mg prilocaine 2%. We hypothesized that in knee arthroscopy, the use of 2-chloroprocaine would be associated with a faster full recovery from motor block than the use of prilocaine.

METHODS

This study was registered by EudraCT (Ref: 2015-001944-13) and was carried out at Zaans Medical Centre, Zaandam, the Netherlands. Written informed consent was obtained from all patients.

Study design

The study was a prospective, randomized, double-blind, single-center study of 150 patients undergoing a knee arthroscopy in ambulatory surgery. Patients scheduled for knee arthroscopy with spinal anesthesia were eligible for participation in the study if they were 18 years or older and had an American Society of Anesthesiologists' physical status I–II. Patients were excluded if they were pregnant or if they had a study drug allergy, contraindication to neuraxial anesthesia, lower extremity neuropathy, or previous involvement in the study.

Sample size

Previous studies report 78–117 min to motor block recovery for 40 mg chloroprocaine and 76.8–92 min for 40 mg intrathecal hyperbaric prilocaine. Based on literature and a total number of 10–15 patients with knee arthroscopy per day in an operating theater, a difference of 15 min was considered

clinically relevant for the primary outcome time to full recovery of motor block (Tmb0).[10–12 16] The required sample size was calculated using SD of 25 min (2-chloroprocaine) and SD 35 min (prilocaine). Assuming two-sided testing at a 5% significance level using an independent samples t-test, a total number of 66 patients per group was found to yield 80% power. Allowing for possible dropouts, the total sample size was set at 75 patients per group.

Randomization and blinding procedure

Using block randomization (block size of four patients, computer-generated sequence) 150 patients were randomly allocated to receive an intrathecal injection of 40 mg of either preservative-free plain 2-chloroprocaine 1% (Ampres, Sintetica, Switzerland) or hyperbaric prilocaine 2% (Prilotecal, Nordic Group, Netherlands). One of the anesthesiologists administered the intrathecal injection in the preoperative holding area according to the randomization list without disclosing the group allocation to anybody. Then, this anesthesiologist left the preoperative holding area and was not further involved in any part of the trial. A second anesthesiologist (observer blinded) assumed responsibility for the patient during surgery and recovery.

Anesthesia and perioperative care

Approximately 1 hour before surgery all patients received oral acetaminophen 1 g and were offered oral midazolam 7.5 mg. Patients were asked to void at the ward; none of the patients received an indwelling urinary catheter before surgery. Patients were in sitting position during performance of the spinal procedure. After local anesthesia of the skin at the puncture site (preferably midline at L3–L4), the local anesthetic was intrathecally injected using a 25 G b-bevel needle. After obtaining a free flow of cerebrospinal fluid with the orifice of the needle facing upwards, the trial drug was injected slowly. The patient was immediately placed in supine position.

The surgical procedures were performed by orthopedic surgeons experienced in knee arthroscopy. During surgery, a thigh tourniquet (250 mm Hg) was used. Perioperative monitoring consisted of pulse oximetry, electrocardiography, non-invasive blood pressure measurement and heart rate (HR). In case of insufficient anesthesia to perform the surgical procedure, sedatives or opioids were administered to complete surgery. The rescue anesthetic procedure was general anesthesia consisting of intravenous propofol 2 mg/kg and intravenous sufentanil 0.25 µg/kg.

Postoperative pain medication was tailored individually and consisted of either acetaminophen or a non-steroidal anti-inflammatory drug.

Assessments

Immediately after intrathecal injection, a stopwatch was started representing time 0. An observer blinded to the group allocation recorded the evolution of the intrathecal block until achievement of home discharge criteria. Motor block was assessed using a modified Bromage scale (0—able to move entire leg or knee, 1—unable to raise whole leg but able to flex knee, 2—unable to flex knee, only foot moving, 3—unable to move knee or foot) at 5, 10, 15, 20 and 30 min and then once every 15 min until full recovery of motor block, with a maximum of 190 min.[17] The spread of the sensory block was assessed as the highest dermatome level without cold sensation to ice cubes at 2, 4, 6, 8, 10, 15, 20, 25 and 30 min, then once every 15 min until full regression was observed, with a maximum of 190 min. Both sensory and motor block were assessed bilaterally. In patients with successful spinal anesthesia, unilateral measurements were taken during the arthroscopy procedure at the non-interventional leg, after exclusion of an asymmetrical or 'patchy' block.

Twenty minutes after intrathecal injection of the study drug, the mean arterial pressure (MAP20) and HR (HR20) were retrieved from the patient data management system. At 20 min, both study drugs were expected to have achieved the maximum level of sensory block, linked to the maximum degree of sympathetic block.[10 12]

Patients who had to undergo the rescue anesthetic procedure were excluded from all further assessments.

Thirty minutes after surgery, the urinary bladder was scanned by means of ultrasound and single catheterization was performed, if necessary. The following rules were applied:

- 0–199 mL of urine: reassessment after 2 hours unless spontaneous voiding.
- 200–499 mL of urine: patient is asked to void and reassessment after 1 hour as needed.
- ≥500 mL of urine: single catheterization of the bladder if spontaneous voiding was not possible.

The time to first spontaneous voiding (Tv) was registered. After return to the surgical ward, further treatment was according to the hospital's standard procedure. The time to hospital discharge (Thd) was recorded, defined as the time between intrathecal injection and the moment the subject met the discharge criteria for this study, that is, spontaneous voiding and recovery from motor block. On the first and seventh postoperative days, patients were interviewed by telephone about symptoms of TNS following a standardized checklist. To verify the patients blinding for the randomization, patients were asked on day 7 which drug they thought they had received.

During the follow-up calls, nausea/vomiting was also recorded and patient satisfaction about the spinal anesthesia was recorded on a 10-point scale (0 not satisfied, 10 very satisfied). The completed questionnaires were reviewed to determine whether symptoms could be related to TNS, according to the differential diagnosis criteria.[18]

Statistics

For all variables, double data entry was used for verification and reconciliation in case of transcription errors and discrepancies caused by illegible data. Categorical variables were summarized per group by means of frequencies and percentages and compared between groups using the χ^2 test (proportion of patients reporting headache at day 7, proportion of patients reporting nausea/vomiting and proportion patients using vasopressor drugs and medication used for postoperative pain management) or using Fisher's exact test in case of an expected cell count below 5 (proportion of patients with insufficient block, with sufficient block but no motor block, with urine retention needing catheterization and reporting headache at day 1). Continuous variables that were normally distributed were summarized by their mean and SD (age, body mass index, weight, height, duration of surgery, time from spinal anesthesia to start surgery, Tv and Thd) and compared between groups using the independent samples t-test (Tv and Thd). Normality was assessed visually using normal probability plots. Median and IQR were reported for continuous variables that were not normally distributed and ordinal variables were summarized by means of median and IQR. Primary outcome Tmb0 was compared between groups using Kaplan-Meier analysis and the log-rank test in which patients not reaching complete

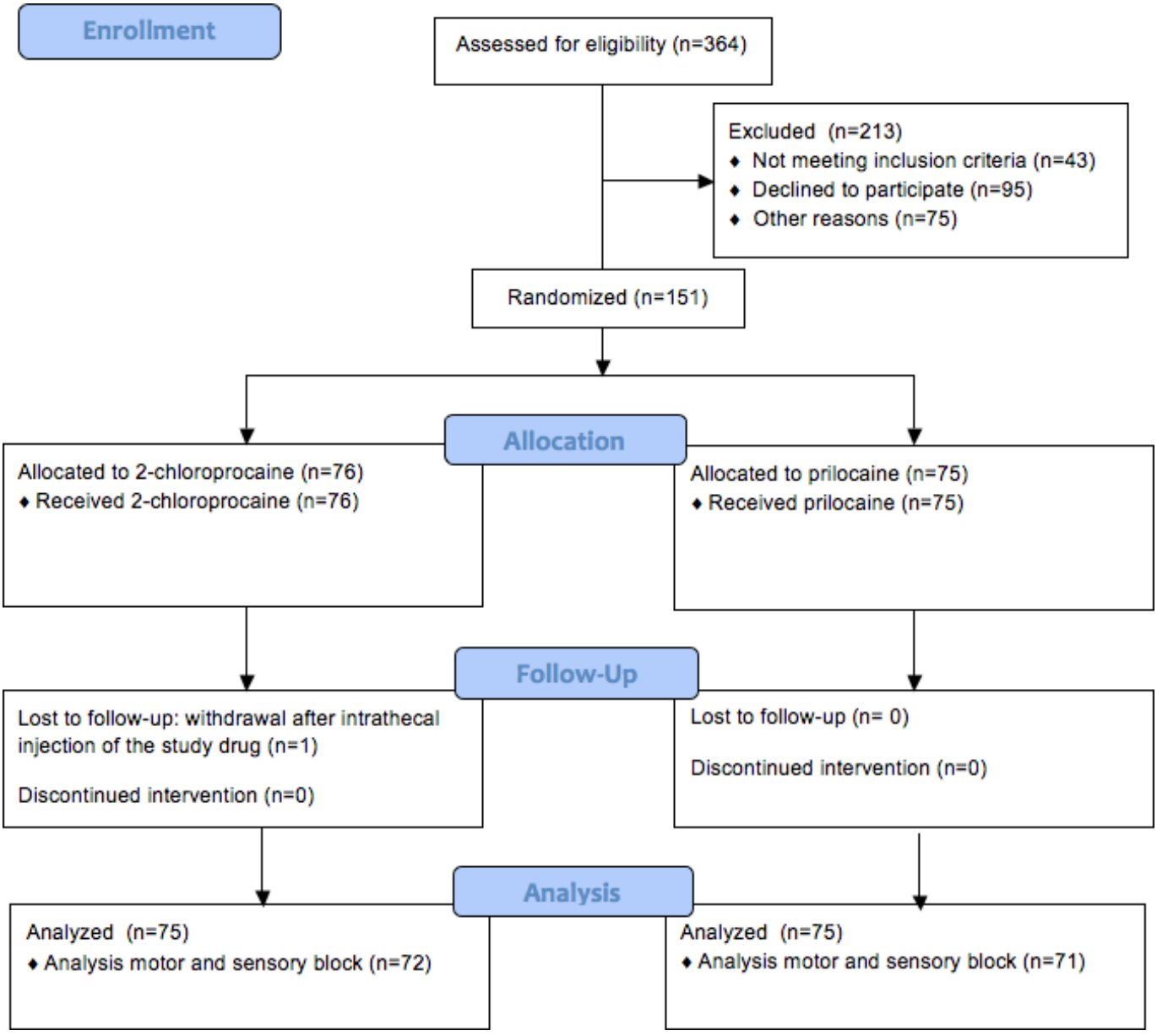

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

block recovery within 190 min of follow-up were censored at time of last available measurement. Time to full regression of sensory block and time to onset of recovery block were tested in a similar way. As primary outcome Tmb0 could not be assessed in the patients in the rescue procedure, we had to exclude these patients from the analysis. Patients with sufficient sensory block after spinal anesthesia, but no motor block had to be excluded for the motor block analysis as well, but not for the secondary endpoints. In addition to comparing Tmb0 between the arms in those patients who reached motor block after spinal anesthesia, we also compared the proportion of patients who did have sufficient sensory but no motor block between the two groups. For all analyses, a two-sided significance level of 5% was used.

RESULTS

Patients were recruited between November 2016 and June 2018. Three hundred and sixty-four patients were assessed for eligibility and 151 were included after the preoperative visit by the anesthesiologist (figure 1). One patient withdrew from the study right after injection of the study drug and was replaced by another patient, yielding once more the planned total of 150 patients. The 7-day follow-up of the last included patient was completed in June 2018. Table 1 reveals baseline characteristics.

In total, four patients in the prilocaine arm and two in the 2-chloroprocaine group (5.3% vs 2.7%, p=0.68) had an insufficient block with spinal anesthesia at the start and consequently the rescue procedure, that is, conversion to general anesthesia. No further perioperative and postoperative study assessments were taken for these six patients, therefore they were not included in the statistical analysis for the endpoints time to motor and sensory block. Of the remaining 144 patients, seven did not reach a motor block (Bromage=0), but sensory block was sufficient to complete surgery with spinal anesthesia. All seven patients were male and belonged to the prilocaine group (9.9% vs 0%, p=0.006). These seven patients were younger (mean difference: 11.2 years, 95% CI 2.1 to 20.3, p=0.016) and taller (mean difference: 9.8 cm, 95% CI 2.6 to 17.1, p=0.008) than the other 137 patients.

Table 1 Patient characteristics and surgery data

	2-Chloroprocaine (n=75)	Prilocaine (n=75)
Gender, male, n (%)	41 (54.7)	44 (58.7)
ASA II, n (%)	35 (46.7)	30 (40.0)
Premedication, yes, n (%)	31 (41.3)	33 (44.0)
Preoperative voiding	67/72 (93.1%)	59/73 (80.8%)
Age (years)	54.0 (12.5)	49.8 (11.2)
BMI	27.4 (4.1)	27.8 (3.7)
Weight (kg)	85.7 (14.6)	87.5 (14.8)
Height (cm)	176 (10.6)	177 (8.4)
Fluid intake (mL)	50 (0–500)	50 (0–600)
Duration of surgery (min)	21.1 (6.5)	20.7 (7.7)
Time from spinal anesthesia to start surgery (min)	18.8 (9.3)	21.3 (9.9)

Age, body mass index (BMI), weight, height, duration of surgery and time from spinal anesthesia to start surgery presented were normally distributed and summarized by mean (SD). Gender, ASA status, premedication, and preoperative voiding are presented as numbers (%). Fluid intake was not normally distributed and summarized by median (range).
ASA, American Society of Anesthesiologists.

Among patients with successful spinal anesthesia, 2-chloroprocaine resulted in a shorter time to complete recovery from motor blockade compared with prilocaine (p=0.004) (table 2, figure 2). 2-Chloroprocaine also showed faster onsets of sensory block (p=0.010), faster full regression of sensory block (p<0.001)(figure 3) and faster hospital discharge (mean difference: 57 min; 95% CI 38 to 77, p<0.001). Time to onset of motor block was shorter for chloroprocaine compared with prilocaine group (p=0.007), with 80.8% of patients in the chloroprocaine group reaching motor block within 5 min compared with 66.2% in the prilocaine group.

In the 2-chloroprocaine group, peak sensory block was higher (median: T9; IQR: T6–T12 compared with median: T10; IQR: T8–T12, p<0.008, p=0.008), the MAP at 20 min was lower (p=0.04) and the use of vasopressor drugs (ephedrine or phenylephrine) was higher (22.7% vs 10%, p=0.049) than in the prilocaine group. The HR20 was equal in the two groups (p=0.62). Frequency and kind of medication for postoperative pain management did not differ between the two groups (p=0.20).

Table 2 Primairy and secondary outcomes with significant difference between the groups

	N 2-Chloroprocaine /N Prilocaine	2-Chloroprocaine	Prilocaine	P value
Time to onset sensory block, Tsb (min)	72/71	2 [2–4]	4 [2–6]	0.010*
Time to full motor block recovery, Tmb0 (min)	73/64	60 [60–82.5]	75 [60–90]	0.004*
Time to full sensory block recovery, Tsb0 (min)	72/71	120 [90–135]	165 [135–190]	<0.001*
Time to first voiding, Tv (hours)	71/68	3.3 (1.0)	4.3 (0.7)	<0.001†
Time to hospital discharge, Thd (hours)	75/75	3.7 (1.2)	4.7 (0.7)	<0.001†

Times from intrathecal injection to complete recovery of motor and sensory functions, unassisted ambulation, and first voiding in patients receiving intrathecal injection of 40 mg of either 2% hyperbaric prilocaine or 1% plain 2-chloroprocaine. Outcomes summarized by median [IQR] or mean (SD).
*Not normally distributed, median (IQR), p value for log-rank test.
†Normally distributed, mean±SD, p value for independent samples t-test.

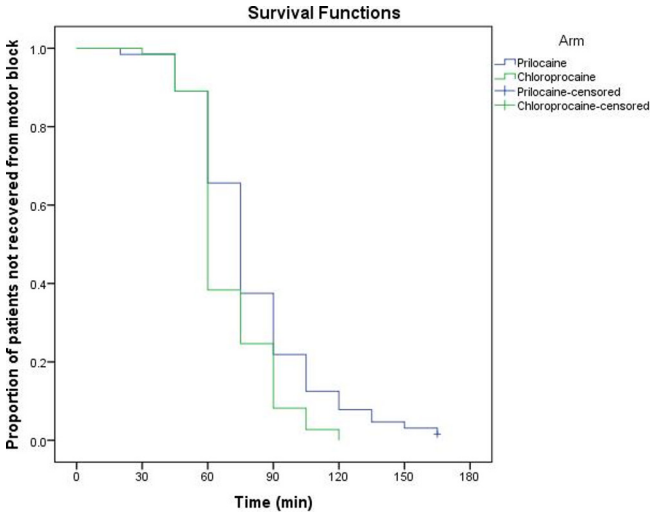

Figure 2 Kaplan-Meier curve time to recovery from motor block.

The Tv and Thd were shorter in the 2-chloroprocaine group than in the prilocaine group (mean difference: 57 min, 95% CI 40 to 75, p<0.001 and mean difference: 57 min, 95% CI 38 to 77, p<0.001, respectively) (table 2). Other secondary endpoints were not significantly different between the groups (table 3). Among the 151 patients who received the study drug, there were no deaths or hospital readmissions within 30 days after surgery.

DISCUSSION

The results of this study confirm earlier observations that both short-acting local anesthetics 2-chloroprocaine and prilocaine, using 40 mg dosages, result in adequate spinal anesthesia with quick recovery of sensory/motor functions for knee arthroscopy in the ambulatory setting. We found a low incidence of 4% (6/150) of spinal anesthesia failure (SAF) resulting in conversion from spinal to general anesthesia, which is in accordance with literature reporting an SAF incidence of 6.2%.[19]

Our findings may indicate that the use of 2-chloroprocaine is preferable over the use of prilocaine, as 2-chloroprocaine resulted in a shorter offset time from motor blockade, a faster onset of sensory block and faster full regression of sensory block than prilocaine. Additionally, spontaneous voiding was

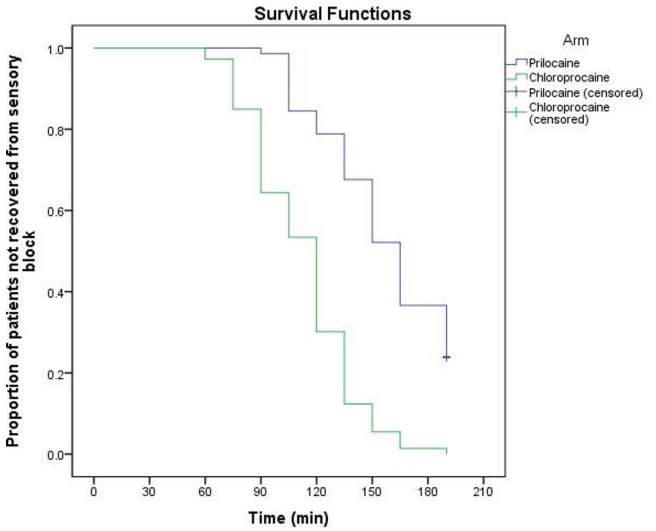

Figure 3 Kaplan-Meier curve time to full regression of sensory block.

Table 3 Secondary outcomes without significant difference between the groups

	N 2-Chloroprocaine /N Prilocaine	2-Chloroprocaine	Prilocaine	P value
Urine retention needing catheterization, yes, n (%)	75/75	1 (1.3)	6 (8.0)	0.12*
Headache day 1, yes, n (%)	68/62	7 (10.3)	2 (3.1)	0.17*
Headache day 7, yes, n (%)	69/68	16 (23.2)	15 (22.1)	0.87†
Nausea/vomiting day 1, yes, n (%)	68/64	6 (8.8)	5 (7.8)	0.83†
Nausea/vomiting day 7, yes, n (%)	69/68	6 (8.7)	5 (7.4)	0.77†
Patient satisfaction day 1	68/63	9 [8–10]	9 [8–10]	0.47‡
Patient satisfaction day 7	69/68	9 [8–10]	9 [8–9]	0.16‡

*Proportions of patients with urine retention needing catheterization and headache at day 1 are presented as numbers (%) and compared with Fisher's exact test.
†Proportions of patients with headache at day 7 and nausea/vomiting at days 1 and 7 are presented as numbers (%) and compared with χ^2 test.
‡Patient satisfaction scores were not normally distributed and are presented as median and interquartile range [IQR] and compared with Mann-Whitney test.

facilitated in patients undergoing spinal anesthesia with 2-chloroprocaine than with prilocaine. Whether or not these variables translate into medical, economic or strategic advantages to a patient and/or hospital is unclear, but with an expected advantage for 2-chloroprocaine.

We compared equal widely used doses of the two study drugs, but an equipotent dose is hard to define and not known from the literature. The different pharmacological and physicochemical characteristics of both local anesthetics may have contributed—to a greater or lesser extent—to the observed differences in this study. Baricity, protein binding and the difference between ester (2-chloroprocaine) and amide (prilocaine) compounds affect the duration of action.[20–26] It should be noted that 7 of the 75 patients (9.3%) in the prilocaine group had no motor block at all (Bromage=0). Although the orthopedic procedures were successfully completed in all seven patients, a lack of motor block might have consequences for the orthopedic surgeon and the procedure since a low muscle tension is preferred. The absence of such a differentiated block in the 2-chloroprocaine group suggests that 40 mg 2-chloroprocaine is more potent than 40 mg prilocaine. This potency difference is confirmed in our secondary endpoint analysis: 2-chloroprocaine showed a faster and higher sensory block, a lower MAP at t=20 min and as a result more need for vasopressor support. Guntz and colleagues performed a dose finding study using 2% hyperbaric prilocaine in knee arthroscopy, the authors suggested 40 mg as the dose required to provide an adequate sensory and motor block (Bromage=3).[27] However, the mean height of the patients in this study was 170.8 cm. In our study the 40 mg dose of hyperbaric prilocaine results in an absent motor block in a subgroup of tall men (n=7), suggesting that the 40 mg dose seems to have some limitations and a higher dose would be recommended within this population.

Our study has several limitations. The first limitation is the intrathecal injection carried out by 14 different anesthesiologists and the assessments by seven assessors. However, our study design of randomization and blinding should have minimized the effects of possible variation in drug administration and assessments on the study endpoints.

Although urinary retention needing catheterization was not significantly different between the groups, a preoperative bladder scan to assess residual bladder volumes and peroperative fluid intake should have been taken into account. Furthermore, measurement of MAP difference compared with baseline values would have provided more information about the hemodynamic consequences of both drugs than the absolute values at t=20 min. Finally, our primary outcome could not be evaluated in patients with failed spinal anesthesia and patients who had sufficient sensory block without motor block. A formal intention-to-treat analysis could therefore not be presented. Nevertheless, we tried to give a full picture regarding the comparative effectiveness in the general population by first comparing proportion of patients with failed spinal anesthesia between the groups, subsequently comparing the proportion of patients for which no motor block was reached after successful spinal anesthesia and finally comparing time to motor block recovery in groups of patients in which motor block was reached.

In conclusion, in knee arthroscopy under successful spinal anesthesia, the use of 2-chloroprocaine results in a faster recovery of motor and sensory block. In line with this, we also found times until hospital discharge to be shorter for 2-chloroprocaine.

Author affiliations
[1]Clinical Pharmacy, Zaans Medisch Centrum, Zaandam, Noord-Holland, The Netherlands
[2]Clinical Pharmacy, Leids Universitair Medisch Centrum, Leiden, , The Netherlands
[3]Anesthesiology, Zaans Medisch Centrum, Zaandam, Noord-Holland, The Netherlands
[4]Anesthesia, Pain and Palliative Medicine, Radboudumc, Nijmegen, , The Netherlands
[5]Orthopedic Surgery, Zaans Medisch Centrum, Zaandam, Noord-Holland, The Netherlands
[6]Clinical Pharmacy, Onze Lieve Vrouwe Gasthuis, Amsterdam, , The Netherlands
[7]Epidemiology and Biostatistics, Amsterdam University Medical Centres, Amsterdam, , The Netherlands
[8]Clinical Pharmacology and Pharmacy, Amsterdam University Medical Centres, Amsterdam, , The Netherlands
[9]Faculty of Medicine, VU University, Amsterdam, , The Netherlands
[10]Anesthesiology, Amsterdam UMC, Amsterdam, , The Netherlands

Contributors EW participated in the design of the study, coordinated the study, performed the database validation and wrote the manuscript. GJvdH coordinated the patient recruitment, assessments and follow-up, performed the data entry, and participated in writing the manuscript. RvdV participated in the design of the study, enrolled patients, administered anesthesia and participated in writing the manuscript. CS and MdL participated in the design of the study and in writing the manuscript. JvdA performed surgical procedures and participated in writing the manuscript. EF participated in writing the manuscript. PvdV performed statistical analyses and participated in writing the manuscript. NS and CB participated in writing the manuscript and approved the final version of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Ethics approval This study received approval from the Ethical Committee of VUmc (Ref: NL53492.029.15).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

REFERENCES

1 Gebhardt V, Zawierucha V, Schöffski O, *et al*. Spinal anaesthesia with chloroprocaine 1% versus total intravenous anaesthesia for outpatient knee arthroscopy: A randomised controlled trial. *Eur J Anaesthesiol* 2018;35:774–81.
2 MARTIN M, Ollé G, Oferil F, *et al*. Recovery time and patient satisfaction in ambulatory knee arthroscopyProspective study comparing three anaesthetic methods. *Ambul Surg* 2005;12:75–9.
3 Lacasse M-A, Roy J-D, Forget J, *et al*. Comparison of bupivacaine and 2-chloroprocaine for spinal anesthesia for outpatient surgery: a double-blind randomized trial. *Can J Anesth/J Can Anesth* 2011;58:384–91.

4 Camponovo C, Wulf H, Ghisi D, *et al*. Intrathecal 1% 2-chloroprocaine vs. 0.5% bupivacaine in ambulatory surgery: a prospective, observer-blinded, randomised, controlled trial. *Acta Anaesthesiol Scand* 2014;58:560–6.
5 Saporito A, Ceppi M, Perren A, *et al*. Does spinal chloroprocaine pharmacokinetic profile actually translate into a clinical advantage in terms of clinical outcomes when compared to low-dose spinal bupivacaine? A systematic review and meta-analysis. *J Clin Anesth* 2019;52:99–104.
6 Schneider M, Ettlin T, Kaufmann M, *et al*. Transient neurologic toxicity after hyperbaric subarachnoid anesthesia with 5% lidocaine. *Anesthesia & Analgesia* 1993;76:1154–7.
7 Zaric D, Pace NL. Transient neurologic symptoms (TNS) following spinal anaesthesia with lidocaine versus other local anaesthetics. *Cochrane Database Syst Rev* 2009;(2).
8 Hampl KF, Heinzmann-Wiedmer S, Luginbuehl I, *et al*. Transient neurologic symptoms after spinal anesthesia: a lower incidence with prilocaine and bupivacaine than with lidocaine. *Anesthesiology* 1998;88:629–33.
9 de Weert K, Traksel M, Gielen M, *et al*. The incidence of transient neurological symptoms after spinal anaesthesia with lidocaine compared to prilocaine. *Anaesthesia* 2000;55:1020–4.
10 Manassero A, Fanelli A. Prilocaine hydrochloride 2% hyperbaric solution for intrathecal injection: a clinical review. *Local Reg Anesth* 2017;10:15–24.
11 Casati A, Fanelli G, Danelli G, *et al*. Spinal anesthesia with lidocaine or preservative-free 2-chlorprocaine for outpatient knee arthroscopy: a prospective, randomized, double-blind comparison. *Anesth Analg* 2007;104:959–64.
12 Goldblum E, Atchabahian A. The use of 2-chloroprocaine for spinal anaesthesia. *Acta Anaesthesiol Scand* 2013;57:545–52.
13 Förster JG, Rosenberg PH, Harilainen A, *et al*. Chloroprocaine 40 mg produces shorter spinal block than articaine 40 mg in day-case knee arthroscopy patients. *Acta Anaesthesiol Scand* 2013;57:911–9.
14 Mulroy MF, Alley EA. Management of bladder volumes when using neuraxial anesthesia. *Int Anesthesiol Clin* 2012;50:101–10.
15 Kreutziger J, Frankenberger B, Luger TJ, *et al*. Urinary retention after spinal anaesthesia with hyperbaric prilocaine 2% in an ambulatory setting. *Br J Anaesth* 2010;104:582–6.
16 Gebhardt V, Hausen S, Weiss C, *et al*. Using chloroprocaine for spinal anaesthesia in outpatient knee-arthroscopy results in earlier discharge and improved operating room efficiency compared to mepivacaine and prilocaine. *Knee Surg Sports Traumatol Arthrosc* 2018;62.
17 Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. *Acta Anaesthesiol Scand* 1965;9:55–69.
18 Pollock JE, Neal JM, Stephenson CA, *et al*. Prospective study of the incidence of transient radicular irritation in patients undergoing spinal anesthesia. *Anesthesiology* 1996;84:1361–7.
19 de Sá Oliveira RR, Módolo MP, Mizubuti GB, *et al*. Total spinal anesthesia failure: have you assessed the sensory anesthesia in sacral dermatomes? *Anesth Analg* 2017;124:1674–7.
20 Casati A, Danelli G, Berti M, *et al*. Intrathecal 2-chloroprocaine for lower limb outpatient surgery: a prospective, randomized, double-blind, clinical evaluation. *Anesthesia & Analgesia* 2006;103:234–8.
21 Covino BG. Pharmacology of local anaesthetic agents. *Br J Anaesth* 1986;58:701–16.
22 Butterworth J. Clinical pharmacology of local anaesthetics. In: Cousins MJ, Bridenbaugh Phillip O, eds. *Cousins and Bridenbaugh's neural blockade in clinical anesthesia and pain medicine*. 4th ed. Lippincott Williams & Wilkins, 2012.
23 Peck TE, Hill SA, Williams M. Basic Principles. In: *Pharmacology for anaesthesia and intensive care*. Cambridge; New York: Cambridge University Press, 2008.
24 Hocking G, Wildsmith JAW. Intrathecal drug spread. *Br J Anaesth* 2004;93:568–78.
25 Camponovo C, Fanelli A, Ghisi D, *et al*. A prospective, double-blinded, randomized, clinical trial comparing the efficacy of 40 mg and 60 mg hyperbaric 2% prilocaine versus 60 mg plain 2% prilocaine for intrathecal anesthesia in ambulatory surgery. *Anesth Analg* 2010;111:568–72.
26 Pitkänen M. Spinal subarachnoid blockade. In: Cousins MJ, Bridenbaugh Phillip O, eds. *Cousins and Bridenbaugh's neural blockade in clinical anesthesia and pain medicine*. 4th ed, 2012.
27 Guntz E, Latrech B, Tsiberidis C, *et al*. ED50 and ED90 of intrathecal hyperbaric 2% prilocaine in ambulatory knee arthroscopy. *Can J Anesth/J Can Anesth* 2014;61:801–7.