ED90 of spinal 2-chloroprocaine 1% in ambulatory knee arthroscopy up to 45 min: a randomized biased-coin- up-and-down sequential allocation trial

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ABSTRACT

Background A short acting spinal anesthetic facilitates smooth flow since quick recovery of motor function will facilitate unassisted ambulation. The aim of this study was to estimate the effective dose (ED90) of intrathecal 2-chloroprocaine 1% in outpatient knee arthroscopy.

Methods Two cohorts were included in two different hospitals. In cohort I, a randomized biased-coin up-and-down design with 40 patients was used to find the ED90. Four dose-levels of plain 2-chloroprocaine 1% were used: 25, 30, 35 and 40 mg. The identified primary outcome, the ED90, was validated in 50 patients in cohort II with an open label design. Secondary outcomes included time to complete recovery from motor and sensory block with spinal injection as time zero, peak sensory block level, urine retention and time until hospital discharge.

Results Forty patients were included in the final analysis in cohort I. The ED90 was estimated at 27.8 mg, successful spinal anesthesia was obtained in 38 patients (95%). Fifty patients were included in the final analysis in cohort II, 49 patients had successful anesthesia with a fixed round dose of 28 mg. In this Cohort, peak sensory block was T10/T11 (range: (L4–T4)). The median time to full recovery of the motor block was 60 min (45–60) and 90 min (75–105) for the sensory block. The mean time to hospital discharge was 2.9 hours (0.7).

Conclusion The ED90 of 2-chloroprocaine 1% in knee arthroscopy was estimated to be 27.8 mg. In an external population, the ED90 resulted in successful anesthesia in 98% of the patients (95% CI 89% to 100%).

Trial registration number Netherlands Trial Registry (NL6769).

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INTRODUCTION

Most practitioners have abandoned intrathecal lidocaine because of the high incidence of transient neurological syndrome (TNS).[1] In recent years, preservative-free 2-chloroprocaine 1% has regained interest as short acting spinal anesthetic for lower limb surgery lasting up to 60 min.[2] Several double-blind randomized controlled studies have demonstrated that, compared with other local anesthetics, the short duration of block of 2-chloroprocaine 1% favors a fast hospital discharge in outpatient anesthesia.[3–11] Our previous study, in which we compared intrathecal prilocaine and 2-chloroprocaine 1% in ambulatory knee arthroscopy, inspired us to investigate the optimal dose of 2-chloroprocaine 1% for this indication. 2-Chloroprocaine 1% (40 mg) not only showed a faster offset of motor and sensory function than prilocaine (40 mg), it also had high peak levels suggesting a lower dose may further reduce an unnecessary prolonged length of stay.[11]

To date, two prospective randomized dose-finding studies in 45 American Society of Anesthesiology physical status (ASA) I–II patients undergoing lower limb surgery lasting up to 60 min were performed.[12] Three different drug doses (30, 40 and 50 mg) of 2-chloroprocaine 1% were administered.[6] Significantly more patients in the 30 mg group required supplemental intraoperative analgesic as a result of insufficient analgesia, and time to complete block recovery was significantly prolonged when a dose of 50 mg was used. However, neither study distinguished between different types of lower limb surgery, nor included ASA III patients.[6 7]

In addition, previous dose-finding studies used a design with preassigned doses in each arm. However, to determine the minimum effective dose, a sequential design is preferable as it allows measurement of the response at any point along the dose response curve.[13–17]

So far, the minimum effective dose of 2-chloroprocaine 1% for knee arthroscopies lasting 15–20 min without the need of additional analgesics is unknown. In our study, we aimed to establish and externally validate the effective dose of 2-chloroprocaine 1% in 90% of the patients (ED90) of intrathecal 2-chloroprocaine 1% in ambulatory knee arthroscopy.

MATERIALS AND METHODS

Study design

This was an investigator-initiated, prospective, randomized and adaptive dose-finding study conducted in two centers in The Netherlands. Cohort I was included between July 2018 and January 2020 in the Department of Anesthesiology in Maasstad Ziekenhuis, Rotterdam. Subsequently, cohort II was included between January 2020 and February 2021 in the Department of Anesthesiology in Zaans Medisch Centrum, Zaandam. Institutional approval was obtained for both centers. The study was prospectively registered within the Netherlands

Trial Register (November 16, 2017, https://www.trialregister.nl/trial/6769). Written informed consent was obtained from all participants before entering the study. An independent data and safety monitoring board oversaw the study and reviewed blinded safety data.

Patients

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 ASA I–III. Patients were excluded if they were pregnant, had an allergy to 2-chloroprocaine 1%, a contraindication to neuraxial anesthesia or a previous neuropathy to the lower extremities, had previously participated in the study for the other knee, had a language barrier or were otherwise unable to complete follow-up.

Randomization

In cohort I, a biased-coin up-and-down design was used with 40 patients to find the ED_{90}, defined as the minimum dose where anesthesia was successful in 90% of the patients. Patients received intrathecal plain 2-chloroprocaine 1% (Ampres, Sintetica, Switzerland). Four different dose-levels were used in the design: 25, 30, 35 and 40 mg. The design uses a sequential method where the 2-chloroprocaine 1% dose that a patient receives depends on the previous patient's dose and response. If anesthesia was not successful in a patient, then the following patient received the next higher dose or the maximum dose of 40 mg if the maximum dose had already been reached. If anesthesia was successful in a patient, the following patient received the same dose with a probability of 89% and the next lower dose with probability of 11%. If the patient with successful anesthesia already received the lowest dose of 25 mg, the next patient also received 25 mg. Randomization probabilities were chosen to converge around the ED90. Randomization was done using computer-generated lists. The first patient received 35 mg because this dose was expected to be close to the ED90. One of the anesthesiologists administered the spinal anesthetic according to the randomization without disclosing the group allocation to anybody. This anesthesiologist then left the operating theater and was not further involved in any part of the trial. Patient, observer, orthopedic surgeon and a second anesthesiologist who assumed responsibility for the patient during surgery and recovery, were blinded for the dose.

In cohort II, the ED90 established in cohort I was validated in a new sample of 50 patients. Every patient received the same dose of 2-chloroprocaine 1%. Study procedures were similar for cohort II but without randomization and blinding.

Intraoperative and postoperative care

Approximately 1 hour before surgery all patients received oral acetaminophen 1 g or a non-steroidal anti-inflammatory drug (NSAID) 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. Fluid intake was minimalized before surgery, patients were only allowed to drink half a glass of water for the intake of oral premedication. Perioperative monitoring consisted of pulse oximetry, electrocardiography, non-invasive blood pressure measurement and heart rate. Postoperative pain medication was tailored individually and consisted of either acetaminophen or an NSAID diclofenac 50 mg or naproxen 500 mg.

In order to attempt a time to incision of 10–15 min after the intrathecal injection with 2-chloroprocaine 1%, spinal anesthesia was administered in the operating theater. Patients were in sitting position while the spinal anesthesia was performed. After local anesthesia of the skin at the puncture site (preferably midline at L3–L4), the spinal anesthetic was injected using a 25-gage or 27-gage needle (Pencan, B.Braun AG, Germany). After obtaining a free flow of cerebrospinal fluid with the orifice of the needle facing upwards, the investigational medical product was injected slowly. The patient was then immediately placed in supine position.

Assessments

Immediately after spinal injection, a stopwatch was started (=time zero). Start criteria for incision were complete loss of cold sensation at the L2 dermatome and a score of 0–2 on an 11-point (0–10) numerical rating scale (NRS) following inflation of the thigh tourniquet (300 mm Hg).[18] At incision, if the NRS was not zero, the spinal anesthesia was considered not successful and the rescue procedure was started.

An observer blinded to the group allocation recorded the evolution of spinal block until achievement of home discharge criteria. At 5, 10, 15, 20 and 30 min, motor block was assessed using a modified Bromage 4-point scale (0–3; 0_Able to move entire leg or knee – 3_Unable to move knee or foot).[19] Sensory block was assessed using loss of cold sensation (tested with ice cubes) at 2, 4, 6, 8, 10, 15, 20, 25 and 30 min. Thereafter, motor and sensory blocks were assessed once every 15 min until full regression was observed. 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. 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. (table 1).

The time of first spontaneous voiding was registered. After return to the surgical ward, further treatment was according to the hospital's standard procedure. The time to hospital discharge was recorded, defined as the time between spinal injection and the moment the subject met the discharge criteria for this study, that is, spontaneous voiding, recovery from motor block, no perioperative nausea and vomiting and a low pain level (NRS≤4). On the first and seventh postoperative day, patients were interviewed by telephone about symptoms of TNS and postdural headache following a standardized checklist.

Rescue procedure

The rescue anesthetic procedure was general anesthesia consisting of intravenous propofol 2 mg kg^{-1} and intravenous sufentanil 0.25 $\mu g\ kg^{-1}$.

Primary outcome

The primary outcome was the effective dose ED90 of spinal 2-chloroprocaine 1% in knee arthroscopy.

Table 1 Interventions urinary bladder volume

Volume	Intervention
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

Secondary outcome

Secondary outcome parameters included time to complete recovery from motor and sensory block, peak sensory block level, urine retention and time until hospital discharge.

Statistical analysis

For cohort I, simulations were performed to assess statistical properties of the biased-coin up-and-down sequential method at the planned sample size of 40 patients. Dose–response curves of sigmoid-shape were considered where the ED90 was varied between 27.5 and 37.5 in steps of 2.5 (five settings) and the percentage of effective anesthesia at the lowest dose of 25 mg was varied from 40% to 70% in steps of 10% (four settings). In the 20 settings considered, the probability of selecting a dose that is effective in less than 80% of the patients was only 10%. The probability of selecting a dose that is effective in at least 85% of the patients was found to be higher than 75%. Average probability of successful anesthesia for patients in this part of the study ranged from 86% to 93% between settings.

The modified isotonic regression estimator described by Stylianou and Flournoy was used to determine the ED90 in cohort I of the study.[16]

For cohort II, sample size was based on the expected width of the 95% CI around the estimated proportion of successful anesthesia. A sample size of 50 patients with 45 (90%) patients with successful anesthesia results in an exact 95% CI that ranges from 78% to 96%.

An exact 95% Clopper-Pearson interval was calculated for the proportion of patients with successful anesthesia at the selected ED90. Descriptive statistics were used to summarize distribution of the secondary outcome parameters.

RESULTS

In cohort I, 226 patients were screened for inclusion, 42 of whom fulfilled the inclusion criteria and gave informed consent. Of these, one had to be excluded, due to a failed spinal puncture. Another patient was lost to follow-up due to inadvertently subdural spread of the anesthetic. In cohort II, of the 131 patients eligible for participation, 50 patients were included. The flow diagrams of both cohorts are presented in figure 1.

The patient and surgery characteristics of all patients who completed the study are presented in table 2. In cohort I, there were 38 patients with successful spinal anesthesia with 2-chloropraine and 2 patients with a failure. Both patients received the 25 mg dose in combination with general anesthesia in order to be able to complete the surgery. Following the step-up-and-down design, no patients were eligible to receive 40 mg. No patients received additional sufentanil. The sequence of successful and failed blocks in cohort I is depicted in figure 2. After completion of all 40 patients in cohort I, the ED90 was estimated at 27.8 mg.

In cohort II, the ED90 was used as a fixed round dose of 28 mg in 50 patients. Successful anesthesia was achieved in 49 patients, 2 patients received additional sufentanil (<0.2 µg/kg) intraoperatively. One patient had a failure using the 28 mg dose and a 25-gage needle at L2/L3 insertion level. In this patient, 10 min after intrathecal injection of 2-chloroprocaine 1% the sensory block was only at L5 level. In order to be able to start surgery, the escape procedure with general anesthesia was used. After recovery of general anesthesia there was a sensory block of L4 at 105 min. This suggests a block with a very slow onset. The proportion of patients in which anesthesia was successful was 98%, 95% CI 89% to 100%.

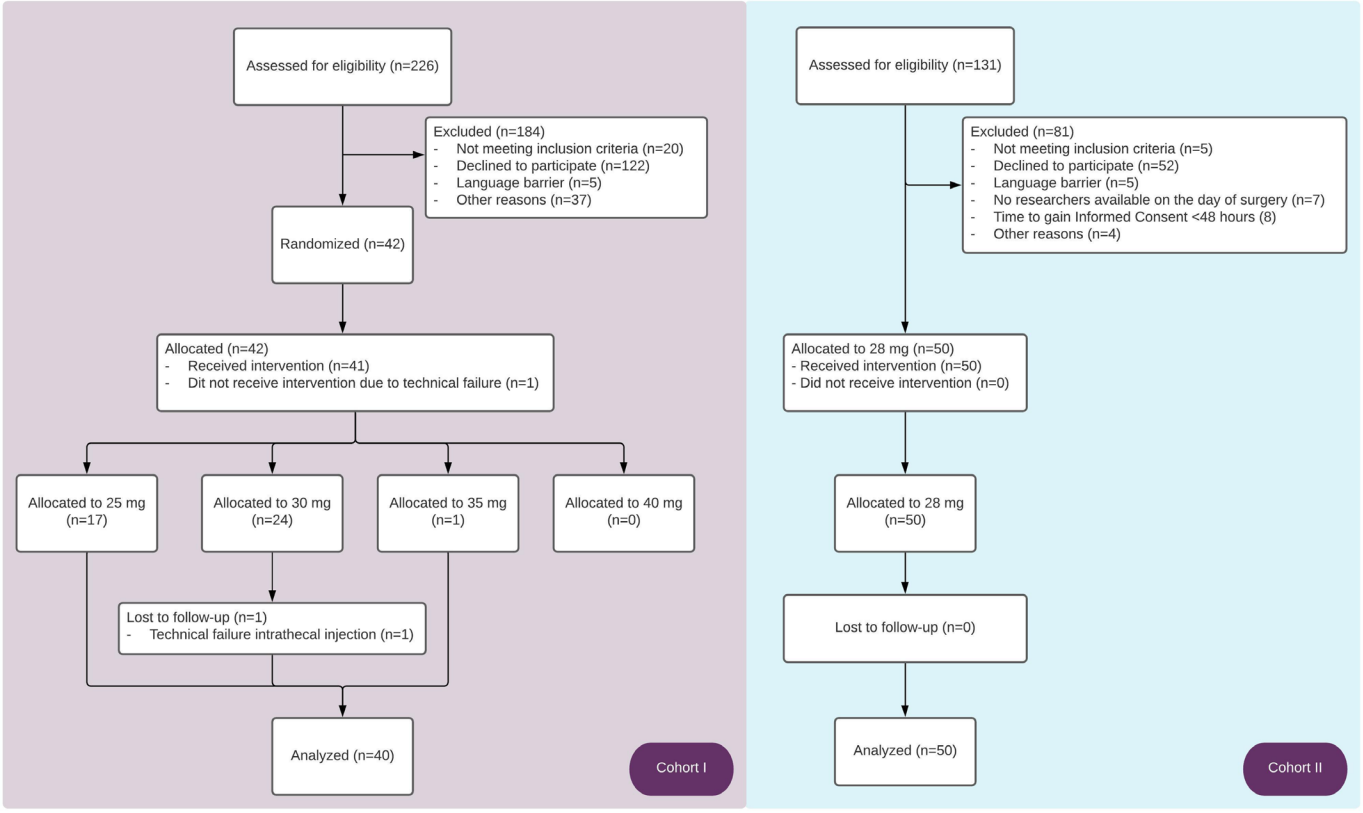

Figure 1 Flow diagram of participants in cohort I and II of the study.

Table 2 Patient and surgery characteristics

	Cohort I (N=40)	Cohort II (N=50)
Gender=male (n, %)	25 (62.5)	27 (54.0)
ASA=I (n, %)	14 (35.0)	23 (46.0)
ASA=II (n, %)	23 (57.5)	23 (46.0)
ASA=III (n, %)	3 (7.5)	4 (8.0)
Premedication=yes (n, %)	36 (90)	50 (100)
Preoperative voiding (n, %)	40 (100)	46/49 (93.9)
Age (years)	52.6 (12.5)	51.5 (12.4)
Body mass index (kg m^{-2})	29.8 (4.6)	27.2 (4.1)
Weight (kg)	92.9 (15.4)	86.0 (16.2)
Height (cm)	176.8 (9.9)	176.8 (10.3)
Duration of surgery (min)	12 (6–45)	15 (6–40)
Time from spinal anesthesia to start surgery (min)	11 (8–18)	9 (2–20)

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

Table 3 shows the secondary endpoints of cohort I and II. After 10 min, a Bromage score of 3 was obtained in 21% and 37% of the patients who achieved successful anesthesia in cohort I and II, respectively. In six patients the Bromage score at 10 min was not assessable because it coincided with the incision. Peak sensory block was T7 (range: (L2–T3)) and T10/T11 (equally divided, range: (L4–T4)) in cohort I and II, respectively. Patients did not experience urinary retention in cohort I, whereas 8% in cohort II needed catheterization. No signs of TNS were observed in both Cohorts. In cohort II, one patient had a postdural puncture headache (PDPH).

DISCUSSION

This is the first dose-finding study with intrathecal 2-chloroprocaine 1% using an up and down method (UDM) to find the lowest effective dose in knee arthroscopy. We found that the ED90 of intrathecal 2-chloroprocaine 1% with a median surgery time of 12 min was 27.8 mg. Validation of a 28 mg dose in an external population showed sufficient block height and analgesia.

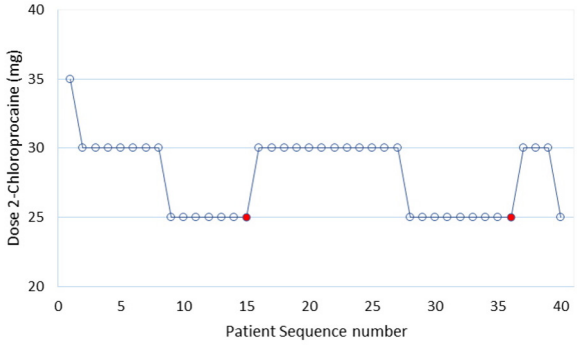

Figure 2 Sequential block results of spinal anesthesia with 2-chloroprocaine 1% according to the Stylianou and Flournoy up-and-down method. An effective dose (successful anesthesia) is denoted by an open blue circle; an ineffective dose (anesthesia not achieved) is denoted by a red circle.

Table 3 Secondary endpoints in cohort I and II

	Cohort I (n=40)	Cohort II (n=50)
Time to onset sensory block (min)	2 (2, 2)	2 (2, 6)
Proportion of patients with Bromage 3 after 10 min	8 (20%)	16/43 (37.5%)
Peak sensory block	T7 (L2, T3)	T10/T11 (L4, T4)
Time to full motor block recovery (min)	45 (45–75)	60 (45–60)
Time to full sensory block recovery (min)	90 (75–105)	90 (75–105)
Time to first voiding (hours)	2.3 (0.6)	2.6 (0.7)
Time to hospital discharge (hours)	3.5 (1.4)	2.9 (0.7)
Urine retention needing catheterization=yes (n,%)	0 (0)	4 (8.0)

Outcomes summarized by median (range), mean (SD) or frequency (percentage).

Our results differ from other dose finding studies with 2-chloroprocaine 1% reporting that a dose of 30 mg did not provide adequate anesthesia in lower limb surgery.[5 6] There might be several explanations for this discrepancy. First, the mean surgical time (16 min) in cohort II was considerably shorter than the reported mean surgical time (45 min) by Casati *et al*.[6] Ghisi *et al* included lower limb surgeries up to 40 min. They also concluded that the 30 mg dose resulted in a higher secondary failure rate compared with 40 and 50 mg.[5] Both studies included different types of lower limb surgery, while we focused on ultrashort knee arthroscopy. The authors' suggestion that a 30 mg dose of spinal 2-chloroprocaine 1% may be adequate in outpatient procedures shorter than 30 min, was confirmed in our study. It should be noted that the time between intrathecal injection and start of surgery is of great importance if a low dose as 28 mg is used, therefore the performance of spinal anesthesia in the operation theater is highly recommended. If any form of delay is expected or the intrathecal injection is performed on the preoperative holding area, a higher dose than the ED90 will allow the anesthesiologist to reduce the risk for a secondary failure.[20]

Not all patients achieved a maximum Bromage score of 3 during surgery in this study, indicating that a substantial part of the cohort (63%) maintained, to a greater or lesser extent, their motorfunction during surgery. Since patients did not experience any pain, this is an indication that 28 mg may indeed be close to the minimum effective dose with the thick motor nerve fibers being less susceptible for a low dose local anesthetic than the thin nerve fibers responsible for pain and touch (differential blockade).[21]

The time to hospital discharge of 2.9 hours after intrathecal injection of 28 mg 2-chloroprocaine 1% in cohort II is consistent with a 30 mg dose described in literature.[5 6 11 22] The offset time of motoric and sensory block (60 and 90 min, respectively), were not the dominant factors for discharge anymore. In general, since it is still a discharge criterium in most centers, the moment of voiding is closely related to the time of discharge. The relative high incidence of urinary retention needing catheterization (8%) in cohort II is remarkable and not consistent with literature. In contrast with long acting spinal anesthetics, urinary retention is unlikely in short acting anesthetics.[23] All four patients had bladder volumes ≥500 mL within 1 hour after surgery, which is frequently associated with inability to void spontaneously. One patient did not succeed in voiding preoperatively, which may explain the excessive bladder volume. While it remains unclear if 2-chloroprocaine 1% contributed to urinary retention in the other three patients, risk factors such as perioperative fluid administration and gender may have played

a role too. Nevertheless, in spite of the short acting character of 2-chloroprocaine 1%, awareness for the occurrence of urinary retention following spinal anesthesia should be maintained.

The dose-finding design we used was different from the non-sequential design with preassigned doses used in previous dose-finding studies with 2-chloroprocaine 1%.[5 6] An UDM allows measurement of the response at any point along the dose–response curve, making this a preferable design for establishing the minimum effective dose.[13–15 17] Ethical concerns also may favor a sequential design to ensure that the fewest subjects receive a non-effective or an unnecessary high dose. The UDM is designed to provide a reliable estimate of the 50% point along the dose–response curve (ED_{50}); the dose at which 50% of the population responds is considered the median estimated dose. However, anesthesiologists are mainly interested in the ED90/95 of a drug. The ED90 is typically calculated from the ED_{50}, but there may be a lack of symmetry outside the median point. We used a biased-coin up-and-down design as proposed by Stylianou and Flournoy.[16] This design is an adaptation to the UDM method in which the randomization probabilities can be set to converge to the doses around the ED90. This makes the method suitable for direct and a more accurate determination of the ED90 without the need to extrapolate along the dose–response curve.

Some limitations of our study should be discussed. First, although protocolized, the spinal injection was carried out by different anesthesiologists. The injection rate and rate of turning supine after injection may have had individual differences. Second, although in both centers pencil-point needles were used, the choice of needle caliber was not standardized. Contrary to cutting-needles, there is no association between needle gage and PDPH for pencil-point needles, but preferably one caliber would have been used.[24] Another factor that may have influenced the intrathecal spread of the injected solution, is the volume of the different doses of 2-chloroprocaine 1% in cohort I (2.5–3.5 mL). Although most studies suggest there is no significant influence of the injection volume, it may have led to individual differences.[25] Furthermore, our study is limited by the fact that, we did not perform a preoperative bladder scan. Patients did void prior to surgery but it was not ensured whether a residue was left in situ due to stress or other factors. Therefore, we are not able to completely explain the high rate of urinary retention in cohort II.

CONCLUSION

In conclusion, the ED_{90} of intrathecal 2-chloroprocaine 1% for knee arthroscopy with a median surgery time of 15 min, is established in this study at 28 mg. The fast onset time and offset time makes this dose very effective for a smooth patient flow in the ambulatory setting.

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Contributors EJW participated in the design of the study, coordinated the study, performed the database validation, wrote the manuscript and was the guarantor. JSHAK 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; PMvdV participated in the design of the study, performed statistical analyses and participated in writing the manuscript; JvdA performed surgical procedures and participated in writing the manuscript; YZ, CS, FW and LK performed assessments and participated in writing the manuscript; EF, ELS and CB participated in writing the manuscript and approved the final version of the manuscript; MAdL participated in the design of the study, writing the manuscript and approved the final version of the manuscript.

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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.

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