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REPORTS OF ORIGINAL INVESTIGATIONS

ED_{50} and ED_{90} of intrathecal hyperbaric 2% prilocaine in ambulatory knee arthroscopy

DE_{50} et DE_{90} de la prilocaïne 2 % intrathécale hyperbare dans l'arthroscopie du genou en ambulatoire

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Abstract

Purpose *Hyperbaric 2% prilocaine (HP) is increasingly used for spinal anesthesia in day-case surgery. The aim of this prospective double-blind study was to determine the effective dose $(ED)_{50}$ and the ED_{90} of HP for patients undergoing knee arthroscopy.*

Methods *Doses of HP were determined using an up-and-down sequential allocation technique. Sequences were analyzed by isotonic regression analysis. A subsequent observational study was performed with the calculated ED_{90} in 50 patients to confirm the initial result and to describe the induced blockade effects and side effects. Times corresponding to onset and duration of sensory and motor block, surgical data, and side effects were recorded.*

Results *The ED_{50} was estimated at 28.9 mg (95% confidence interval [CI]: 26.5 to 35.3) and the ED_{90} was estimated to be 38.5 mg (95% CI: 35.7 to 39.5). A 40 mg dose of HP provided efficient anesthesia in 46 patients (92%, 95% CI: 82 to 98). The average (SD) time to effective anesthesia was 14.5 (3.9) min. Complete sensory block at level T12 was obtained after ten minutes in 44 of 50 patients. The average (SD) duration of the sensory block was 205 (36.1) min. Maximal level of sensory block was obtained at the T8-T11 levels in 41 of 50 patients without hemodynamic instability. A Bromage 3 score was obtained in 40 of the 46 patients who achieved successful anesthesia after 30 min. Patients did not experience urinary retention, nor were any signs of transient neurologic symptoms observed.*

Conclusion *This study determined the ED_{50} of HP is 28.9 mg and suggests that a 40-mg dose of HP is adequate to provide successful spinal anesthesia for outpatient knee arthroscopy.*

Résumé

Objectif *La prilocaïne 2 % hyperbare (PH) est de plus en plus utilisée pour la rachianesthésie en chirurgie d'un jour. Le but de cette étude prospective à double insu était de déterminer la dose efficace (DE_{50} et DE_{90}) de la PH pour les patients subissant une arthroscopie du genou.*

Méthodes *Des doses de PH ont été établies au moyen d'une technique d'allocation séquentielle haute-et-basse. Les séquences ont été analysées avec une méthode de régression isotonique. Une étude observationnelle subséquente a été réalisée avec la DE_{90} chez 50 patients afin de confirmer le résultat initial, décrire les effets de blocage induits ainsi que les effets indésirables. Les temps correspondant à l'installation et à la durée du bloc moteur et sensitif, les données chirurgicales et les effets indésirables ont été consignés.*

Résultats *La DE_{50} a été estimée à 28,9 mg (intervalle de confiance [IC] à 95 %: 26,5 à 35,3) et la DE_{90} a été estimée à 38,5 mg (IC à 95 %: 35,7 à 39,5). Une dose de PH de 40 mg a procuré une anesthésie efficace chez 46 patients (92 %; IC à 95 %: 82 à 98). Le délai moyen*

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Author contributions *Emmanuel Guntz* designed and conducted the study and prepared the manuscript. *Bausard Latrech, Constantin Tsiberidis,* and *Jonathan Gouwy* performed the data collection. *Yota Kapessidou* helped design the manuscript, and *Yota Kapessidou* and *Emmanuel Guntz* reviewed the manuscript.

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(ET) d'obtention d'une anesthésie efficace a été de 14,5 (3,9) minutes. Un bloc sensitif complet au niveau D12 a été obtenu après 10 minutes chez 44 des 50 patients. La durée moyenne (ET) du bloc sensitif a été de 205 (36,1) minutes. Le niveau le plus élevé du bloc sensitif obtenu était compris entre D8 et D11 chez 41 des 50 patients sans instabilité hémodynamique. Une note de 3 au score de Bromage a été obtenue chez 40 des 46 patients ayant obtenu une anesthésie réussie après 30 minutes. Les patients n'ont pas présenté de rétention urinaire et aucun symptôme neurologique transitoire n'a été observé.

Conclusion *Cette étude a établi que la DE_{50} de la PH est 28,9 mg et suggère qu'une dose de 40 mg de PH est adéquate pour réussir une rachianesthésie chez les patients ambulatoires ayant une arthroscopie de genou.*

Spinal anesthesia offers clear advantages in ambulatory surgery by reducing both pain scores and the requirement for postoperative analgesia.[1] Increasing interest in outpatient spinal anesthesia has led to further evaluation of short-acting local anesthetics with rapid onset, predictable duration of sensory block, rapid recovery of motor block, and minimal side effects.[2,3] For over 40 years, hyperbaric lidocaine was the most frequently used spinal local anesthetic for this purpose However, its use for this indication has now been abandoned largely because of the high risk for transient neurologic symptoms (TNS) that are independent of the administered dose.[4,5] Other local anesthetics, such as mepivacaine or low dose bupivacaine and ropivacaine have limitations as well. These limitations include, but are not limited to, a relatively high incidence of TNS from mepivacaine and relatively long discharge times and limited intraoperative analgesia associated with low dose bupivacaine and ropivacaine, respectively.[4,6,7] Therefore, in an ongoing search for suitable alternatives for spinal anesthesia in ambulatory surgery, other short-acting local anesthetics with a lower risk for TNS (compared with lidocaine) have been considered.

Hyperbaric prilocaine (HP) is an amide-type local anesthetic[8] that was withdrawn from market in 1978 because the formulation was considered unstable. Consequently, it failed to show obvious advantages over the then popular lidocaine. Recently, a new formulation of prilocaine hydrochloride, constituted with glucose in a 2% hyperbaric solution, has been developed. The formulation is very stable with a shelf life at ambient temperature of five years, and the 2-methylaniline content is $< 0.10\%$ throughout the entire duration of shelf life. Moreover, formation of coloured contaminants is not observed, as described for previous formulations. Detailed information concerning the manufacture of the new HP is available in the European Patent Specification (http://worldwide.espacenet.com). This new formulation has received regulatory approval for intrathecal administration in the member states of the European Union. (e.g., German approval: http://www.hma.eu).

Recent studies of HP for short surgical procedures under spinal anesthesia, such as knee arthroscopy, gynecological, and urogenital surgery, suggest that prilocaine is efficacious for ambulatory surgery.[8-11] In regards to side effect profile, TNS are rather rare with prilocaine, and not yet specifically investigated for HP.[12,13] The proposed inrathecal doses of both plain and hyperbaric prilocaine solutions for various surgical procedures range from 10-80 mg. In one recent study, doses of HP from 40-60 mg were reported for outpatient surgeries.[8] In another report, a low dose of prilocaine (20 mg plain solution in the presence of fentanyl) was shown to provide adequate anesthesia for knee arthroscopy.[9] One trial which evaluated HP specifically for knee arthroscopy sought to identify the incidence of urinary retention after spinal anesthesia with a 60-mg dose.[14] Thus, even though the drug is in clinical use, optimal doses of HP required for specific types of surgery warrant further refinement, for example, as reported by Gebhardt *et al.* for patients undergoing perianal surgery.[11]

The aim of the present study was to determine the ED_{50} and ED_{90} of intrathecal HP for patients undergoing ambulatory knee arthroscopy. We include the results of a follow-up observational study with the defined ED_{90} value to evaluate efficacy and side effect profile associated with the ED_{90} dose of intrathecal HP for ambulatory anesthesia.

Methods

This study was approved by the local Medical Ethics Committee (Centre Hospitalier Interregional Edith Cavell, Research Ethics Board number: code EC 332, OM 157; date of protocol approval: 19 of April 2011; protocol number: B322201110977). After written informed consent, patients meeting the following criteria were enrolled in this study (October 2011 to January 2013): American Society of Anesthesiologists (ASA) physical status I-II, aged 18-70 yr, body mass index (BMI) 20-30 $kg \cdot m^{-2}$, height 155-190 cm, and scheduled for day-case knee arthroscopy under spinal anesthesia. Exclusion criteria were standard contraindications to neuraxial block, neurological impairment, and known allergy to local anesthetics.

In the first part of the study, the injected dose of HP was varied according to the modified up-and-down sequential allocation method (UDM) established by Dixon and Massey.[15] The dose of HP that a patient received was determined by the previous patient's response. If successful anesthesia was obtained, the next patient's dose was decreased. Conversely, if anesthesia was not successful, the next patient's dose was increased. Considering the wide range of doses reported in the literature (from 10-80 mg), we chose to start the first patient with a dose of 80 mg. The dose decrement/increment for each subsequent patient was set at 5 mg. Two anesthesiologists were involved in this part of the study. The first anesthesiologist prepared the dose to inject and performed the spinal anesthesia. The second anesthesiologist, blinded to the dose, was absent during the procedure and assessed each block. Furthermore, all patients were unaware of the injected dose of HP.

In the second part of the study, all patients received the ED_{90} dose determined in the first part. This observational section was performed with a chosen sample of patients scheduled for the same type of surgery (*Statistics, Part I*).

All patients were premedicated with midazolam 1 mg *iv* and received Ringer's lactate solution 10 $mL \cdot kg^{-1}$ *iv via* peripheral access as regular fluid therapy throughout the entire operation. Continuous electrocardiography and pulse oximetry (SpO_2) were applied to each patient, and noninvasive arterial blood pressure was measured at three-minute intervals during the procedure. With the patient in the sitting position, spinal anesthesia was performed under aseptic conditions using the midline approach at the L3-L4 interspace with a 25G Whitacre needle (Becton Dickenson, Madrid, Spain). The needle bevel was always oriented cranially. Following observation of spontaneous flow of cerebrospinal fluid, hyperbaric 2% prilocaine (Sintetica SA, 6850 Mendrisio, Switzerland) at room temperature and without any adjuncts was injected slowly. Immediately after lumbar puncture, patients lay supine in the neutral position. Sensory and motor blockade was assessed five, ten, 20, and 30 min after intrathecal injection of HP, corresponding to T0. Whereas pinprick (needle of a Dejerine reflex hammer, Neurologicals 5038) and cold test were used to evaluate the level of sensory block, four levels of the Bromage scale were used to evaluate the motor block (0 = no motor block; 1 = hip blocked; 2 = hip and knee blocked; and 3 = hip, knee, and ankle blocked).

For purposes of the study, anesthesia was considered successful when there was complete loss of pinprick and cold sensation at the T12 dermatome and when pain was inferior to two following inflation of the tourniquet and zero upon incision. The tourniquet was inflated equally for each patient at a pressure of 340 mmHg.

Pain was assessed using a 10-cm horizontal visual analogue scale anchored by the investigator with "no pain" at one end and "worst possible pain" at the other end. The patients were asked to put a mark on the scale to indicate pain intensity. The distance from "no pain" to the patient's mark rated the pain numerically on the other side of the scale.

For occurrences of inadequate analgesia, a continuous infusion of remifentanil was administered intravenously. Hypotension (a decrease in systolic blood pressure of $> 20\%$ of initial value) was treated with ephedrine 5-10 mg *iv* at the discretion of the attending anesthesiologist.

After surgery, patients' follow-up continued in the postanesthesia care unit every ten minutes until complete recovery of motor block was observed (Bromage score = 0). Resolution of the sensory block was recorded when all the tests were negative and when patients declared regaining full sensitivity. At this time, the patient was considered eligible for discharge to home. In order to avoid any confounding influence of analgesic adjuncts on spinal anesthesia during the perioperative period, only paracetamol and diclofenac were administered in the recovery room.

Overall, the blinded investigator recorded the following variables:

1. onset and duration of sensory block
2. maximum level of sensory block
3. onset and duration of motor block
4. times to inflation of tourniquet
5. start and end time of surgery
6. side effects including hypotension, bradycardia (variations $> 20\%$ below the baseline) or urinary retention (incapacity to void after complete resolution of the block)
7. time to eligibility for home discharge, defined by complete regression of sensory block.

For the first 30 days after surgery, patients were asked to report any postoperative problems to the anesthesiologist involved in the study.

Statistics

Demographic (sex, age, weight, height, BMI, ASA physical status) and surgical data were collected throughout the study. Categorical data are presented as count (percent) and continuous data are presented as mean (standard deviation) or median (P25, P75) if the sample data were skewed. The present study included

Table 1 Part I – Demographic characteristics ($n = 39$)

Age (yr)	48.3 (11.6)
Weight (kg)	75.5 (14.0)
Height (cm)	172.6 (9.8)
BMI ($kg \cdot m^{-2}$)	25.2 (3.1)
ASA	1:23 II: 16
Sex	F:16 M:23

Absolute numbers and means (SD). BMI = body mass index; ASA = American Society of Anesthesiologists

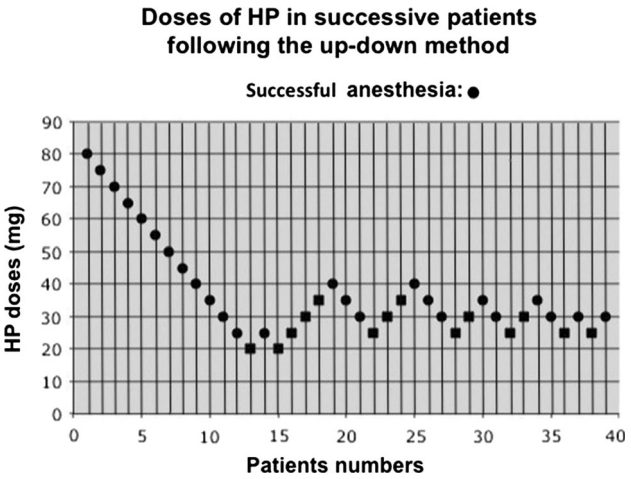

Fig. 1 Doses of hyperbaric prilocaine (HP) in 39 successive patients following the up-and-down method

two parts. In Part I, the sample size for each patient was determined according to the UDM sequential allocation technique established by Dixon and Massey.[15] A minimum of six independent crossovers or six consecutive pairs of patients with sufficient/insufficient anesthesia was required to calculate the ED_{50} value. Nevertheless, as proposed by Pace *et al.,* including at least 20-40 patients provides stable estimates of the target dose.[16] Hence, we chose to stop the study upon the last successful anesthesia before the 40th patient after six independent crossovers had already been achieved. Obtained sequences were analyzed by isotonic regression[17,18] to obtain the probability of ED_{50} and ED_{90} successful anesthesia and the associated 95% confidence interval. Calculations were performed using R software (R 3.0.1. for Windows; R Foundation for Statistical Computing, Vienna, Austria).

In Part II, we arbitrarily chose a sample size of 50 patients to corroborate the estimated ED_{90} dose. This resulted in a 95% CI of 82 to 98 with this population.[19,20] Consequently, with the estimated dose of ED_{90}, spinal anesthesia should succeed in 41-49 of 50 patients.

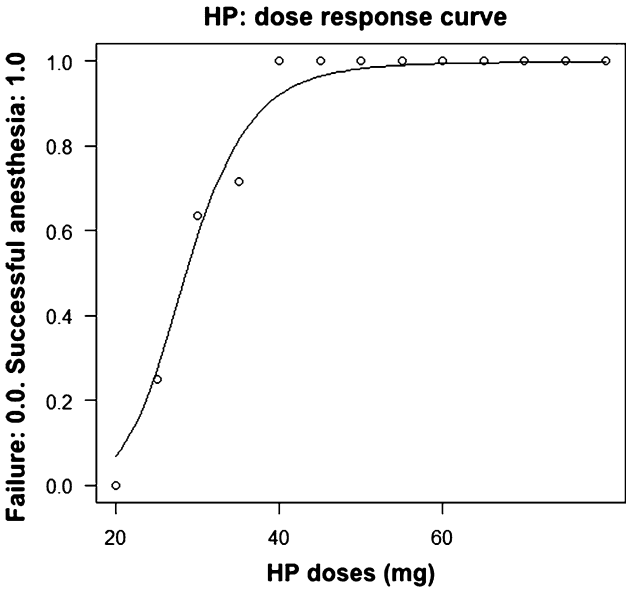

Fig. 2 Dose-response to curve of hyperbaric prilocaine (HP) provided by isotonic regression analysis

Table 2 Part II – Demographic characteristics ($n = 50$)

Age (yr)	53.0 (11.4)
Weight (kg)	74.8 (11.5)
Height (cm)	170.8 (8.3)
BMI ($kg \cdot m^{-2}$)	25.6 (3.1)
ASA	I: 29 II: 21
Sex	F: 20 M: 30

Absolute numbers and means (SD). BMI = body mass index; ASA = American Society of Anesthesiologists

Results

Part I

According to the previously presented stopping rules for the study, the sample size consisted of 39 consecutive patients. Demographic data for these patients are presented in Table 1. The sequence of sufficient and insufficient anesthesia is shown in Fig. 1. The ED_{50} and ED_{90} values obtained from isotonic regression were 28.9 mg (95% CI: 26.5 to 35.3) and 38.5 mg (95% CI: 35.7 to 39.5), respectively. The estimated regression model is shown in Fig. 2.

Part II

Demographic data for the 50 patients enrolled in the second part of the study were similar to those for the patients in Part I and are presented in Table 2. Considering the calculated value of ED_{90}, spinal anesthesia was performed using 40 mg of HP for ease of dose preparation. According to the predetermined

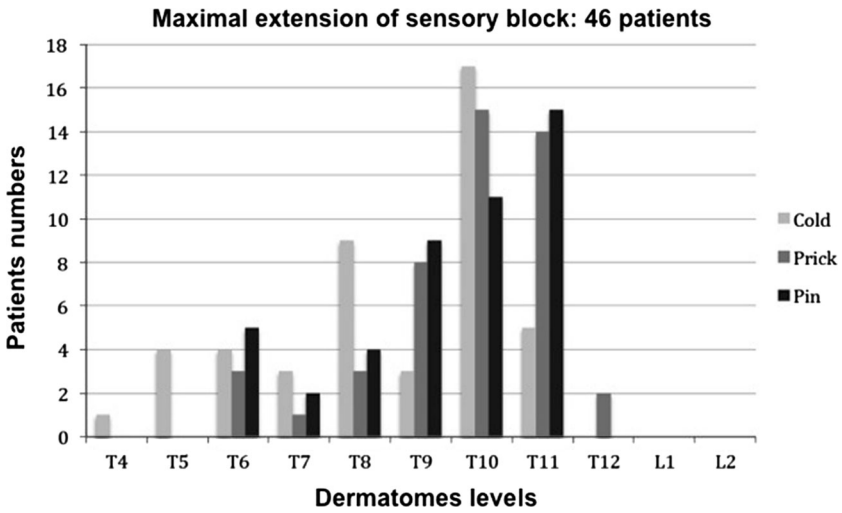

Fig. 3 Maximal extension of sensory block evaluated with pin-prick and cold tests (46 patients)

Table 3 Part II - Variables of blocks and surgical data (in minutes)

	DMB	DSB	TT	BS	DS
Mean	87.3	205.0	5.1	15.4	21.4
SD	23.9	36.1	2.2	3.9	8.2

DMB = duration of motor block; DSB = duration of sensory block; TT = time to tourniquet inflation; BS = beginning of surgery; DS = duration of surgery

criteria, successful anesthesia and surgery were obtained in 46 (92%) of these patients (95% CI: 82 to 98). Due to pain from tourniquet inflation and introduction of the arthroscope in the four remaining patients, spinal anesthesia required analgesic supplementation with a continuous intravenous infusion of remifentanil to complete the surgery.

For the group as a whole, sensory block to the T12 dermatome was observed in 41 of 50 (82%) patients after five minutes, in 44 (88%) patients after ten minutes, and in 46 (92%) patients after 20 min. Considering the 46 patients with successful anesthesia, maximal extension of sensory block was achieved at the T8-T11 levels in 85% and 87% of the cases, as assessed by the pinprick test, respectively. Sensory block was not found to be lower than L1. Maximal sensory block was achieved at the same T8-T11 levels in 74% of the cases, as assessed by the cold test, whereas the T4 level was observed in only one patient (Fig. 3).

Complete motor block (Bromage 3) was obtained after 30 min in 40 of 46 patients with a successful sensory block; however, it was observed in 30% and 72% of the cases after five minutes and ten minutes, respectively, following HP spinal injection. The start of surgery was not delayed for any patient due to the time needed to achieve a motor block since it was not required by the surgeon. Descriptive summaries for blocks and surgical data are presented in Table 3.

No adverse effects, such as hypotension, bradycardia, or urinary retention, were recorded in any patient. No neurologic complications were reported throughout the entire study follow-up.

Discussion

In this study, the ED_{50} of hyperbaric 2% prilocaine was 28.9 mg. This dose may be considered the minimum effective dose for patients undergoing knee arthroscopy and may provide a base for comparison of potency with other local anesthetics. The ED_{90} value was 40 mg. This dose induces a rapid onset and a suitable duration of motor and sensory block with minimal side effects in approximately 90% of patients. Several trials have reported the applicability of HP for short surgical procedures under spinal anesthesia. Most of these studies compared various doses of prilocaine with other local anesthetics, however, not in terms of potency.[2,21] Although the main goal of our study was to determine the ED_{90} of HP, since it is more clinically relevant, in our view, the estimation of the ED_{50} could provide a sensitive research tool in this field. Moreover, the ED_{50} value is significant as it is referred to as the minimum effective dose which sets the limit under which successful anesthesia may not be possible.

The study design was based on the Dixon and Massey up-and-down sequential allocation method to define the injected doses of HP. It is a simple and efficient method that is classically used to calculate the ED_{50} of a drug and requires a smaller sample of patients than traditional dose-response studies.[15,22,23]

This approach has largely been applied in anesthesia research to determine the dose requirements for inhalational and intravenous drugs, and it has also been used to compare the potency of local anesthetics, especially during the first stage of labour.[24-26] In the field of regional

anesthesia, earlier studies have used up-and-down methodology to define administered volumes of local anesthetics. Casati *et al.* compared volumes required for femoral block performed under neurostimulation with those required under ultrasound guidance,[27] and Duggan *et al.* defined the minimum effective volume of local anesthetic for ultrasound-guided supraclavicular block.[28] Recently, Gautier *et al.* estimated the minimum effective anesthetic volume of 0.75% ropivacaine in ultrasound-guided interscalene brachial plexus block.[29] The UDM calculations depend on the initial dose, usually chosen based on previous studies and on the predetermined interval between consecutive doses.[22] In the current study, we chose 80 mg as the initial dose, which was high compared with the ED_{50} dose ultimately determined. Nevertheless, starting from elevated effective doses and approaching the ED_{50} with rapidly succeeding intervals minimized the number of patients subjected to potentially inadequate analgesia. Additionally, taking into account the concentration of HP (20 $mg \cdot mL^{-1}$), we chose 5 mg as the dose interval, which corresponds to a 0.25 mL volume and which we consider as the minimum relevant volume variation for spinal injection.

The UDM is designed to provide a reliable estimate of ED_{50}; estimates of other quantiles, such as ED_{90}, may not be reliable. Hence, in Part II of the observational study, we applied 40 mg of HP intrathecally in 50 patients in order to validate the estimated ED_{90} and provide further description of the resulting effects and side effects. Notably, we found that spinal anesthesia was performed successfully in 46 of 50 patients accordingly to the predetermined criteria. The resulting 95% CI of 82 to 98 can be interpreted as the plausible range for the true success rate using 40 mg of HP. Moreover, it supports the applicability of the statistical model we chose for the present trial.

Complete loss of pinprick and cold sensation at the T12 dermatome was achieved in ten-20 min. The 40-mg dose also permitted inflation of the tourniquet after five minutes and thereby decreased the time required to begin the surgery in 92% of the patients. Altogether, these onset times allowed the operation to begin rapidly after 15 min. These results are consistent with those previously reported by Camponovo *et al.* who underlined that reducing the dose of HP from 60 mg to 40 mg does not reduce its efficacy in terms of onset of sensory block.[8] Maximum extension of sensory block was never above T6 as assessed by the pinprick test and the cold test. Of particular interest are the adverse hemodynamic effects that local anesthetics induce on spinal block. Hendriks *et al.* recorded a T6 level in 16% of patients and a T4 extension in 14% of patients; however, they used 50 mg of plain prilocaine.[10] Interestingly, 25% of patients required treatment with ephedrine and atropine to counteract the hemodynamic side effects. In contrast with the former results, our study importantly highlights that the maximum level of sensory block is lower with 40 mg of HP; furthermore, this dosage assures the hemodynamic stability of the patient. Another convincing argument is that this finding is not related to fluid pre-loading, deliberately omitted in our spinal block protocol. Notably, the mean duration of sensory block was 205 min. This long-lasting sensory block considerably exceeded the short mean duration of surgery of 21 min, thereby providing adequate anesthesia for all our patients without analgesic supplementation.

We were particularly interested in the complete motor block (Bromage 3) induced by the HP and consider that it was attained slowly after 30 min in 86% of the cases, which contrasts with its full rapid mean recovery time of 87 min. These times are consistent with those previously reported for the same dose of hyperbaric prilocaine.[8] In the present study, 6.8% of patients did not experience motor block; however, neither the onset nor the quality of motor block hindered surgery or patient satisfaction.

In our trial, all patients were able to void spontaneously by full recovery of sensory function. Kreutziger *et al.*[14] observed 23.3% of urinary retention with 60 mg of HP, whereas Hendriks *et al.*[10] reported that 8.3% of their patients required bladder catheterization when using 50 mg of plain solution. Considering their results, we advocate that lower doses of prilocaine are advantageous in the ambulatory setting in order to avoid urinary retention.

The time to eligibility for home discharge after complete resolution of the sensory block was 205 min, similar to the time reported by Camponovo *et al.* with the same dose of HP.[8] Finally, we did not observe any TNS throughout the entire study follow-up involving 89 patients subjected to HP doses ranging from 10-80 mg.

In conclusion, under the study's conditions, the estimated ED_{50} of hyperbaric 2% prilocaine is 28.9 mg, which may be considered the minimum effective dose for ambulatory anesthesia for knee arthroscopy. . It would be of interest to make a further comparison of HP's potency with other local anesthetics. We estimated the ED_{90} of HP to be 38.5 mg, which was supported by the observed 92% success rate with a dose of 40 mg in the second part of the study. Based on these results, lower doses of HP for ambulatory spinal anesthesia, might also be effective if co-administered with an adjunct adjuvant though this would need to be determined by future clinical trials.[9]

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Conflicts of interest None declared.

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