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S.P. LACROIX[1], P.R. MALAISE[2], S.V. DEGEY[3], E.P. DEFLANDRE[2,3,4]

PREDICTABILITY OF THE DURATION OF MOTOR BLOCKADE INDUCED BY UNIQUE INJECTION OF INTRATHECAL PRILOCAINE – AN OBSERVATIONAL STUDY

[1]Department of Anesthesia, Extracorporeal Circulation Team, Clinique Saint-Luc de Bouge, Namur, Belgium;
[2]Department of Anesthesia, University of Liege, Liege, Belgium; [3]Cabinet Medical ASTES, Jambes, Belgium;
[4]Department of Anesthesia and Department of Ambulatory Surgery, Clinique Saint-Luc de Bouge, Namur, Belgium

Prilocaine is widely used for spinal anesthesia. Its intermediate effect makes it a valuable choice for one-day surgery. The duration of the motor blockade (DMB) may have an impact on the length of stay. The goal of this study was to establish a correlation between the DMB and different parameters (hyperbaric prilocaine dose, puncture level, surgical position, age, patient weight, and patient height). We prospectively enrolled adult patients scheduled for ambulatory surgery (n = 384). Univariate and multivariate regressions (backward stepwise) were applied. A P value lower than 0.05 was considered significant. We performed first analyzes on the entire population. We achieved same on a subgroup only composed of patients who received 60 mg of hyperbaric prilocaine between L4 and L5 and staying on dorsal position during surgery. The univariate analyses of the entire population demonstrate a significant correlation between DMB and 1) the prilocaine dose ($P < 0.001$), and 2) the BMI ($P = 0.011$). On the same population, the multivariate analyses confirm these two independent parameters correlated to the DMB: the patient height ($P = 0.03$) and the hyperbaric prilocaine dose ($P < 0.001$). The second analyses performed on the subgroup (n = 65), demonstrate a wide variability in the DBM (mean ± SD): 90.12 ± 30.36 minutes. For this concern, univariate analyses illustrate that only the patient height was significantly correlated to the DMB ($P = 0.005$). The multivariate analyses confirm that patient height could be considered as an independent parameter of DBM ($P = 0.005$). Within our entire population, there exists a considerable variation in the duration of the motor block after a unique injection of hyperbaric prilocaine. The prilocaine dose and the patient height were the only independent factors of the extension of the DMB. However, this relation is extremely weak and only allows explaining the variability of the DMB in a minority of the patients. This unknown pharmacological property of hyperbaric prilocaine could restrict its use for day-care surgery.

Key words: *prilocaine, spinal anesthesia, intrathecal, motor blockade, transient neurological syndrome, ambulatory surgery*

INTRODUCTION

For many years, lidocaine has been the local anesthetic of choice for short duration spinal anesthesia (1). The discovery of the high incidence of the transient neurological syndrome (TNS) following intrathecal injection of lidocaine (2) has led to a significant decrease in its use since the end of the nineties. Some clinicians performed short-lasting anesthesia with a low dose of bupivacaine, levobupivacaine, and ropivacaine (3, 4). Recently, FDA (Food and Drug Administration) reintroduced prilocaine for spinal anesthesia in the ambulatory setting (5-7).

Prilocaine has been synthesized in 1953 and used for spinal anesthesia since 1965. It was then only available in the isobaric form, but since 2010, prilocaine is also available in hyperbaric (HB) form. Spinal anesthesia with prilocaine can be used for all surgeries requiring sensory block up to metameric level T10 of duration shorter than 90 minutes. Prilocaine has low systemic toxicity. Its metabolite (o-toluidine) can induce methemoglobinemia, but this side effect has never been described in the context of spinal anesthesia.

In the last decades, there was a trend in developing individualized perioperative medicine. Regarding spinal anesthesia, this individualized approach concerns the prevention of hypersensitivity (8), the prevention of side effects, and the duration of motor blockade (DMB). Some authors described that with HB 2% prilocaine, the maximum level and length of the sensory block, depth of motor blockade, the DMB, and time to urinary voiding vary regarding the amount of prilocaine injected (7). The time to complete recovery from the sensory block has been reported to be (SD) 132 [34] minutes with 60 mg of prilocaine (7). Some authors suggested that ambulatory surgery patients may be discharged before urinary voiding after short-acting spinal anesthesia (9). Considering this, one of the main limiting factors then becomes DMB. Unilateral spinal anesthesia has been shown to efficiently reduce the time to recovery from the motor, and the sensory block on the un-operated side, as well as the time to urinary voiding (10). The time to complete motor block recovery could be proportional to the dose injected.

However, to the best of our knowledge, the association between DMB, the injected dose of prilocaine, and other

physiological parameters were never studied in clinical practice. Firstly, this study aimed to evaluate the predictability of DMB following a unique intrathecal injection of hyperbaric prilocaine. Secondly, this study tried to establish a correlation between the DMB and different factors (hyperbaric prilocaine dose, puncture level, surgical position, patient age, patient weight, and patient height).

MATERIAL AND METHODS

The study was approved by the Institutional Ethics Committee (Dr. P. van der Rest, Clinique Saint-Luc de Bouge, Namur, Belgium and Pr. P. Evrard, Cliniques Universitaires Mont-Godinne, Namur, Belgium) with the reference number: 108/2015, B039201525876. Because this study is limited to an analysis of data and use of the usual technique and medication in our institution, the IRB waived the written informed consent. This study received the registration on ClinicalTrail.gov: NCT02282280. This study has been carried out in accordance with the Declaration of Helsinki.

Patients

Following patient informed oral consent, we enrolled prospectively all adult patients scheduled for elective surgery for ambulatory surgery in the Clinique Saint-Luc of Bouge (Namur, Belgium) between 2015/09/01 and 2015/12/16.

This study was an observational study. The doses and the injection levels were chosen at the discretion of the anesthetist. We excluded the patients for whom the spinal anesthesia failed or if they did not experience a Bromage score of 3, ten minutes after injection of hyperbaric prilocaine.

Procedures

Before anesthesia, during surgery, and in the Post Anesthesia Care Unit (PACU) patients were infused with a crystalloid solution (Hartmann Viaflo, Baxter™, Lessines, Belgium). We performed spinal anesthesia with the patient in sitting position. We used 27-Gauge (BD Whitcare™, Madrid, Spain) or 25-Gauge (Vygon™, Ecouen, France) needles. Hyperbaric prilocaine (Tachipri, Nordic Group™, Antwerpen, Belgiulm) was injected without adjuvant. Level of puncture and dose of hyperbaric prilocaine were in anesthesiologist's hands. During surgery and in the PACU, patients were monitored with ECG, noninvasive arterial pressure monitoring, and pulse oximetry (Datex-Ohmeda S/5™, Helsinki, Finland).

A first investigator recorded the time of injection and the physiological parameters. Parameters encoded were patient identification, date of birth, date of surgery, patient height, patient weight, the dose of hyperbaric prilocaine injected, level of puncture, type of surgery, and surgical position. To assess the motor blockade, we used the Bromage score (11). This score classify the intensity of the motor block on a scale from 0 to 3 (0: fully able to flex knees and feet, 1: just able to move knees, 2: unable to move knees, able to move feet only, 3: unable to move knees or feet). In the PACU, a nurse (blinded regarding studied parameters) checked every 5 minutes the end of the motor blockade (Bromage score). She used a separate document to archive the time corresponding to the end of the motor blockade that we defined as the Bromage score of 1. A third investigator collected the whole data and encoded them in the database used for statistical analysis.

Statistical analysis

To achieve a 95% power with a 5% level of significance, and an effect size of 0.2 (pilot study on DMB, not published), a minimum of 314 patients were required (G*Power, version 3.1.9.2). The normality of data distribution and the normality of residuals were evaluated using a Shapiro-Wilk test. Proportions were analyzed using Chi-squared tests, and normally distributed data were compared between groups using two-tailed unpaired t-tests. Correlation between parameters and DMB were analyzed using univariate and multivariate regressions (using the backward stepwise methodology). A two-tailed P value lower than 0.05 was considered significant. We performed the first analyses on the entire population.

When making statistical analysis of the data, we saw that there exists an important subgroup composed of patients who received 60 mg of prilocaine at the L4-L5 level and staying in dorsal position during the surgery. We achieved the same analyses on this subgroup. This combination corresponds to the

Table 1. Characteristic of patients.

	Entire population n = 384	**Subgroup** n = 65	**Statistics**
Age	55.7 ± 16	49.9 ± 16.33	0.008 *
Male/Female (%)	32.46 / 67.54	72.31 / 27.69	< 0.0001 *
Height (m)	1.72 ± 0.09	1.75 ± 0.09	0.090
Weight (kg)	80.28 ± 16.66	84.12 ± 20.22	0.097
Body mass index (kg m^{-2})	26.91 ± 4.84	27.49 ± 5.93	0.390
Prilocaine (ml)	3.06 ± 0.37	3	0.180
Duration of motor blockade (min)	89.8 ± 29.33	90.12 ± 30.36	0.936
ASA (%) 1 / 2 / 3	20.26 / 72.21 / 7.53	24.6 / 70.77 / 4.63	0.570
Level of puncture (%) L3-L4 / L4-L5	29.43 / 70.57	0 / 100	< 0.0001 *
Position (%) Dorsal/Gynecological/Lateral	76.62 / 23.38 / 0	100 / 0 / 0	< 0.0001 *

Data are mean ± SD, %, or median (IQR). * significant difference at $P < 0.05$. BMI, body mass index; DMB, duration of motor blockade.

most frequent practice in our institution. Analyses were performed using XLSTAT for Mac (Addinsoft SARL®, Paris, France, v. 18.07.39180) and NCSS (NCSS 12 Statistical Software (2018). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss).

RESULTS

We included 400 consecutive adult patients in this study. No patients refused to participate in the study. Spinal anesthesia failed in 9 patients (no motor blockade and no sensitive anesthesia); and 7 patients did not experience a Bromage score of 3, ten minutes after injection of hyperbaric prilocaine. These 16 patients (0.04%) were excluded from the data analysis. Final analyses were performed on 384 adult patients. Sixty-five patients composed the subgroup who received 60 mg of hyperbaric prilocaine between L4 and L5, and for whom surgery was performed on dorsal position. The patients included in the subgroup were younger and more frequently male gender than the entire population. *Table 1* synthesizes the characteristics of patients.

For the entire population, univariate analyses demonstrate a significant correlation between DMB and the hyperbaric prilocaine dose ($P < 0.0001$), and the BMI ($P = 0.011$). The multivariate regression model confirmed that the patient height ($P = 0.03$) and the prilocaine dose ($P < 0.0001$) were independent factors for DMB (*Figs*. *1* and *2*). *Table 2* presents the significant results of the multivariate analyses. The statistical model can be expressed as follows: DMB (min) = 93.699 – (46.109*height (m)) + (24.700*dose (ml)). The multiple correlation coefficient (R^2) was weak (0.106).

Analyses performed on the subgroup also demonstrates a wide variability in the DBM (mean SD): 90.12 [30.36] minutes. Maximum and minimum values varied from 199 to 40 minutes. Interquartile ranges varied from 65 to 106 minutes. *Fig*. *3* illustrates this data. Univariate analyses illustrate that only the patient height is significantly correlated to the DMB ($P = 0.005$). The multivariate analyses confirm that patient height could be considered as an independent parameter of DBM ($P = 0.005$, *Table 3*, *Figs*. *4* and *5*). The statistical model can be expressed as follows: DMB (min) = 292.691 – (116.003*height (m)). The multiple correlation coefficient (R^2) was weak (0.116).

DISCUSSION

The first aim of this study was to evaluate the predictability of DMB following a unique intrathecal injection of hyperbaric prilocaine. Our results show that there exists a wide variation in this DMB. This unpredictability related to a unique injection of intrathecal prilocaine could restrict its use in some ambulatory surgery center.

The second goal of this study was to establish if there exist a significant correlation between the DMB and different factors. Our study demonstrates that the dose ($P < 0.0001$) and the height ($P = 0.03$) are independent factors affecting the DMB. In the subgroup of patients for whom we injected 60 mg of prilocaine at the L4-L5 level, only the patient height represents an independent factor influencing the DMB ($P = 0.005$).

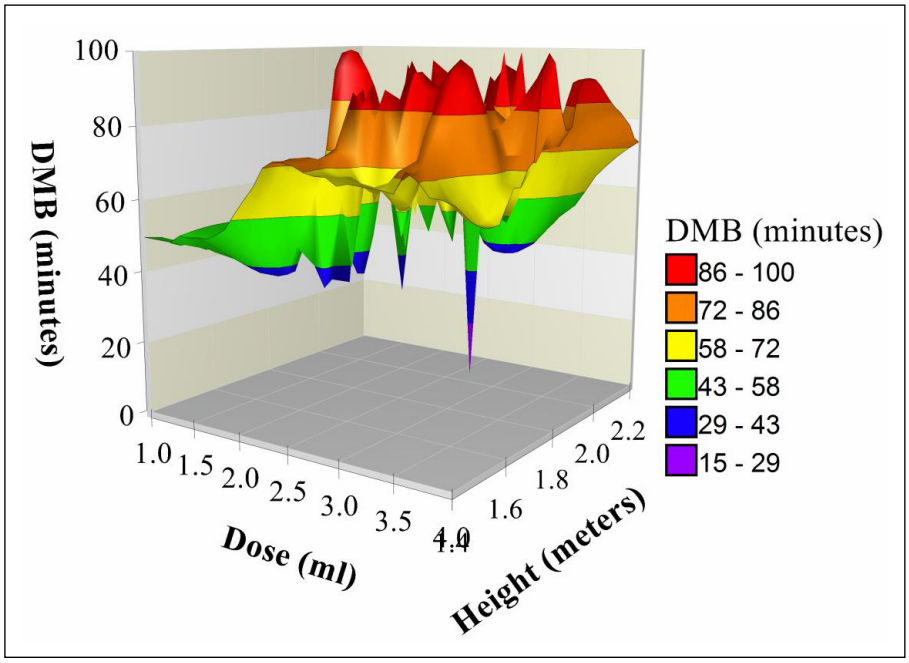

Fig. *1*. 3D plot illustrating distribution of duration of motor blockade (DMB) according to administrated dose of prilocaine and patient height. These data correspond to the whole population. The figure illustrates the wide variation of DMB following a unique injection of intrathecal prilocaine, and the absence of a predictive factor regarding this DMB.

Table 2. Multivariate analyses on the entire population.

Source	Value	Standard error	P value	95% confidence intervals	
				Lower bound	Upper bound
Intercept	93.699	27.210	0.001	40.198	147.200
Height	–46.108	15.350	0.003	–76.289	–15.926
Dose	24.700	3.841	< 0.0001	17.148	32.252

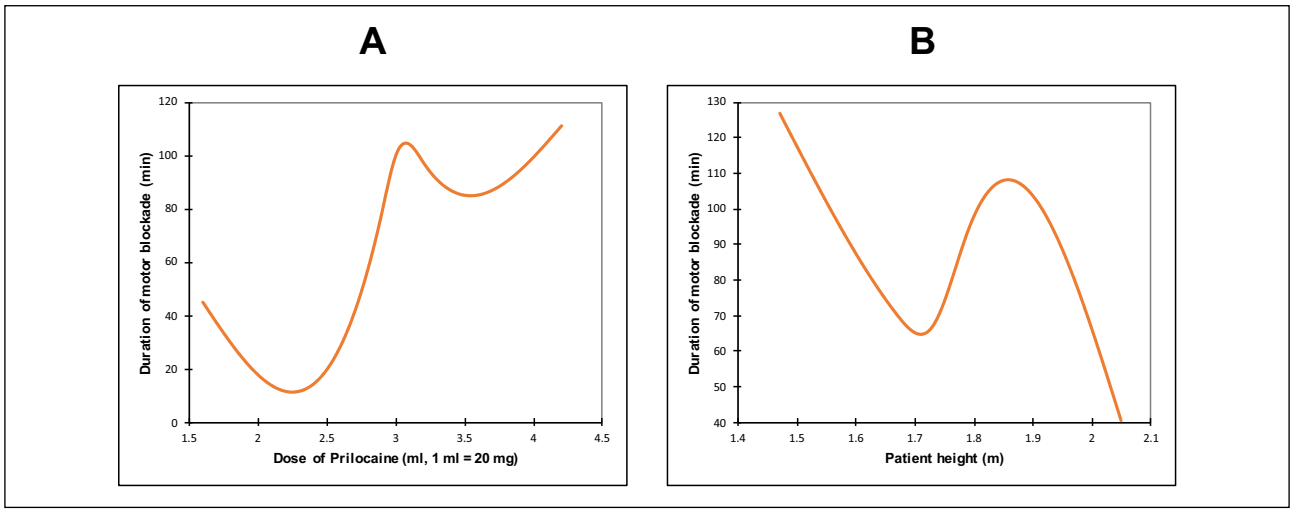

Fig. 2. Cubic splines illustrating the relationship between the duration of motor blockade (DMB) and: A) injected dose of prilocaine, and B) patient height. These data correspond to the whole population. These figures illustrate the absence of correlation between DMB and the dose of prilocaine (A) and the patient's height (B).

Table 3. Multivariate analyses on the subgroup.

Source	Value	Standard error	P value	95% confidence intervals	
				Lower bound	Upper bound
Intercept	292.692	70.392	< 0.0001	152.024	433.359
Height	–116.003	40.259	0.005	–196.455	–35.552

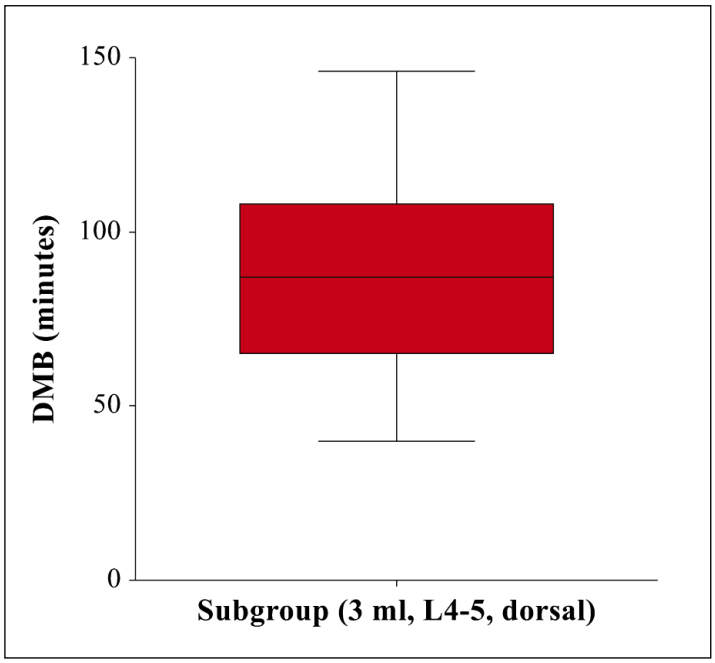

Fig. 3. Box plot illustrating median and interquartile range of duration of motor blockade (DMB) in the subgroup - 3 ml (60 mg) of prilocaine administrated in L4-L5 and surgery in dorsal position. This figure illustrates the wide variation of DMB following the unique injection of intrathecal prilocaine.

Unfortunately, these multivariate regressions are weak and can only explain the variability of the DMB in approximately 11% of the patients. Reasonably, we can conclude that in our population, there exists a lack of predictability of DMB related to a hyperbaric prilocaine injection, and that this wide variation in the DMB could not be explained by the studied parameters.

Our results emphasize a characteristic of intrathecal hyperbaric prilocaine that is poorly known about clinicians. Its wide variation in the DMB cannot be explained by the variables usually involved in this DMB. To the best of our knowledge, it is the first study exhibiting such results for prilocaine.

Kooger Infante *et al*. have demonstrated that the intrathecal spread of hyperbaric spinal anesthesia modified the DMB (12). In their study, patients were placed either in a horizontal position or with the torso elevated at 30 degrees. The patients in a horizontal position had a greater extent of local anesthetic solution and a shorter duration of the spinal block. In our study, we did not find any influence of the surgical position on the DMB.

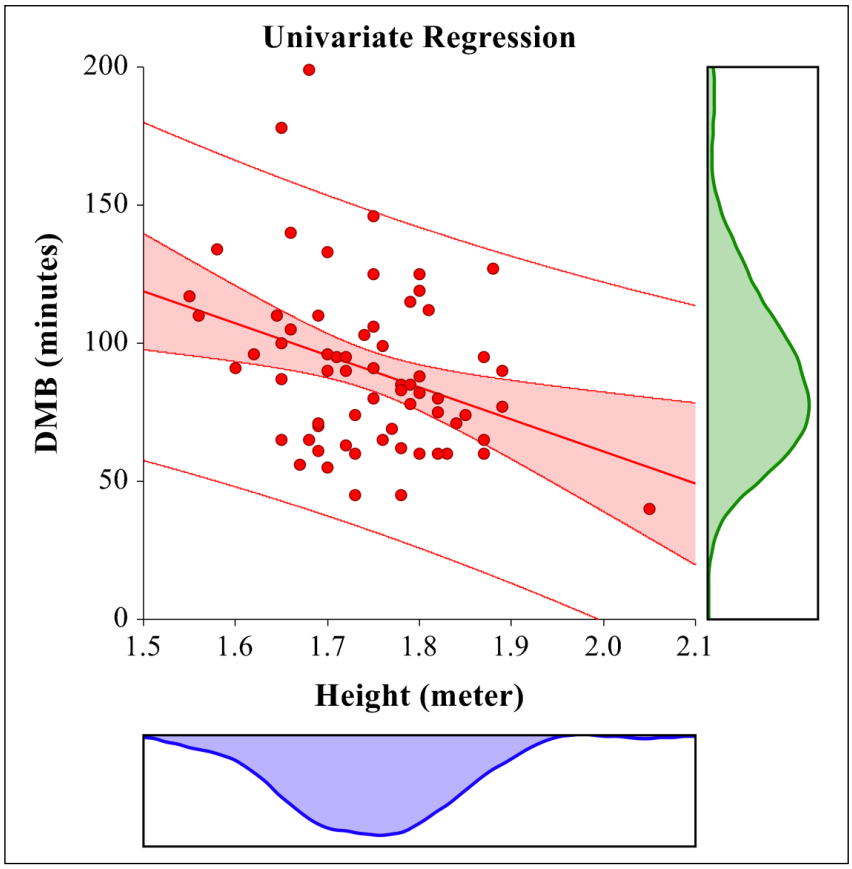

Fig. 4. Univariate regression between duration of motor blockade (DMB) and patient height. Red fill zone corresponds to 95% confidence intervals (CI) of regression model, red lines illustrates 95% CI of patient distribution. Green fill zone represents density plot of DMB, while blue fill zone represents density plot of patient height. These data correspond to the subgroup of patients receiving 3 ml (60 mg) of prilocaine administrated in L4-L5 and for surgery in dorsal position.

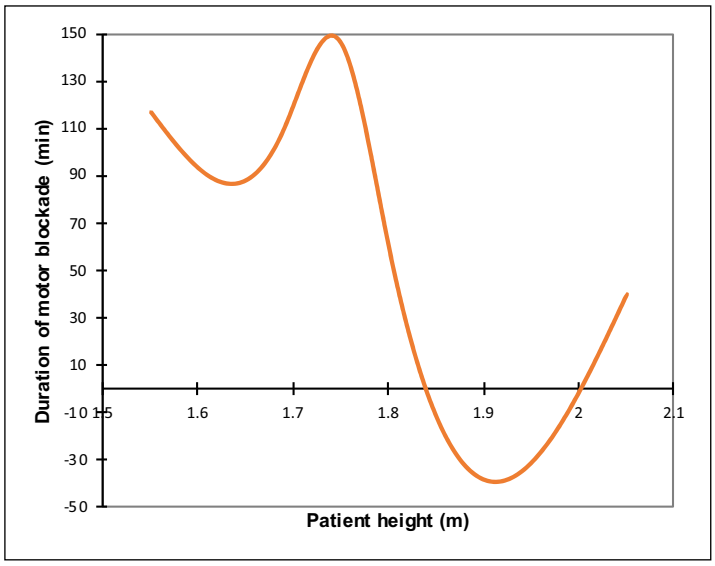

Fig. 5. Cubic spline illustrating the relationship between the duration of motor blockade (DMB) and the patient height. These data correspond to the subgroup of patients receiving 3 ml (60 mg) of prilocaine administrated in L4-L5 and for surgery in dorsal position. This figure illustrates the absence of correlation between DMB and the patient's height.

In a study including 90 patients, Camponovo *et al*. studied the DMB when using prilocaine (7). Even if the aim of their study was different from the present one, they also found wide variability in the DMB in the patients receiving intrathecal prilocaine. They demonstrated that the injected dose represents an independent parameter of DMB. Even if the population was smaller than the one of our study, this study was compatible with our results. Other smaller studies exhibit the same results (13).

The patients included in the subgroup were younger and more frequently male gender. We do not have a hypothesis to explain this difference. As mentioned above, we did not constitute initially this group during the inclusion of patients, but we did it during statistical analysis when we discovered that a large number of patients experience the same spinal anesthesia (L4-L5 level of puncture, 3 ml of hyperbaric prilocaine, and dorsal position).

However, our study has three limitations. Firstly, we did not use ultrasonography for the location of the puncture level. Even if this technique is not widely used, future studies should address this point in the intent of better accuracy. Secondly, block height was not recorded in the parameters. It was not the current practice in our institution. However, future studies

should also address this limitation. Thirdly, we did not study if the variation of DMB had an impact in the discharge criteria (length of stay).

In conclusion, during the last years, the use of hyperbaric prilocaine was more frequent in our practice. According to its pharmacokinetic properties, the duration of action should be shorter than for other products such as bupivacaine. In that respect, some authors identify the prilocaine as the molecule of choice for day surgery. It's important to note that side effect of prilocaine could also influence the discharge criteria (14). Guntz *et al*. suggested that a dose of 40 mg of prilocaine could be adequate for the lower limb surgery (15), and we perfomed this study with higher dose. Nevertheless, our study demonstrates on a large sample size that there exists a wide variation in the recovery of intrathecal hyperbaric prilocaine that cannot be explained by the studied factors. Even if the results of study must be evaluated in clinical practice (discharge criteria, length of stay), this unknown property of hyperbaric prilocaine should influence some physicians to change their practice in ambulatory surgeries for whom the discharge criteria are clearly important.

Abbreviations: BMI, body mass index; DMB, duration of motor blockade; FDA, Food and Drug Administration; HB, hyperbaric; PACU, Post Anesthesia Care Unit; SD, standard deviation; TNS, transient neurologic syndrome

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Authors' contribution: S. Lacroix - design of the study and writing manuscript; P. Malaise - design of the study and the data collection; S. Degey - data analyses; E. Deflandre - design of the study, in the data analyses and in the review of the manuscript.

Conflict of interests: None declared.

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Author's address: Dr. Eric P. Deflandre, Chaussee de Tongres, 29, B-4000 Liege, Belgium.
E-mail: eric.deflandre@gmail.com