

Received: 2015.05.30
Accepted: 2015.08.14
Published: 2015.09.01

Effect of Concentration on Median Effective Dose (ED₅₀) for Motor Block of Intrathecal Plain Bupivacaine in Elderly Patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDE **Ming-quan Chen**
EF **Zhong-yuan Xia**

Department of Anesthesiology, Renmin Hospital of Wuhan University, Wuhan, Hubei, P.R. China

Corresponding Author: Zhong-yuan Xia, e-mail: xiazhongyuan2005@aliyun.com
Source of support: Departmental sources

Background: The aim of the study was to determine the median effective dose (ED₅₀) for motor block of various concentrations of intrathecally administered plain bupivacaine.





Material/Methods: Between 2011 and 2013, 64 patients aged ≥70 years, undergoing transurethral, or lower limb surgery with combined spinal and epidural anesthesia in a single hospital were enrolled. The patients were randomized into 3 groups to receive intrathecal 0.75% bupivacaine (Group 1), 0.375% bupivacaine (Group 2) or 0.25% bupivacaine (Group 3). Spinal anesthesia was achieved using injections of up-and-down doses of 0.75%, 0.375%, or 0.25% plain bupivacaine. The first patient in each group received 7.5 mg bupivacaine, and the testing interval was set at 0.75 mg. The efficacy of motor block in both legs was determined using a modified Bromage and a hip motor function scale. The ED₅₀ for motor block was estimated according to the Dixon's up-and-down method.

Results: The ED₅₀ for motor block of bupivacaine was 6.10 (95% CI 5.58-6.66) mg in Group 1, 6.04 (95% CI 5.82-6.28) mg in Group 2, and 5.43 (95% CI 5.19-5.67) mg in Group 3. There were significant differences in the ED₅₀ for motor block among the groups (P=0.008).

Conclusions: The ED₅₀ doses for motor block with 3 bupivacaine concentrations were significantly different in elderly patients; the ED₅₀ dose of 0.75% bupivacaine being significantly higher than that of 0.25% bupivacaine.

MeSH Keywords: **Bupivacaine • Injections, Spinal • Microbial Sensitivity Tests**

Full-text PDF: <http://www.medscimonit.com/abstract/index/idArt/894842>

 2621  4  1  36



Background

Both motor blockade and sensory level can be used as a primary endpoint to evaluate the relative potency of local anesthetics. The potency can be determined by investigating the median effective doses (ED_{50}) of motor block using the up-down sequential allocation technique [1,2]. The ED_{50} for motor block of several anesthetics (bupivacaine, levobupivacaine, and ropivacaine) have been determined [3,4]. Using these approaches, we previously determined the ED_{50} for motor block of spinal 0.75% plain bupivacaine in adult patients undergoing urological or lower limb surgery, and found this to be 10.22 mg in patients aged 20–30 years, and 5.78 mg in those aged 70–80 years [5].

Some researchers have reported that the concentration of local anesthetic is an important factor determining the maximum sensory level and motor block of spinal anesthesia [6,7]. Camorcia et al. [8] reported that the concentration of local anesthetic affected the ED_{50} for motor block in adults. In our previous study, we also found that the concentration of plain bupivacaine influenced the ED_{50} in young patients, demonstrating that the ED_{50} for motor block of intrathecally administered bupivacaine with 0.75% bupivacaine was higher than that of the lower concentration (0.375% bupivacaine) [9].

Researchers have found that the spinal cord and nerves changed significantly with age in the biochemical, morphological, and histochemical patterns, and in the anatomical structure [10–12]. It has been reported that age not only affects the compound action potential amplitude of the muscle and its duration on motor and sensory nerves [13,14], but also affects the conduction velocity of the motor nerve [15–17].

There are no reports in the literature about the ED_{50} for motor block in elderly patients using different concentrations of bupivacaine solutions. The aim of the study was to determine the median effective dose (ED_{50}) for motor block using 3 different concentrations of intrathecally administered plain bupivacaine in elderly patients.

Material and Methods

This study was registered in the Chinese Clinical Trial Registry (ID: ChiCTR-TRC-12001897). The registration information can be found on the following website: <http://www.chictr.org/cn/proj/show.aspx?proj=2420>. The local ethics committee of the First College Of Clinical Medical Science, China Three Gorges University, Yichang, China, approved the study on July 8, 2010. Written informed consents were obtained from all patients prior to their enrollment. Between October 8, 2011 and July 8, 2013, we enrolled 64 American Society of Anesthesiologists (ASA) stage I–II patients aged ≥ 70 years undergoing transurethral

prostatectomy, anorectal surgery, and under-knee lower limb surgery, with combined spinal and epidural anesthesia (CSE). Patients with diabetes, obesity, bleeding diathesis, hypersensitivity to amide local anesthetics, neuromuscular disease, or abnormalities of the lumbar vertebrae were excluded.

The patients were randomly assigned into 3 groups according to a computer-generated random number table: Group 1 received 0.75% bupivacaine; Group 2 received 0.375% bupivacaine; and Group 3 received 0.25% bupivacaine.

The anesthesiologist in charge performed the entire anesthetic procedure and 1 nurse assessed the clinical results and collected the data, and was blinded to the local anesthetic dose; a second nurse was responsible for preparing the research drug according to the assessed results.

No premedication was used before the patients entered the operating room. Before the CSE was performed, 500 mL of lactated Ringer's solution was infused within 30 minutes. For CSE, the patient was positioned in the left lateral decubitus position, and punctured at the L3/4 interspace with a 16-gauge Tuohy needle. The epidural space was identified using loss of resistance to 2 mL air. The dura was punctured with a 25-gauge Whitacre spinal needle. The hole of the needle was oriented in the cranial direction when inserted through the Tuohy needle. The study anesthetic solution was injected into the subarachnoid space at a rate of 0.2 mL/second after cerebro-spinal fluid (CSF) appeared in the spinal needle hub. The epidural catheter was threaded 3 cm into the epidural space, and the patient was placed in a supine neutral position. After the study determinations were made, the patient's position was changed according to the requirements of the surgical procedure.

Based on our previous research [5], the initial dose chosen was 7.5 mg (1.0 mL) of the 0.75% plain bupivacaine solution (Bupivacaine. ZHAOHUI Company, Shanghai, China), and the dose interval was set at 0.75 mg (0.1 mL) in all groups. In Group 1, the 0.75% plain bupivacaine solution was used directly; in the Group 2, a concentration of 0.375% bupivacaine was achieved by adding the same volume of 0.9% saline; and in Group 3, a concentration of 0.25% bupivacaine was obtained by adding 2/3 volume of 0.9% saline. The subsequent doses of the drug in each group were decided depending on the outcome in the previous patient in the same group according to Dixon's up-and-down method [18].

The efficacy of the drug was determined using the modified Bromage scale [19] and the hip motor function scale [20]. It was assessed from completion of the spinal injection every minute for 5 min, and at 10 min (Table 1). An ineffective outcome was defined as a Bromage and a hip motor function score of 0 in either leg within 5 min of injection. If this occurred, the

Table 1. Evaluation scales for motor block.

Score	Motor block
Bromage scale	
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
Hip motor function scale	
0	Complete ability to raise straight legs (>300)
1	Partial ability to raise straight legs (<300)
2	Inability to raise straight legs

bupivacaine dose was incremented of 0.75 mg for the next patient in the same group. An effective outcome was defined as a modified Bromage and a hip motor function score >0 in either leg within 5 min of injection. In this case the bupivacaine dose was decreased 0.75 mg for the next patient in the same group. The median ED₅₀ for motor block of bupivacaine was obtained from the midpoints of the ineffective-to-effective crossover. Patients were enrolled until 6 pairs were obtained, as per Paul and Fisher's study [21]. According to our previous experience, 20 patients per group is a sufficient sample size [5].

A technical failure was defined as a patient that did not feel heat or numbness sensations in the leg and sacral dermatomes with 2 min of spinal injection. Then, the same dose was repeated in the next patient of the same group. Sensory block was also tested bilaterally in the lumbar and sacral dermatomes. The highest level of pinprick sensation in the midaxillary line was assessed and recorded at 5 min and 10 min after completion of spinal injection (Table 2). The highest sensory level blocked was also determined, and the duration of the motor blockade was also recorded.

Table 2. Maximum cephalic anesthesia level.

	Number of patients (ineffective/effective)	Maximum cephalic anesthesia level at 5 min			Maximum cephalic anesthesia level at 10 min		
		Ineffective	Effective	Total	Ineffective	Effective	Total
Group 1	9/12	T ₁₂ (T ₁₁ , L ₂)	L ₁ (T ₁₁ , L ₄)	T ₁₂ (T ₁₁ , L ₄)	T ₁₂ (T ₁₁ , L ₂)	T ₁₁ (T ₉ , L ₃)	T ₁₂ (T ₉ , L ₃)
Group 2	10/11	L ₁ (T ₁₀ , L ₃)	L ₁ (T ₁₀ , L ₃)	L ₁ (T ₁₀ , L ₃)	T ₁₁ (T ₈ , L ₁)	T ₁₁ (T ₄ , L ₁)	T ₁₁ (T ₄ , L ₁)
Group 3	9/11	L ₃ (L ₂ , L ₃)	L ₂ (T ₉ , L ₃)	L ₂ (T ₉ , L ₄)	L ₂ (T ₁₂ , L ₃)	T ₁₁ (T ₇ , L ₃)	T ₁₂ (T ₇ , L ₃)
Total	28/34	L ₁ (T ₁₀ , L ₃)	L ₁ (T ₉ , L ₄)	L ₁ (T ₉ , L ₄)	T ₁₂ (T ₈ , L ₃)	T ₁₁ (T ₄ , L ₃)	T ₁₂ (T ₄ , L ₃)

Data are reported as the median (range). L – lumbar dermatome level; T – thoracic dermatome level. There were no significant differences among the groups in maximum cephalic analgesia level at 5 min and 10 min.

Ten minutes after spinal injection, supplemental doses of 2% lidocaine were given through an epidural catheter if the level of anesthesia was not sufficient for surgery. General anesthesia was used if required. The number of cases requiring epidural local anesthetic reinforcement and the total volume of local anesthetic used, the number of cases with incomplete motor block (Bromage scale <2), and the number of cases requiring general anesthesia were recorded. Such patients were excluded from the data collected for duration of motor block. Any adverse effects were also recorded.

Intraoperative monitoring, included noninvasive blood pressure (BP), heart rate (HR), and O₂ saturation by pulse oximetry values, were recorded before anesthesia, and at 5 and 10 min after intrathecal injection of bupivacaine. Arterial hypotension was defined as a 30% decrease in the systolic BP compared to the baseline value, and was treated by the intravenous administration of 5 mg ephedrine. Heart rate decrease to under 55 beats/min was treated with 0.25 mg of atropine.

Statistical analysis

SPSS 17.0 package for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Data are expressed as the mean (SD), median (range), or count/number. The means were compared using one-way analysis of variance (ANOVA), while medians (ranges) were analyzed by Kruskal-Wallis one-way analysis, and counts or proportions were analyzed by using the Fisher's exact test. The ED₅₀ for motor block was determined according to the up-and-down sequences method of Dixon and Massey [22], while the probit regression analysis was used as a backup or sensitivity test. One-way analysis of variance (ANOVA) was used for comparisons of the ED₅₀, and the Tukey multiple comparison test was used for multiple comparisons between groups. Based on the study by Paul and Fisher, patients were enrolled until 6 crossovers were obtained [21]; therefore, we could complete the study enrollment when we had enrolled 64 patients. A P value <0.01 was considered statistically significant.

Table 3. Group characteristics and demographic data.

Group	Number of patients (M/F)	Age (yr)	Weight (kg)	Height (cm)	Operation time (min)	Motor block time (min)
Group 1	11/10	76.0±3.9	59.9±7.4	6168.0±5.1	91.2±32.5	151.4±15.3
Group 2	12/9	75.5±4.3	64.4±10.8	167.5±5.4	108.8±24.9	218.2±57.7
Group 3	11/9	76.4±5.3	62.5±8.6	165.3±5.	103.2±33.0	219.9±99.4
Total	34/28	76.0±4.5	61.6±10.4	166.9±5.4	101.0±30.9	198.4±82.0

Data are reported as the means ± standard deviations (SDs). The means were compared using one-way analysis of variance (ANOVA), and multiple comparisons between groups were made using the LSD test. There were not significant differences among groups.

Results

The patient characteristics and demographic data were not significantly different among the 3 groups (Table 3). One patient in Group 1 and 1 patient in Group 2 required general anesthesia due to technical difficulty during epidural space detection; these patients were excluded from the analysis. Sixty-two patients were punctured successfully and felt sensations of heat or numbness in the leg and sacral dermatomes within 2 min, indicating that the study drug had been correctly injected into the subarachnoid space. In Group 3, there were 3 patients whose motor nerves were not blocked completely during the entire period of surgery (Bromage scale <2). There was 1 patient each in Group 2 and 3 whose level of analgesia did not allow surgery; therefore, they were administered epidural supplement drugs. One patient in Group 3 needed epidural supplementation because of longer surgery. One patient in group 1 needed general anesthesia because the sensory block level was insufficient to start surgery. These patients were excluded from the data collected for duration of motor block. The number of patients who needed supplemental epidural anesthesia did not differ significantly among the 3 groups. Surgery was completed successfully in all enrolled patients.

There were no significant differences among the groups in maximum sensory block level at 5 min and 10 min after completion of spinal injection (Table 2). The sequences of effective and ineffective outcomes are shown in Figure 1. The ED₅₀ for motor blockade of bupivacaine was 6.10 (95% CI 5.58–6.66) mg in Group 1, 6.04 (95% CI 5.82–6.28) mg in Group 2, and 5.43 (95% CI 5.19–5.67) mg in Group 3. The ED₅₀ for motor block of bupivacaine was significantly different among groups (one-way analysis of variance: p=0.008), and the ED₅₀ for motor block of Group 1 was significantly higher than Group 3 (Tukey multiple comparison test: p=0.005). Using probit regression analysis, the ED₅₀ for motor block was 6.04 (95% CI 5.10–6.89) mg in Group 1, 5.90 (95% CI 5.35–6.42) mg in Group 2, and 5.30 (95% CI 5.05-5.57) mg in Group 3 (Table 4).

Discussion

The present study showed that the ED₅₀ for motor block in older patients was significantly different when various concentration of intrathecal plain bupivacaine solutions were used, which was significantly higher when 0.75% bupivacaine was used compared to when 0.25% bupivacaine was used.

This study used the motor blocking minimum local anesthetic dose methodology to assess the motor block potencies of various concentrations of anesthetic solution, administered as spinal anesthesia, in older patients. This approach for estimating ED₅₀ has been described in previous studies [3–5].

Camorcia et al. reported that the ED₅₀ for motor block of intrathecal ropivacaine was 50% higher in a 0.1% solution [23], but this trend was not consistent with our present findings. This phenomenon can be explained as follows. First, plain ropivacaine has lower lipid solubility, which results in lower distribution of ropivacaine into the cord. Second, the plain ropivacaine solution is slightly hypobaric, and the spread is likely to be more dependent on other factors such as injection rate, and volume and doses of ropivacaine. This may result in unpredictable effects, as reported by others [24,25]. Finally, the great difference of anesthetic concentration (a 10-fold difference) results in a different trend. In the present study only a 3-fold difference in hyperbaric bupivacaine was used for spinal anesthesia. Peng et al. [26] observed that slightly increasing local anesthetic concentration (lidocaine), and comparing it with a small increase in the dose at a lower concentration, achieved the same degree of motor and sensory block. However, with the plain bupivacaine in the present study, we noted that the doses for motor block were higher in the higher concentration group. This is probably because the density of the local anesthetic solution determines the spread of the anesthetic drugs. According to previous research using highly precise equipment to accurately measure the density of commonly used intrathecal drugs in human CSF at 37°C, plain bupivacaine is indeed hypobaric [27–29].

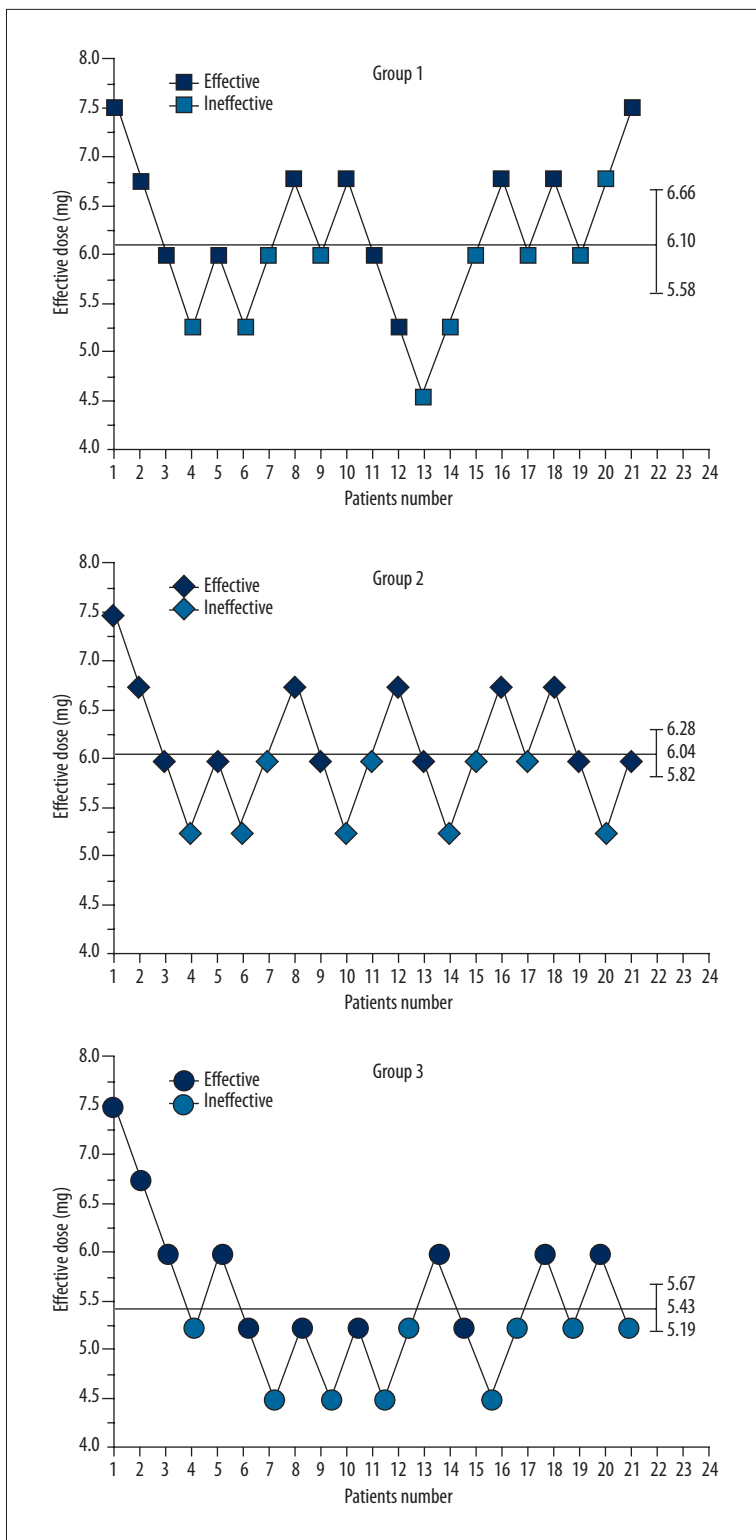


Figure 1. Motor blocking minimum local anesthetic doses (MMLAD) sequences. Median effective doses and 95% confidence intervals are depicted in the figure. Solid and open symbols (circles, triangles, or squares) represent the effective and ineffective doses, respectively.

In a previous study, we determined the ED₅₀ for motor block with 0.75% plain bupivacaine for spinal anesthesia, and compared the values between adults of various age groups. The ED₅₀ was found to be 5.78 mg in adults aged 70–80 years [5], which

is similar to the result of the present study. Furthermore, we have measured the ED₅₀ for motor block of 2 different concentrations of bupivacaine (0.375% and 0.75%) in young patients, and observed that the ED₅₀ for motor block of intrathecally

Table 4. Results of up-down sequences for motor block.

Group	Dixon and Massey (mg)		Probit regression (mg)	
Group 1	6.10	(5.58, 6.66)*	6.04	(5.10, 6.89)
Group 2	6.04	(5.82, 6.28)	5.90	(5.35, 6.42)
Group 3	5.43	(5.19, 5.67)	5.30	(5.05, 5.57)

Data are presented as the median effective dose (95% confidence interval). One-way analysis of variance: $p=0.008$. Tukey multiple comparison test: * group 1 vs. group 3, $p=0.005$.

administered bupivacaine with higher concentration (0.75%) was higher (9.998 mg) than that of a lower concentration (0.375%, 8.890 mg) [9]. Age-related differences probably remained, and were justified before.

Many factors influence the level of spinal sensory anesthesia, including the dose and volume of the anesthetics and the lumbosacral CSF volume. Lee et al. [30] found that the ratio of the long axis and the transection area of the abdomen also affected maximal spinal level. In this study, although dosage variations existed between different individuals and also the volume of bupivacaine solution was different in different groups, the level of sensory analgesia was similar at 5 min and 10 min after spinal injection, differing by just 1 or 2 sensory dermatomes among the 3 groups. This is probably because the volumes of local anesthetic used in our current study (<3 mL) are substantially lower than the lumbosacral CSF volumes, which have been reported to range from 42.7 to 81.1 mL [31]. Previous studies have also shown that the volume of intrathecal bupivacaine is not an important determinant of local anesthetic spread [32].

Kim et al. [33] and Bachmann et al. [34] achieved a T10 sensory peak block level using low hyperbaric bupivacaine doses (6 and 7 mg, respectively) and used head-down tilt to reach it, thus explaining the differences with our work (lower sensory block level reached). For reducing the incidence of hypotension and fast recovery from anesthesia, Errando et al. [35,36] used very low hyperbaric bupivacaine doses (3.75 mg) at very low concentration (0.25%) for fracture repair in the elderly, but some of their patients needed intravenous anesthesia rescue in hip fracture repair surgery. In our study, we determined the ED_{50} was 5.43 mg in 0.25% plain bupivacaine, a slightly higher dose.

References:

1. Columb MO, Lyons G: Determination of the minimum local analgesic concentrations of epidural bupivacaine and lidocaine in labor. *Anesth Analg*, 1995; 81(4): 833-37
2. Camorcia M, Capogna G, Lyons G, Columb M: Epidural test dose with levobupivacaine and ropivacaine: determination of ED_{50} motor block after spinal administration. *Br J Anaesth*, 2004; 92(6): 850-53
3. Camorcia M, Capogna G, Berritta C, Columb MO: The relative potencies for motor block after intrathecal ropivacaine, levobupivacaine, and bupivacaine. *Anesth Analg*, 2007; 104(4): 904-7
4. Camorcia M, Capogna G, Columb MO: Estimation of the minimum motor blocking potency ratio for intrathecal bupivacaine and lidocaine. *Int J Obstet Anesth*, 2008; 17(3): 223-27

The average duration of motor block in the 3 groups assessed here was 150-220 min, with no significant difference among groups.

The limitations of our study are:

- The sample size was obtained in an indirect manner.
- The volume of CSF was not determined in the spine and the height of a patient would affect the sensory level, and also affect the results of this study.
- Ten minutes after injection completion could be an insufficient time lapse to evaluate the motor block and sensory level characteristics during spinal anesthesia. However, we imposed this time limitation due to clinical/practical reasons.

Moreover, as we have previously described [5,9], although the up-and-down method is often used in small samples to determine the ED_{50} of a drug, the ED_{95} cannot be accurately assessed using this approach. Therefore, further investigations are required to determine the ED_{95} of bupivacaine for different anesthetic concentrations and injection volumes. In addition, although our results showed statistically significant differences, in the clinical setting these could be less important.

Conclusions

The concentration of bupivacaine solutions affects the ED_{50} for motor block with intrathecally administered bupivacaine in elderly patients. The ED_{50} doses of these 3 concentrations were significantly different and the dose of 0.75% bupivacaine was significantly higher than that of 0.25% bupivacaine.

5. Chen M, Chen C, Ke Q: The effect of age on the median effective dose (ED50) of intrathecally administered plain bupivacaine for motor block. *Anesth Analg*, 2014; 118(4): 863–68
6. Bengtsson M, Malmqvist LA, Edstrom HH: Spinal analgesia with glucose-free bupivacaine – effects of volume and concentration. *Acta Anaesthesiol Scand*, 1984; 28(5): 583–86
7. Van Zundert AA, Grouls RJ, Korsten HH, Lambert DH: Spinal anesthesia. Volume or concentration – what matters? *Reg Anesth*, 1996; 21(2): 112–18
8. Camorcia M, Capogna G, Lyons G, Columb MO: The relative motor blocking potencies of intrathecal ropivacaine: effects of concentration. *Anesth Analg*, 2004; 98(6): 1779–82
9. Chen MQ, Chen C, Ke QB: Determination of the median effective dose for motor block of intrathecally administered different concentrations of bupivacaine in younger patients. The influence of solution concentration. *Saudi Med J*, 2014; 35(1): 44–49
10. Fontana PA, Barbeito CG, Goya RG et al: Impact of very old age on the expression of cervical spinal cord cell markers in rats. *J Chem Neuroanat*, 2009; 37(2): 98–104
11. Keorochana G, Taghavi CE, Tzeng ST et al: Magnetic resonance imaging grading of interspinous ligament degeneration of the lumbar spine and its relation to aging, spinal degeneration, and segmental motion. *J Neurosurg Spine*, 2010; 13(4): 494–99
12. Cartwright MS, Mayans DR, Gillson NA et al: Nerve cross-sectional area in extremes of age. *Muscle Nerve*, 2013; 47(6): 890–93
13. Huang CR, Chang WN, Chang HW et al: Effects of age, gender, height, and weight on late responses and nerve conduction study parameters. *Acta Neurol Taiwan*, 2009; 18(4): 242–49
14. Thakur D, Paudel BH, Jha CB: Nerve conduction study in healthy individuals: a preliminary age based study. *Kathmandu Univ Med J*, 2010; 8(31): 311–16
15. Kommalage M, Pathirana KD: Influence of age and the severity of median nerve compression on forearm median motor conduction velocity in carpal tunnel syndrome. *J Clin Neurophysiol*, 2011; 28(6): 642–46
16. McHugh JC, Reilly RB, Connolly S: Examining the effects of age, sex, and body mass index on normative median motor nerve excitability measurements. *Clin Neurophysiol*, 2011; 122(10): 2081–88
17. Kommalage M, Gunawardena S: Influence of age, gender, and sidedness on ulnar nerve conduction. *J Clin Neurophysiol*, 2013; 30(1): 98–101
18. Columb MO, D'Angelo R: Up-down studies: responding to dosing! *Int J Obstet Anesth*, 2006; 15(2): 129–36
19. Bromage PR: A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. *Acta Anaesthesiol Scand Suppl*, 1965; 16: 55–69
20. Collis R: Combined spinal epidural (CSE) analgesia is the preferred technique for labour pain relief. *Acta Anaesthesiol Belg*, 2002; 53(4): 283–87
21. Paul M, Fisher DM: Are estimates of MAC reliable? *Anesthesiology*, 2001; 95(6): 1362–70
22. Dixon WJ, Massey FJ: Introduction to statistical analysis. 4th ed. New York: McGraw-Hill, 1983; 428–39
23. Camorcia M, Capogna G, Lyons G, Columb MO: The relative motor blocking potencies of intrathecal ropivacaine: effects of concentration. *Anesth Analg*, 2004; 98(6): 1779–82
24. Kallio H, Snall EV, Tuomas CA, Rosenberg PH: Comparison of hyperbaric and plain ropivacaine 15 mg in spinal anaesthesia for lower limb surgery. *Br J Anaesth*, 2004; 93(5): 664–69
25. Fettes PD, Hocking G, Peterson MK et al: Comparison of plain and hyperbaric solutions of ropivacaine for spinal anaesthesia. *Br J Anaesth*, 2005; 94(1): 107–11
26. Peng PW, Chan VW, Perlas A: Minimum effective anaesthetic concentration of hyperbaric lidocaine for spinal anaesthesia. *Can J Anaesth*, 1998; 45(2): 122–29
27. Richardson MG, Wissler RN: Density of lumbar cerebrospinal fluid in pregnant and nonpregnant humans. *Anesthesiology*, 1996; 85(2): 326–30
28. Richardson MG, Wissler RN: Densities of dextrose-free intrathecal local anesthetics, opioids, and combinations measured at 37 degrees C. *Anesth Analg*, 1997; 84(1): 95–99
29. Lui AC, Polis TZ, Cicutti NJ: Densities of cerebrospinal fluid and spinal anaesthetic solutions in surgical patients at body temperature. *Can J Anesth*, 1998; 45(4): 297–303
30. Lee YH, Wang YC, Wang ML et al: Relationship of abdominal circumference and trunk length with spinal anesthesia level in the term parturient. *J Anesth*, 2014; 28(2): 202–5
31. Carpenter RL, Hogan QH, Liu SS et al: Lumbosacral cerebrospinal fluid volume is the primary determinant of sensory block extent and duration during spinal anesthesia. *Anesthesiology*, 1998; 89(1): 24–29
32. Malinovsky JM, Renaud G, Le Corre P et al: Intrathecal bupivacaine in humans: influence of volume and baricity of solutions. *Anesthesiology*, 1999; 91(5): 1260–66
33. Kim JE, Kim NY, Lee HS, Kil HK: Effects of intrathecal dexmedetomidine on low-dose bupivacaine spinal anesthesia in elderly patients undergoing transurethral prostatectomy. *Biol Pharm Bull*, 2013; 36(6): 959–65
34. Bachmann M, Pere P, Kairaluoma P et al: Randomised comparison of hyperbaric articaïne and hyperbaric low-dose bupivacaine along with fentanyl in spinal anaesthesia for day-case inguinal herniorrhaphy. *Eur J Anaesthesiol*, 2012; 29(1): 22–27
35. Errando CL, Peiro CM, Gimeno A, Soriano JL: Single shot spinal anesthesia with very low hyperbaric bupivacaine dose (3.75 mg) for hip fracture repair surgery in the elderly. A randomized, double blinded study. *Rev Esp Anesthesiol Reanim*, 2014; 61(9): 481–88
36. Errando CL, Soriano-Bru JL, Peiro CM, Ubeda J: Single shot spinal anaesthesia with hypobaric bupivacaine for hip fracture repair surgery in the elderly. Randomized, double blinded comparison of 3.75 mg vs. 7.5 mg. *Rev Esp Anesthesiol Reanim*, 2014; 61(10): 541–48