Determination of the median effective dose for motor block of intrathecally administered different concentrations of bupivacaine in younger patients

The influence of solution concentration

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ABSTRACT

الأهداف: تحديد الجرعة الفعالة الوسطية (ED_{50}) للتقييد الحركي الناتج عن التركيزات المختلفة لعقار بيوبيفاكايين المعطاة داخل سحايا النخاع في المرضى الأصغر سناً.

الطريقة: تم إجراء هذه الدراسة في قسم التخدير، الكلية الأولى لعلم الطب الإكلينيكي، الصين، جامعة ثري جورجز، الصين، على 40 مريض من الشباب (40–18 عام) طبقاً للجمعية الأمريكية لأخصائي التخدير (ASA) I–II وخضعوا لإجراء جراحة في الطرف السفلي. تم تقسيم هؤلاء المرضى إلى مجموعتين طبقاً لجدول أرقام عشوائية منتج من الحاسوب (المجموعة أ– 0.375% بيوبيفاكايين، والمجموعة ب–0.75% بيوبيفاكايين). تم تخدير الحبل الشوكي عن طريق تناول أقراص البلع بجرعات مختلفة عالية –و– منخفضة من 0.375%، أو 0.75% من البيوبيفاكايين العادي. يتم تحديد هذه الجرعات العالية والمنخفضة بطريقة ديكسون صعوداً وهبوطاً. تم إعطاء المريض الأول من كل مجموعة 7.5 مجم من البيوبيفاكايين، وتم ضبط فاصل الاختبار عند 0.75 مجم. كانت الجرعة أعلى أو أقل بزيادة 0.75 مجم بحسب فشل أو نجاح تقييد حركة المريض السابق. تم تقييم مدى التقييد الحركي بعد الإعطاء الشوكي للبيوبيفاكايين عن طريق مقياس بروماج المعدل ونتيجة الوظيفة الحركية للفخذ. تم تقدير الجرعة الفعالة الوسطية ED_{50} من التتابعات صعوداً وهبوطاً باستخدام طريقة ديكسون وماسي.

النتائج: أظهرت نتائجنا أن الجرعة الفعالة الوسطية ED_{50} للتقييد الحركي الناتج عن إعطاء عقار البيوبيفاكايين داخل سحايا النخاع كانت 8.890 ملجم في المجموعة أ، و 9.998 ملجم في المجموعة ب، ونسبة فعالية العقار النسبية للتقييد الحركي كانت 1.12.

خاتمة: كانت الجرعة الفعالة الوسطية ED_{50} للتقييد الحركي الناتج عن إعطاء عقار البيوبيفاكايين داخل سحايا النخاع بتركيزات أعلى، أعلى بقليل من تلك ذات التركيز الأقل.

Objectives: To determine the median effective dose (ED_{50}) for motor block of intrathecally administered different concentrations of bupivacaine in younger patients.

Methods: This study was conducted at the Department of Anesthesiology, The First College of Clinical Medical Science, China Three Gorges University, China, on 40 American Society of Anaesthesiologists (ASA) I-II younger patients (18-40 years) undergoing lower limb surgery. These patients were classified into 2 groups according to a computer-generated random number table (Group A - 0.375% bupivacaine, and Group B - 0.75% bupivacaine). Spinal anesthesia was established by bolus administration of various up-and-down doses of 0.375%, or 0.75% plain bupivacaine. These up-and-down doses were determined by Dixon's up-and-down method. The first patient of each group was given 7.5 mg bupivacaine, and the testing interval was set at 0.75 mg. The dose was up, or down, 0.75 mg increments according to the failure or success of the preceding patient's motor block. The degree of motor block after intrathecal administration of bupivacaine was evaluated by the modified Bromage and Hip motor function score. The ED_{50} were estimated from the up-down sequences using the method of Dixon and Massey.

Results: Our results showed that ED_{50} for motor block of intrathecal bupivacaine was 8.890 mg in Group A, and 9.998 mg in Group B, and the relative motor blocking potency ratio was 1.12.

Conclusion: The ED_{50} of intrathecal bupivacaine to produce motor block in younger patients was slightly influenced by the anesthetic concentration.

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In clinical studies, many researchers have built a model using the up-down sequential allocation technique in regional anesthesia to evaluate the relative potency of local anesthetic motor block.[1,2] This allowed the determination of the minimum local anesthetic doses of motor block (MMLAD) for spinal anesthesia, defined as the median effective doses (ED_{50}) of local anesthetics, which were then used to estimate the relative potency ratios.[3] With the same method, some researchers have defined the effect of 2 different ropivacaine concentrations on ED_{50} for motor block, and they confirmed that the ED_{50} of motor block with intrathecal ropivacaine in pregnant patients was significantly influenced by the concentration of the local anesthetic, with dose requirements being increased by 50% for the smaller concentration.[3] All of these studies regarding ED_{50} for motor block were based on pregnant patients.[4,5] Whether local anesthetic concentration may affect the ED_{50} of the spinal block with smaller doses of bupivacaine in younger non-pregnant patients or not remains to be demonstrated. The aim of this study was to estimate the ED_{50} for motor block with different concentrations of bupivacaine with spinal anesthesia in younger non-pregnant patients, and then to determine the effects of different bupivacaine concentrations on $ED_{50}$for motor block.

Methods. The ethical considerations were followed by obtaining approval from the local ethics committee of The First College of Clinical Medical Science, China Three Gorges University, Yichang, China, and written informed consent from all the enrolled patients. The present work was performed in 40 younger patients (18-40 years) undergoing lower limb surgery (American Society of Anaesthesiologists [ASA] physical status I-II) from July 8, 2010 to July 8, 2011 at The First College Of Clinical Medical Science, China Three Gorges University, China. The patients were randomly classified into groups according to a computer-generated random number table (Group A - 0.375% bupivacaine, Group B - 0.75% bupivacaine). All enrolled patients were clinically fit for performing the combined epidural-spinal anesthesia (age: 18-40 years). The exclusion criteria included patients with diabetes, obesity, bleeding diathesis, hypersensitivity to amide local anesthetics, neuromuscular disease, lumbar vertebrae abnormality, or who were pregnant. After the patient is brought into the operating room, the intravenous infusion of lactated Ringer's solution was established before the spinal injection. The combined epidural-spinal anesthesia was performed on the left lateral decubitus position, using a midline approach at the L3/L4 interspace with a 16-gauge Tuohy needle, and distinguished the epidural space according to the sudden disappearance of air resistance. The air that detected the disappearance of air resistance was no more than 2 mL. The anesthesiologist punctured the dura with a 25-gauge Whiteacre spinal needle through the Tuohy needle. The study drug was injected into the subarachnoid space at a rate of 0.1 ml/s when the cerebrospinal fluid (CSF) appeared in the spinal needle. An epidural catheter was placed 3 cm at the head direction after the spinal injection was completed, and then the patient was placed in a supine horizontal position. After the research was completed, the patient's position was placed according to surgery requirements. The study solutions were freshly prepared using commercially available plain solutions of 0.75% bupivacaine in Group B, and adding the same volume 0.9% saline as the diluent to achieve the 0.375% bupivacaine in Group A. The dosages were varied according to Dixon's up-and-down method for evaluation of the spinal ED_{50} for local anesthetics.[6] According to previous studies,[4,5] considering the difference of parturient and non-parturient, and clinical measurement, the initial dose was chosen to be 7.50 mg (1.0 ml) plain solution of 0.75% bupivacaine, and the testing dose interval was set at 0.75 mg (0.1 ml) for both groups, which was prepared in a syringe immediately before injection. The next patient's dosages of local anesthetic in each group were selected according to the reaction of the previous patient in the same group with the up-down sequential allocation technique. The efficacy of the studied drug was assessed using the Bromage scale,[7] and the Hip motor function scale[8] every minute for 5 minutes, and at 10 minutes after the spinal injection was completed (**Table 1**). The stopwatch was started when the spinal injection of the local anesthetic solution was completed. The end point was decided according to motor blockade in any lower limb as assessed by the 2 scales within 5 minutes after the spinal injection of the study solution.

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 (>30^0)
1	Partial ability to raise straight legs (<30^0)
2	Inability to raise straight legs

If a modified Bromage[7] and Hip motor function score[8] = 0 in either leg within 5 min, it was defined as a failure case, which directed a 0.75mg (0.1 ml or 0.2 ml) increment of the study drug for the next patient assigned to that group. If a modified Bromage[7] and Hip motor function score[8] >0 in either leg within 5 minutes, it was defined as a successful case, which directed a 0.75mg (0.1 ml or 0.2ml) decrement of the study drug for the next patient assigned to that group. The median effective dose of bupivacaine (ED_{50}) required for motor block was obtained from the midpoints involving a crossover, that is failure to success. According to the study of Paul and Fisher,[9] cases were enrolled until 6 pairs were obtained. The anesthesiologist used the 25-gauge needle to examine pinprick sensation at the lumbar and sacral dermatomes bilaterally every minute up to 5 minutes. If the loss of pinprick sensation was observed very fast (within 5 minutes), the patient was considered a technical successful case. Otherwise, the patient was considered a technical failure case, and the same dosage was repeated in the next patient of the same group. At the same time, the highest level of pinprick sensation in the midaxillary line was assessed and recorded. The recovery time from motor blockade was recorded. However, if the analgesia level during the operation were not satisfactory after the observation was completed, the supplement 2% lidocaine would be administered through the epidural catheter. If the patient felt uncomfortable during the procedure, we might give some analgesia drugs, or perform general anesthesia. The cases of required epidural, local anesthetic, and general anesthesia administration, and the total volume of local anesthetic administration were recorded. The assessment of urinary retention, or pain, and post-spinal headache was recorded. The anesthesiologists who performed all of the assessments were blinded.

The blood pressure (BP) and heart rate (HR) were monitored by a machine (Datex-Ohmeda, Helsinki, Finland), and these values were recorded throughout the study at 5-minute intervals. Hypotension (defined as the systolic BP decreased by more than 30% below the pre-anesthetic value, or to less than 90 mm Hg) was administrated with 5 mg ephedrine intravenously. Bradycardia (HR <55 beats/min) was treated with atropine sulphate 0.25 mg intravenously.

The statistical analysis was performed using the Statistical Package for Social Sciences version 17 for Windows (SPSS Inc., Chicago, IL, USA). Data were expressed as mean (standard deviation [SD]), median (range), and count as appropriate. Demographic data were collected and presented as mean (SD). Means (SD) were analyzed using one-way analysis of variance (ANOVA) and medians (range) were analyzed with Mann-Whitney U-test. Counts were analyzed using the Fisher's exact test. The ED_{50} were estimated from the up-and-down sequences using the method of Dixon and Massey[10] and logistic regression. According to the study by Paul and Fisher,[9] patients were enrolled until 6 crossovers were obtained. A $p<0.01$ was considered statistically significant.

Results. Characteristics and demographic data were similar between groups (**Table 2**). All patients had a sensory block quickly in 5 minutes, indicating the correct injection of the study drug into the subarachnoid space. Analgesia was adequate for surgery in all patients, and all enrolled patients successfully completed the surgery. Using the formula of Dixon and Massey,[10] ED_{50} of bupivacaine for motor blockade was 8.890 mg (95% confidence interval [CI]: 8.350-9.466 mg) in Group A, and 9.998 mg (95% CI: 9.498-10.524 mg) in Group B, and the relative motor blocking potency ratio was 1.12

Table 2 - Group characteristics and demographic data (n=20).

Variables	Group	Group B	*P*-value
Age, years	34.0 (18, 40)	31.0 (18, 42)	0.463
Weight, kg	61.0 (42, 84)	62.5 (45, 95)	0.542
Height, cm	168.5 (152, 180)	170 (147, 181)	0.587
Gender			
Female	8	7	0.587
Male	12	13	0.744

Data were reported as median (range) and number as appropriate. Medians (interquartile ranges) were analyzed with the Mann-Whitney U-test, while numbers or proportions were analyzed with Fisher's exact test

Table 3 - Maximum cephalic anesthesia level (analgesia) (n=20).

Time	Group A			Group B		
	Ineffective	Effective	Total	Ineffective	Effective	Total
5 minutes	L2 (T11, L5)	L1 (T11, L4)	**L2 (T11, L5)**	L2 (T12, L3)	T12 (T10, L3)	**L1 (T10, L3)**
10 minutes	L2 (T12, L4)	T11 (T11, L3)	**L2 (T11, L4)**	T11 (T5, L2)	T10 (T4, T12)	**T10 (T4, L2)**

Data are reported as median (range), L - lumbar dermatome level, T - thoracic dermatome level

Table 4 - Duration of surgery, motor, and sensory blockade data of both groups.

Durations, minutes	Group A			Group B		
	Effective	Ineffective	Total	Effective	Ineffective	Total
Surgery	90 (30, 150)	90 (50, 150)	**90 (30, 150)**	95 (60, 220)	90 (40, 300)	**90 (40, 300)**
Motor blockade	157 (100, 250)	160 (130, 260)	**158.5 (100, 260)**	271 (142, 440)	364 (200, 420)	**291.5 (142, 440)**
Sensory blockade	190 (120, 280)	190 (155, 290)	**190 (120, 290)**	300 (210, 446)	355.5 (150, 660)	**325 (150, 660)**

Data are reported as median (SD)

Table 5 - Hemodynamic data of the studied patients (n=20).

Variable	Group A	Group B	*P*-value
Baseline			
Systolic blood pressure (SBP), mm Hg	117 (95, 155)	117.5 (100, 146)	1.000
Diastolic blood pressure (DBP), mm Hg	74 (60, 95)	71 (50, 89)	0.914
Heart rate (HR), beats/minute (bmp)	70.5 (56,102)	82.5 (50,108)	0.285
5 minutes later			
SBP (mm Hg)	113.5 (97, 159)	115.5 (101, 140)	0.787
DBP (mm Hg)	72 (54, 84)	74.5 (50, 89)	0.735
HR (bmp)	70 (56, 98)	83 (53, 129)	0.133
10 minutes later			
SBP (mm Hg)	112 (99, 159)	117 (97, 135)	0.725
DBP (mm Hg)	75 (52, 87)	71 (55, 91)	0.766
HR (bmp)	72 (56, 95)	78.5 (48, 110)	0.096
Number of patients with bradycardia after 5 minutes	3	2	---
Decrease of HR between baseline and 5 minutes later (bpm)	-0.5 (-11, 10)	-3.0 (-33, 29)	0.357
Number of patients with hypotension after 5 minutes	0	0	---
Decrease of SBP between baseline and 5 minutes later (mm Hg)	2.0 (-16, 23)	0.5 (-30, 31)	0.725
Number of patients with bradycardia after 10 minutes	2	1	---
Decrease of HR between baseline and 10 minutes later (bpm)	1.0 (-10, 23)	-2.0 (-14, 27)	0.343
Number of patients with hypotension after 10 minutes	0	0	---
Decrease of SBP between baseline and 10 minutes later (mm Hg)	-1.0 (-27, 33)	3.0 (-25, 29)	0.832

Data were reported as median (range) and analyzed with Mann-Whitney U-test, bradycardia - HR <60, hypotension - SBP<90

(95% CI: 1.01-1.23). From logistic regression analysis, the ED_{50} for 50% of subjects for motor blockade in Group A was 9.043 mg (95% CI: 8.525-9.638 mg), and in Group B was 9.053 mg(95% CI: 8.251-10.255 mg), and the relative motor blocking potency ratio was 1.00 (95% CI: 0.90-1.10). The maximum cephalic level of anesthesia (analgesia) was higher in Group B compared with Group A (**Table 3**). The duration of motor and sensory blockade was longer in Group B compared with Group A (**Table 4**). Median baseline values for HR were not different for both groups, nor were the incidence of bradycardia after 5 min and 10 min with intrathecal bupivacaine. All enrolled patients in both groups showed no evidence of hypotension (**Table 5**).

Discussion. The MMLAD methodology was described in a previous study,[4,5] and it is a very useful tool. It allows the estimation of ED_{50}, which produces defined results while requiring few patients to be enrolled.[4,5] In our study, we used the up-down sequential allocation design, which is a very powerful tool for estimating the ED_{50} rather than traditional dose-response studies design because it focused all the sampling doses in the immediate vicinity of the ED_{50}. Camorcia et al[3] reported that the ED_{50} of motor block with intrathecal ropivacaine in pregnant patients was significantly influenced by the concentration of the local anesthetic, with dose requirements being increased by 50% for the smaller concentration. In their studies, they used the extreme concentration of ropivacaine, which is seldom used in clinical practice. The great changes of local anesthetic concentration not only define the anesthesia effects, but also bring some unkown risks. Therefore, our results are inconsistent with their studies. We have demonstrated that the minimum local anesthetic dose for motor block with

lower concentration of bupivacaine was slightly higher than that of higher concentration of bupivacaine. The other studies found that when a relatively small hyperbaric spinal anesthetic dose is administered, a larger concentration is required to achieve the same degree of motor and sensory block.[11,12] Our results are consistent with these studies. This phenomenon can be explained as follows: first, we selected younger non-pregnant patients; second, we used the concentration difference just twice; third, as for the same doses of local anesthetic, relatively lower concentration means larger volume of local anesthetic, which results in wide diffusion. Therefore, the block level is higher in lower concentration of bupivacaine with the same doses. Relative higher anesthesia level will reduce the strength of muscle, and also reduce the requirement of local anesthetic.

Variability in lumbosacral CSF volume is the most important factor, which decides the variability in the spread of spinal sensory anesthesia. Some researchers reported that lumbosacral CSF volumes ranged from 42.7-81.1 ml.[13] The volume of local anesthetic that we used in studies is smaller compared with lumbosacral CSF volumes, and it was nearly omitted. Therefore, although the difference existed in the dose and concentration, but because of their smaller volume, they seldom produce the obvious difference in anesthesia level. In our study, although the dosage variations existed in different individual, the sensory block were similar, just one to 2 sensory dermatome difference in 2 groups. The previous studies demonstrated that the dose determines the regression of sensory and motor blockade of spinal anesthesia.[14-16] With the 3 milliliters glucose-free 0.5% bupivacaine subarachnoid injection, the times to recovery from the total disappearance of analgesia were significantly longer in the older group; however, the effect of age on the recovery from motor blockade could not be demonstrated.[17] The large difference in motor block duration was recorded between the one and 4 ml of 0.5% bupivacaine (154 minutes and 286 min).[18] Our results showed that the duration of motor block was 158 minutes in the lower concentration group, and 291 minutes in the higher concentration group. It is proven that motor block recover relatively fast in lower concentration solution with the same smaller anesthetic dose in spinal anesthesia. This is very useful in clinical studies that the lower concentration result in the fast recovery from anesthesia, which may benefit patients by avoiding urological catheters. The present study showed that the local anesthetic dosage, which made the motor block, differed greatly in both groups. Previous studies demonstrated that it just needed median effective dosage of 3.44 mg to make motor block in younger parturient, which was lower than our findings (8.89 mg and 9.99 mg). We can emphasize that the physical status of pregnancy is largely changed in the lumbar lordosis,[19] and in the volume and density of the CSF compared with the non-pregnant patients.[20] These studies were mainly performed in parturient[5] who have different characteristics in physiology compared with other non-parturient patients.

In our study, the doses and volume of solution were adjusted according to the guidelines from previous studies.[4,21] While we adjusted the doses, we changed the volume of solution (although potentially only 0.1 mL or 0.2 mL). We are not sure whether this change in volume of solution affects the ED_{50} for motor block or not. It is a limitation of the present study. The up-and down method is often used in small samples to determine the ED_{50} of drug. Many studies have used logistic regression to determine the ED_{50} of a drug.[22,23] However, as the up- and down method cannot provide reliable insight into the upper tail of the distribution, the ED_{95} of bupivacaine cannot be accurately assessed. This is a shortage of our study and the ED95 of bupivacaine requires further investigation.

In conclusion, our findings in this study showed that ED_{50} of intrathecal bupivacaine to produce motor block in younger patients was slightly influenced by anesthetic concentration.

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