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CLINICAL RESEARCH

Clinical utility of epidural volume extension following reduced intrathecal doses: a randomized controlled trial☆

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Abstract
Background and objectives: Epidural Volume Extension (EVE) involves instillation of normal saline into the epidural space soon after an intrathecal injection, with the aim to augment the sensory block height. Its clinical relevance lies in the possibility of using reduced intrathecal dose and yet achieving the desired sensory block level. Intrathecal dose is a known determinant of the level of sensory block. Whether EVE is dependent on intrathecal dose is not known.
Methods: We conducted a randomized, controlled, double-blind study to compare the maximum sensory level (S_{max}) achieved with or without application of EVE to two different reduced intrathecal doses. Eighty four adult male patients of ASA status I or II with body weight between 50–70 kg and height in the range of 150–180 cm, scheduled for orthopedic lower limb surgery using combined spinal epidural anesthesia were randomized to receive, either intrathecal dose (5 or 8 mg) with or without EVE, in accordance to group allocation.
Results: S_{max} was lowered by application of EVE to 5 mg intrathecal bupivacaine ($T_{8.9} \pm 4.3$ vs. $T_{6.4} \pm 1.9$ with and without EVE respectively; $p = 0.030$). S_{max} was similar when EVE was applied to 8 mg intrathecal bupivacaine than without it ($T_{5.8} \pm 1.8$ vs. $T_{6.4} \pm 2.2$ respectively; $p = 0.324$).
Conclusion: EVE should not be applied to 5 mg plain bupivacaine during a combined spinal epidural block in patients undergoing lower limb orthopedic surgery as it may result in a decrease in the maximum sensory level.

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Introduction

Epidural volume extension involves instillation of 0.9% saline into the epidural space soon after an intrathecal injection. It aims to rapidly increase the level of sensory block obtained by the intrathecal drug deposition.[1] A recent meta-analysis however questioned its utility for increasing the sensory block level, while simultaneously acknowledging a lack of sufficient data to make definitive conclusions.[2]

It is noted that the success of epidural volume extension may depend on several variables.[3] In regional anesthesia practice, intrathecal dose of local anesthetic is a known determinant of the sensory level obtained after spinal block. Thus, the role of intrathecal dose itself in determining the success or failure of epidural volume extension could also be salient.

The intrathecal doses to which epidural volume extension has been applied and its effect evaluated have varied in previous studies. When applied to intrathecal bupivacaine of 8 mg or greater, augmentation of sensory block levels has been amply documented, in both obstetric as well as non-obstetric population.[4–11] On the other hand, there are only two studies using intrathecal doses lower than 8 mg while evaluating block augmentation with epidural volume extension.[12,13] Both the studies were conducted in obstetric patients and demonstrated failure of block augmentation. Thus, there may be a dependence of epidural volume extension on intrathecal dose. What is perplexing is that on the other hand, case reports with successful use of the technique have continued to be published in high-risk patients, following injection of deliberately reduced or sub-optimal intrathecal dose, even as little as 3 mg.[3,14–16] Reduction in intrathecal dose was indeed touted as the primary advantage of epidural volume extension, with the sensory level augmentation induced by normal saline being relied upon for adequate block instead.

We thus decided to evaluate the role of intrathecal dose in determining efficacy of epidural volume extension, while replicating its clinical usage, i.e. when applied to reduced intrathecal doses. We could not locate any previous trials comparing the sensory block augmentation efficacy of epidural volume extension applied to different reduced/sub-optimal doses of intrathecal local anesthetic.

Against this background, we compared application of epidural volume extension to 5 mg and 8 mg intrathecal bupivacaine in non-obstetric patients. The control group for each dose of intrathecal bupivacaine was one wherein no epidural volume extension was applied.

Methods

This prospective, randomized, controlled, double-blinded study was undertaken after obtaining approval from the Institutional Ethical Committee (Institutional Ethics Committee – Human Research; meeting held on October 07, 2016) and written informed consent from all participants. It was registered prospectively with the Clinical Trial Registry of India on December 22, 2016, bearing registration number CTRI/2016/12/007606.

A total of 84 consenting adult male patients of ASA status I or II with body weight between 50–70 kg and height in the range of 150–180 cm, scheduled for orthopedic surgery of lower limb using combined spinal epidural anesthesia were included. Those with contraindications to combined spinal epidural anesthesia including history of spinal disease, hypersensitivity to local anesthetics or coagulation abnormalities; as well as skin infection at site of injection or failure of the block were excluded from the study.

Using computer generated random number table, patients were allocated to one of 4 groups, depending upon the dose of intrathecal bupivacaine and whether epidural volume extension was carried out: groups B5 and BE5 received bupivacaine intrathecally in a dose of 5 mg without and with epidural volume extension, respectively; while groups B8 and BE8 received 8 mg intrathecal bupivacaine without and with epidural volume extension, respectively. We chose plain rather than hyperbaric intrathecal local anesthetic since previous data comparing the two formulations noted success of epidural volume extension with the plain only.[17]

After shifting the patient to the operating table, non-invasive oscillometric blood pressure, lead II electrocardiography and pulse oximetry were attached. Intravenous access was established, and 10 mL.kg^{-1} of Ringer's lactate solution infused as co-load.

Under all aseptic precautions, combined spinal epidural anesthesia was performed with the patient in sitting position, at $L_{4\text{-}5}$ inter-vertebral space via midline approach, using needle through needle technique. The epidural space was identified with an 18G Tuohy needle using loss of resistance to air, limiting the volume of air to less than 2 mL. Subarachnoid space was identified using a 27G Whitacre needle and free flow of cerebrospinal fluid was confirmed. The intrathecal solution as per the group allocation was injected into the cerebrospinal fluid at a rate of 0.5–1 mL.s^{-1} with the orifice of the Whitacre spinal needle facing cephalad.

The time of removal of spinal needle marked completion of intrathecal block. After removal of the spinal needle, the epidural catheter was inserted 4 cm into epidural space, and lack of blood/cerebrospinal fluid on aspiration ascertained through it. Normal saline (10 mL of 0.9%) was injected over 10–15 seconds through epidural catheter in patients of groups BE5 and BE8, while no epidural instillation was made for groups B5 and B8. Epidural catheter was secured in place and patient put in supine position. The time of putting patient into supine position since completion of the intrathecal injection was also noted. Oxygen at flow of 4 L.min^{-1} was administered via facemask, as per our routine practice.

The sensory and motor blockade was assessed by a blinded anesthesiologist every 3 minutes beginning after the patient was put in supine position, till there was no further increase in three consecutive readings. This level of sensory blockade was designated as maximum level of sensory block (S_{max}). The onset time to S_{max} was defined as the time from completion of intrathecal injection to the time when the maximum level was first recorded. Once S_{max} was achieved, level was tested every 15 minutes intraoperatively or every 30 minutes in recovery room till block level receded by two dermatomes or an epidural top-up was administered, whichever was earlier. The maximum motor block and it's time to onset were also noted. All block characteristics were evaluated only until an epidural top-up was administered.

Sensory level of block was assessed using complete absence of sensation to pinprick and the level recorded as the lowest one with no sensation to pinprick. Motor block in the normal lower limb was graded as per modified Bromage scale wherein score 1 means a complete motor block.[18]

The anesthesiologist assessing the block characteristics was blinded to the group allocated and not present in the operating room till the block performance was completed.

Concurrent with the recording of sensory and motor block level, the heart rate and mean arterial pressure were also noted.

Any episode of hypotension during the first 30 minutes after intrathecal drug deposition (and prior to the first epidural top-up) was recorded. Hypotension was defined as the fall in mean arterial pressure of greater than 30% from baseline or a systolic blood pressure of less than 90 mmHg (whichever reading was higher of the two) and treated using 6 mg boluses of mephentermine intravenously.

Incidence of intraoperative nausea, vomiting and pruritus occurring till the first epidural top-up were recorded.

Epidural top-ups were administered intraoperatively if the intrathecal block was inadequate for initiation or continuation of surgery. The catheter was used for providing postoperative analgesia as well.

In addition, the demographic profile of all the patients was recorded. The times for completion of intrathecal block, positioning the patient supine and for first epidural top-up were noted.

The S_{max} for group B5 was compared with group BE5 to assess the effect of epidural volume extension to 5 mg intrathecal bupivacaine.

A similar comparison was done between group B8 and group BE8 to assess the effect of epidural volume extension to 8 mg intrathecal bupivacaine.

Intergroup comparison for S_{max} between group B5 and group BE5was done using unpaired *t*-test. The same was repeated for groups B8 and BE8. For intergroup comparison of normally distributed demographic variables amongst all 4 groups, Analysis of Variance (ANOVA) with post-hoc comparisons with Tukey test was used. Comparison of discrete variables was done using Chi-Square. For the analysis of sensory block level, the dermatomes were numbered sequentially from C_1 to S_5.

The sample size was determined using two-sided, two-sample *t*-test for comparing means at a power of 80% and α error of 5%. Taking previously reported standard deviation of 1 dermatome in the maximum sensory block level after both 5 and 8 mg intrathecal plain bupivacaine in patients undergoing lower limb surgery,[17,19] 17 patients would be required in each group with either dose to detect a difference of 1 dermatome following epidural volume extension. Adding another 10% for possible withdrawals due to various reasons such as failure of block, and 15% in case of maximum sensory level being non-parametric in distribution, at least 21 patients would be required in each group.

Results

The CONSORT flow chart showing final patient enrollment is depicted in Fig. 1. A total of 21 patients were randomized to each of the four groups and the protocol could be completed in 20 each for groups B5, B8 and BE8 and 19 in group BE5.

Baseline patient characteristics including demographic parameters, hemodynamic variables as well as the duration of surgery were statistically similar between groups B5 and BE5; and also, between groups B8 and BE8 ($p > 0.05$) (Table 1). A comparison between all 4 groups for the baseline characteristics also showed statistically similar profile ($p > 0.05$).

Primary outcome measure, the S_{max}, was significantly lower in group BE5 as compared to group B5, $p = 0.030$; but similar between groups B8 and BE8, $p = 0.324$ (Table 2).

The maximum motor blockade, as well as the time to maximum sensory and motor block following the intrathecal injection, evaluated up-to prior to administration of epidural top-up, were statistically similar between groups B5 and BE5; as well as groups B8 and BE8 ($p > 0.05$) (Table 2). The time required to position the patient supine after completion of intrathecal block was similar between groups B5 and BE5 ($p = 0.171$); but significantly longer for group BE8 as compared to group B8 ($p = 0.029$) (Table 2).

The incidence of intraoperative hypotension, pruritus, nausea and/or vomiting were statistically similar between groups B5 and BE5; as well as group B8 and group BE8 (Table 3).

The number of patients who required epidural top-up intraoperatively was statistically similar between groups B5 and BE5; as well as groups B8 and BE8 (Table 4). However, the number of patients who required an intraoperative epidural top-up early on due to inadequate intrathecal block leading to failure to initiate the surgery was statistically similar for groups B5 and BE5, though clinically greater with the latter (5% vs. 26% respectively, $p = 0.247$). It remained similar between groups B8 and BE8 (5% vs. 0% respectively, $p = 0.799$) (Table 4). The first epidural top-up was required significantly earlier in group BE5 as compared to group B5 ($p = 0.034$) (Table 4); while the time of requirement was similar between groups B8 and BE8; ($p = 0.184$) (Table 4).

Discussion

The present study aimed to evaluate whether results of epidural volume extension depend on the amount of intrathecal local anesthetic when used in reduced dose. The primary outcome measure was the $S_{max,}$ achieved with or without epidural volume extension following intrathecal bupivacaine in reduced doses of 5 mg, and also following 8 mg.

Deliberately reduced intrathecal doses were chosen to replicate clinical utility and practice of epidural volume extension. A dose of 8 mg intrathecal bupivacaine was used since it is previously documented as ED50 for lower limb surgeries, implying that an inadequate sensory block level would be present in 50% patients thus justifying use of sensory block augmentation with epidural volume extension. We used 5 mg as the other reduced dose because it is one of the smallest amount used most consistently and successfully with epidural volume extension in clinical practice.[20–22]

Our study was powered to detect a change in even a single dermatome for the sensory block level after appli-

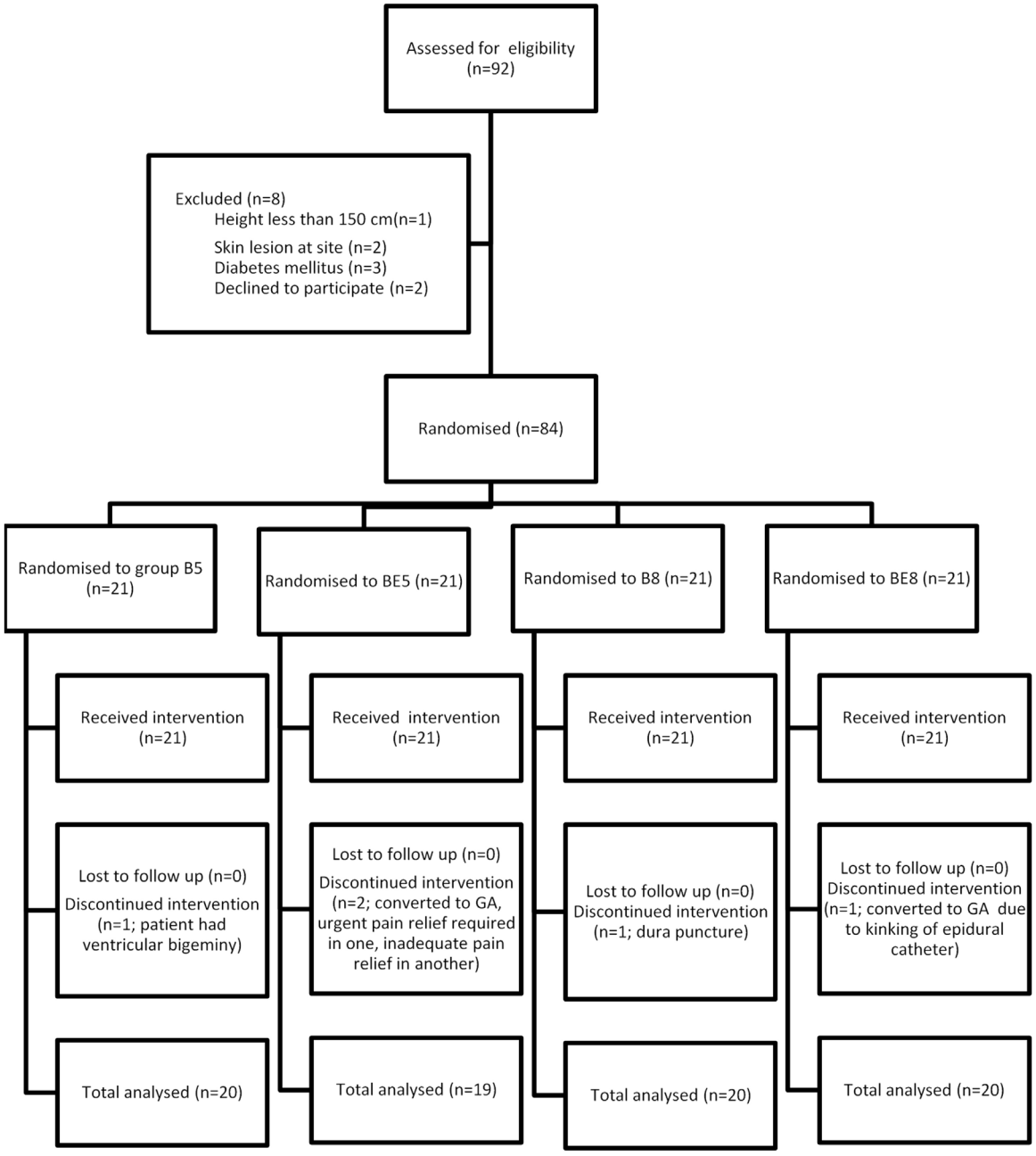

Figure 1 Consort flow chart depicting the patient enrolment for the study.

cation of epidural volume extension. With neither of the used intrathecal doses, i.e., 5 mg or 8 mg, was there any increase in the sensory block level following epidural volume extension. However, a significant but paradoxical decrease in the S_{max} was seen when epidural volume extension was applied to 5 mg dose, along with insignificant increase in requirement of epidural supplementation for initiation of surgery (26% vs. 5%), and significantly faster need of intraoperative epidural top-up. Its application to 8 mg intrathecal bupivacaine did not result in any clinical or statistically significant change in the S_{max} or other evaluated characteristics. This suggests there was no utility of epidural volume extension for sensory block augmentation with either of the two intrathecal doses tested.

Earlier studies evaluating various aspects and effects of epidural volume extension have used intrathecal bupivacaine in a range of 2 mg to 15 mg.[4–13,23–29] None of these studies has compared its results after applying it to various intrathecal doses under similar conditions. The effect of epidural volume extension for a particular dose of intrathecal bupivacaine can, however, be inferred from these studies. While an increase in the sensory level was noted with epidural volume extension applied to $\geq$ 8 mg (8, 9, 10 and 15 mg) intrathecal bupivacaine,[4–11] failure was seen following similar doses of > 8 mg (9 and 12.5 mg).[27,29] To add to the inconsistent results, the failure of epidural volume extension is seen with doses of < 8 mg (2 and 7.5 mg)[12,13] while similarly reduced doses of < 8 mg (3 to 5 mg) have been

Table 1 Patient characteristics and duration of surgery.

	Group B5 (n = 20)	Group BE5 (n = 19)	*p*-value[a]	Group B8 (n = 20)	Group BE8 (n = 20)	*p*-value[b]
Age (years)	35.9 ± 12.4	37.6 ± 12.0	0.593	34.1 ± 14.0	33.6 ± 15.2	0.923
Weight (Kg)	63.8 ± 6.0	65.2 ± 6.5	0.411	60.3 ± 7.0	63.3 ± 6.1	0.160
Height (cm)	164.6 ± 6.5	162.9 ± 7.6	0.572	160.2 ± 7.0	162.2 ± 8.6	0.435
ASA physical status (II:I)	4:16	4:15	0.915	7:13	4:16	0.429
Basal mean arterial pressure (mmHg)	96 ± 9	98 ± 7	0.742	100 ± 14	97 ± 11	0.409
Basal heart rate (min^{-1})	85 ± 15	81 ± 17	0.302	90 ± 17	83 ± 14	0.190
Presence of comorbidity	4 (20)	4 (21)	0.915	7 (35)	4 (20)	0.429
Duration of surgery (min)	112.2 ± 40.0	111.3 ± 40.0	0.942	111.5 ± 28.2	131.3 ± 51.4	0.141

Values are mean ± SD or number of patients.
There were no significant differences amongst groups. Group B5, 5 mg intrathecal plain bupivacaine; Group BE5, 5 mg intrathecal plain bupivacaine with epidural volume extension; Group B8, 8 mg intrathecal plain bupivacaine; Group BE8, 8 mg intrathecal plain bupivacaine with epidural volume extension.
[a] Intergroup comparisons between group B5 and BE5.
[b] Intergroup comparisons between group B8 and BE8.

Table 2 Characteristics of intrathecal block.

	Group B5 (n = 20)	Group BE5 (n = 19)	*p*-value[a]	Group B8 (n = 20)	Group BE8 (n = 20)	*p*-value[b]
S_{max}	$T_{6.4}$ ± 1.9	$T_{8.9}$ ± 4.3	0.030	$T_{6.4}$ ± 2.2	$T_{5.8}$ ± 1.8	0.324
Time to maximum sensory level (min)	8.2 ± 2.7	6.7 ± 3.2	0.108	9.2 ± 3.4	8.7 ± 3.0	0.623
Maximum motor block (Bromage score)	3.6 ± 0.7	3.6 ± 1.5	0.961	3.2 ± 0.7	2.8 ± 0.9	0.170
Time to maximum motor blockade (min)	6.9 ± 2.6	7.0 ± 3.2	0.974	9.0 ± 3.9	9.1 ± 2.9	0.930
Time to position the patient supine (min)	3.4 ± 1.0	4.0 ± 1.4	0.171	3.7 ± 0.9	4.3 ± 1.0	0.029

Values are mean ± SD.
Group B5, 5 mg intrathecal plain bupivacaine; Group BE5, 5 mg intrathecal plain bupivacaine with epidural volume extension; Group B8, 8 mg intrathecal plain bupivacaine; Group BE8, 8 mg intrathecal plain bupivacaine with epidural volume extension.
[a] Intergroup comparisons between group B5 and BE5.
[b] Intergroup comparisons between groups B8 and BE8.

Table 3 Intraoperative adverse events.

	Group B5 (n = 20)	Group BE5 (n = 19)	*p*-value[a]	Group B8 (n = 20)	Group BE8 (n = 20)	*p*-value[b]
Hypotension	5 (25)	8 (42)	0.365	8 (40)	7 (35)	0.799
Nausea and/or vomiting	1 (5)	1 (5)	0.989	0 (0)	1 (5)	0.799
Pruritus	0 (0)	0 (0)	1.000	0 (0)	0 (0)	1.000

Values are number of patients (%).
Group B5, 5 mg intrathecal plain bupivacaine; Group BE5, 5 mg intrathecal plain bupivacaine with epidural volume extension; Group B8, 8 mg intrathecal plain bupivacaine; Group BE8, 8 mg intrathecal plain bupivacaine with epidural volume extension.
[a] Intergroup comparisons between group B5 and BE5.
[b] Intergroup comparisons between group B8 and BE8.

Table 4 Characteristics of first intraoperative epidural top-up.

	Group B5 (n = 20)	Group BE5 (n = 19)	*p*-value[a]	Group B8 (n = 20)	Group BE8 (n = 20)	*p*-value[b]
Frequency of intraoperative epidural top-up	17 (85)	18 (95)	0.607	18 (90)	17 (85)	0.799
Indicated due to inadequate intrathecal block	1 (5)	5 (26)	0.247	1 (5)	0 (0)	0.799
Time to first epidural top-up (min)	75.8 ± 29.2	53.9 ± 33.2	0.034	90.0 ± 32.3	104.3 ± 34.2	0.184

Data are number of patients (%).
Group B5, 5 mg intrathecal plain bupivacaine; Group BE5, 5 mg intrathecal plain bupivacaine with epidural volume extension; Group B8, 8 mg intrathecal plain bupivacaine; Group BE8, 8 mg intrathecal plain bupivacaine with epidural volume extension.
[a] Intergroup comparisons between group B5 and BE5.
[b] Intergroup comparisons between group B8 and BE8.

used in clinical practice of epidural volume extension as per published case reports.[20–22,30] Such results showing success as well as failure despite similar intrathecal doses may be due to epidural volume extension being influenced by several factors other factors viz., characteristics of patient and the epidural injectate.[3]

In contrast to our findings of failed sensory block augmentation with epidural volume extension with both intrathecal doses, contrasting earlier results of success following 8 mg bupivacaine[7,8] and doses of 5 mg or less can be seen.[20–22,30] However, the previous evidence of success with reduced intrathecal doses of 8 mg or less is all from obstetric patients,[7,8,22–24,30] while our study group was non-obstetric patients. It is known that intrathecal drug spread and block characteristics differ between the two patient populations.[31] In non-obstetric patients, previous evidence has shown successful epidural volume extension with intrathecal dose reduced to 10 mg only.[6,9–11] Further reduction in intrathecal dose, to both 8 mg and 5 mg, may render epidural volume extension ineffective in non-obstetric patients.

We observed a paradoxical fall in sensory level seen when epidural volume extension was applied to 5 mg bupivacaine, though not with 8 mg dose. At this time, we are unable to hypothesize a probable reason for this finding. It was an unexpected result that has not been observed before. The observation does add weightage to our own clinical research question regarding the utility of epidural volume extension after intrathecal doses that have been extremely reduced.

What is truly intriguing is that despite no consensus being formed on utility of sensory block augmentation with epidural volume extension, clinical reports using it successfully in high-risk parturients after injecting extremely lowered intrathecal doses continue to add to the dilemma. This could only be explained by the phenomenon being dependent on several variables,[3] intrathecal dose as well as pregnancy being two salient ones. Utility and efficacy of epidural volume extension applied to reduced intrathecal doses may as well be different for obstetric patients in contrast with our results.

A limitation of the present study is that it was powered to detect a difference in the S_{max} only and not to other block characteristics. Also, the reason for the detrimental effect of epidural volume extension to 5 mg of intrathecal bupivacaine cannot be ascertained.

Based on our observations, the intrathecal dose appears to affect efficacy of epidural volume extension. The findings have a repercussion on the clinical application of epidural volume extension, as previous evidence of its successful use in practice focuses on achieving intrathecal dose reduction while achieving an adequate S_{max}. If there is indeed indication for reducing the subarachnoid dose, Epidural Volume Expansion needs to be considered clinically. We have compared only two predetermined reduced doses in non-obstetric patients. The lowest limit of dose reduction will need to be investigated, for both obstetric and non-obstetric patients.

In conclusion, epidural volume extension should not be applied to the smaller intrathecal dose of 5 mg plain bupivacaine during a combined spinal epidural block in patients undergoing lower limb orthopedic surgery. Its application may result in a decrease in the maximum sensory level. When using 8 mg instead of 5 mg intrathecal bupivacaine, although epidural volume extension can be applied without detrimental effects, it does not offer beneficial sensory block augmentation.

Conflicts of interest

The authors declare no conflicts of interest.

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