

## Comparison of Subarachnoid Block Characteristics with Levobupivacaine at 24°C and 37°C for Infra-Umbilical Surgeries - a Randomized Controlled Trial.

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**Background & Aim:** The temperature of a local anaesthetic solution influences its pKa and molecular kinetic activity, thereby affecting baricity. We evaluated the effects of 0.5% Levobupivacaine preheated at 37°C on sensory and motor block characteristics and haemodynamic in patients undergoing infra-umbilical surgeries. **Methods:** This was a prospective, randomised, double blinded study, in which 70 patients were allocated into two groups [Group A (n=35) and Group B (n=35)]. In Group A, patients were administered 3 mL of levobupivacaine 0.5% solution at room temperature (24 -28°C) and patients in Group B were administered with 3 mL of levobupivacaine 0.5% solution at 37°C (Thermostatically controlled digitalized hot bath machine) into the subarachnoid space. Our primary objective was to determine the time of onset of sensory blockade at T10. Time of onset and duration of motor blockade, duration of analgesia, time to two segment regression and other adverse events after spinal anaesthesia were secondary objectives. **Results:** The time to reach a sensory block of T10 was significantly shorter in group B (Mean  $\pm$ SD 2.7 $\pm$ 2.9 min, P 0.005) compared to that in group A (Mean  $\pm$ SD 4.8 $\pm$ 4.5 min). The mean duration of sensory block was longer in group B (Mean  $\pm$ SD 155.5 $\pm$ 25.9 min, P 0.048). Time to onset of motor block, duration of motor block and time to regression of two dermatomal level were not found statistically significant among the two groups. **Conclusion:** Spinal anaesthesia with 0.5% levobupivacaine heated to 37°C shortens sensory block onset time and provides longer block duration.

**Keywords:** Levobupivacaine, Sensory block, Motor block, Warm local anaesthetics, Spinal anaesthesia.

### Introduction

Spinal anaesthesia is the most preferred regional anaesthetic technique for surgeries below the umbilicus because of its faster onset and effective

sensory-motor blockade. Bupivacaine is the most used local anaesthetic in spinal anaesthesia but is associated with hemodynamic disturbances,<sup>1</sup> especially in geriatric patients and those with limited cardiac reserve who commonly present for lower limb and infraumbilical surgeries. In order to reduce the cardiovascular side effects of intrathecal bupivacaine various methods have been studied. While low dose bupivacaine may not always provide adequate level of block despite prevention of cardiovascular side effects,<sup>2</sup> adding adjuncts may cause exaggerated side effects for some patients. Hence, there is always a quest for safer local anaesthetic agents for spinal anaesthesia. Levobupivacaine has become a popular choice

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because of its reduced depressant effect on the cardiovascular system.<sup>3</sup> However it is reported to have significantly slower time to reach T10 sensory block as compared to bupivacaine.<sup>4</sup> Temperature of the drug injected is one of the various factors which affect its spread in subarachnoid space as it increases molecular kinetic energy, facilitating higher levels of spinal anaesthesia.<sup>5, 6</sup> Warming of local anesthetic preparations has been reported by some investigators to reduce the time of onset of sensory block during epidural and local infiltrations.<sup>7,8</sup> This effect on the subarachnoid block characteristics with Levobupivacaine has not been adequately studied. We designed a study to compare the sensory and motor characteristics of the subarachnoid block with levobupivacaine at room temperature (24°C) and at body temperature (37°C). The primary outcome was the time of onset of sensory blockade at T10 and the secondary outcomes were the time of onset and duration of motor blockade, duration of analgesia, time taken for two segment regression and other adverse events after spinal anaesthesia.

### Methodology

This was a prospective, randomized double blinded study conducted at a tertiary care center between March 2017 and December 2017. CTRI registration was obtained. Institutional Ethical committee approval was obtained and seventy patients between 18 to 75 years of age, scheduled for all elective infraumbilical surgeries were enrolled. Surgical procedures included inguinal hernia repair, hydrocele surgery, varicose vein surgery, appendectomy, gynecological procedures such as vaginal hysterectomy, urological procedures such as ureteroscopic lithotripsy, implant exit of lower limbs, fistulectomy and other perianal procedures. Patients less than 150 cm height, any contraindications to spinal anaesthesia, pregnant patients, and patients with any pre-existing neurological deficits were excluded. A thorough pre-anesthetic workup was performed, and a written informed consent was obtained. Oral

premedication of tablet ranitidine 150 mg, tablet perinorm 10 mg and tablet alprazolam 0.5 mg were given on the night before surgery and morning of the surgery. On the morning of the surgery in the preoperative holding area, the patients were randomly allocated into two groups, group A and group B by opening a sealed envelope with one of the study treatment regime mentioned inside it. Patients in group A were planned to received intrathecal levobupivacaine 0.5% 3 ml at room temperature (24 degree Celsius), and patients in group B to receive levobupivacaine 0.5% 3 ml (preheated at 37 degree Celsius). The preheating was done using a Proportional Integral Derivative controlled digitalized dry bath made by Technico<sup>®</sup> Laboratory Products Private Limited. (Figure 1).

**Figure 1:** Digitalized dry bath used for preheating Levobupivacaine.



Preoperatively, intravenous access was secured with an 18-gauge cannula and patients were preloaded with ringer lactate (RL) 10 ml/ kg, 15 minutes prior to spinal anaesthesia. In the operating room, these patients were subjected to standard monitoring (ECG, pulse-oximetry and NIBP) and the baseline measurements were made.

All blocks were performed by an anaesthesiologist who had at least 1 year experience in administering spinal anaesthesia. All blocks were given in lateral position with strict aseptic precautions, using 23-gauge (23G) Quincke tip spinal needle at L2-L3 / L3-L4 interspace by midline approach. Study drug was loaded after patient was positioned left lateral and draped ready for the block. The confirmation of needle tip in the subarachnoid space was done with

the free flow of cerebrospinal fluid. The study drug was injected at a temperature as per the patients' group allocation at the rate of 0.4 ml/ sec without aspirating or barbotage to preserve the temperature of injectate. Patients were turned to supine immediately. The assessment of sensory-motor blockade was done by an independent anesthesiologist who was unaware of the group allocation of the patient.

Assessment of block: Sensory blockade was assessed by loss of cold sensation to ice pack with three point sensory score (0- no sensation, 1- feels the touch not the temperature, 2- feel both the touch and temperature) applied to the skin along the midclavicular line. Motor blockade was assessed using modified Bromage score (0- no motor block, 1- Inability to raise extended leg and able to move knee and feet, 2- Inability to raise extended leg and move knees but able to move feet, 3- complete motor block). The assessment was done every 2 minutes for first 10 minutes followed by every 5 minutes for 1<sup>st</sup> hour and thereafter every 30 minutes until the patient complained of pain (Visual Analogue Score  $\geq 4$ ). The onset of sensory block was considered from needle removal time to sensory score of 1 at T10. The onset of motor block was considered from needle removal time to the Bromage score of 1. The time taken for two-segment regression of block was counted from maximum sensory block height achieved to two-segment regression. The duration of analgesia was considered from needle removal time till the patient first complained of pain. The onset of motor block was considered from needle removal time to Bromage score of 1.

Heart rate, mean arterial pressure and arterial oxygen saturation (SpO<sub>2</sub>) were monitored every 2 minutes for the first 10 minutes and then every 5 minutes till the end of the surgery. In addition, any complications such as bradycardia, hypotension, shivering and vomiting post spinal anaesthesia were carefully observed and noted. Bradycardia was treated with Inj. Atropine 0.02 mg/kg and hypotension was treated with Inj. Mephentermine 6

mg IV boluses. If inadequate sensory level was obtained even after 30 minutes of the spinal injectate, it was considered a failed spinal blockade, and further management of the case was determined by the attending anesthesiologist. Postoperatively, Inj. Tramadol 50 mg IV was administered intravenously for postoperative analgesia. Data were observed and recorded on a separate proforma by the individual anesthetist not involved in performance of the block.

The sample size was calculated based on the previous study done by Golboyu BE et al, where the time taken to achieve a level of T10 with plain levobupivacaine at room temperature was 6 min.<sup>7</sup> We hypothesized that warming the local anaesthetic solution will increase the ascent of the drug in intrathecal space. Therefore, to find the difference of 2 min to achieve T10 level sensory blockade between the groups and a common standard deviation of 2.6 min with a power of 80% ( $\alpha = 0.05$ ), the sample size required was 27. Considering the dropouts and exclusions, we have included a sample size of 35 in each group. Data collection was done by an anesthesiologist who was not part of the study and entered into Microsoft Excel (2016). The parametric variables such as demographic data (age, weight, height), time of onset of sensory and motor block, time to two segment regression of block, duration of surgery, duration of analgesia and duration of the motor block were expressed in mean  $\pm$  SD. These variables were analysed based on normality using student-T test or Mann Whitney- U test. Complications that have occurred during the procedure were mentioned in the form of a number (percentage) and were analysed using the chi-square test. Data were entered and analysed using statistical software SPSS ver.16. A P-value of  $< 0.05$  was considered statistically significant for all the results.

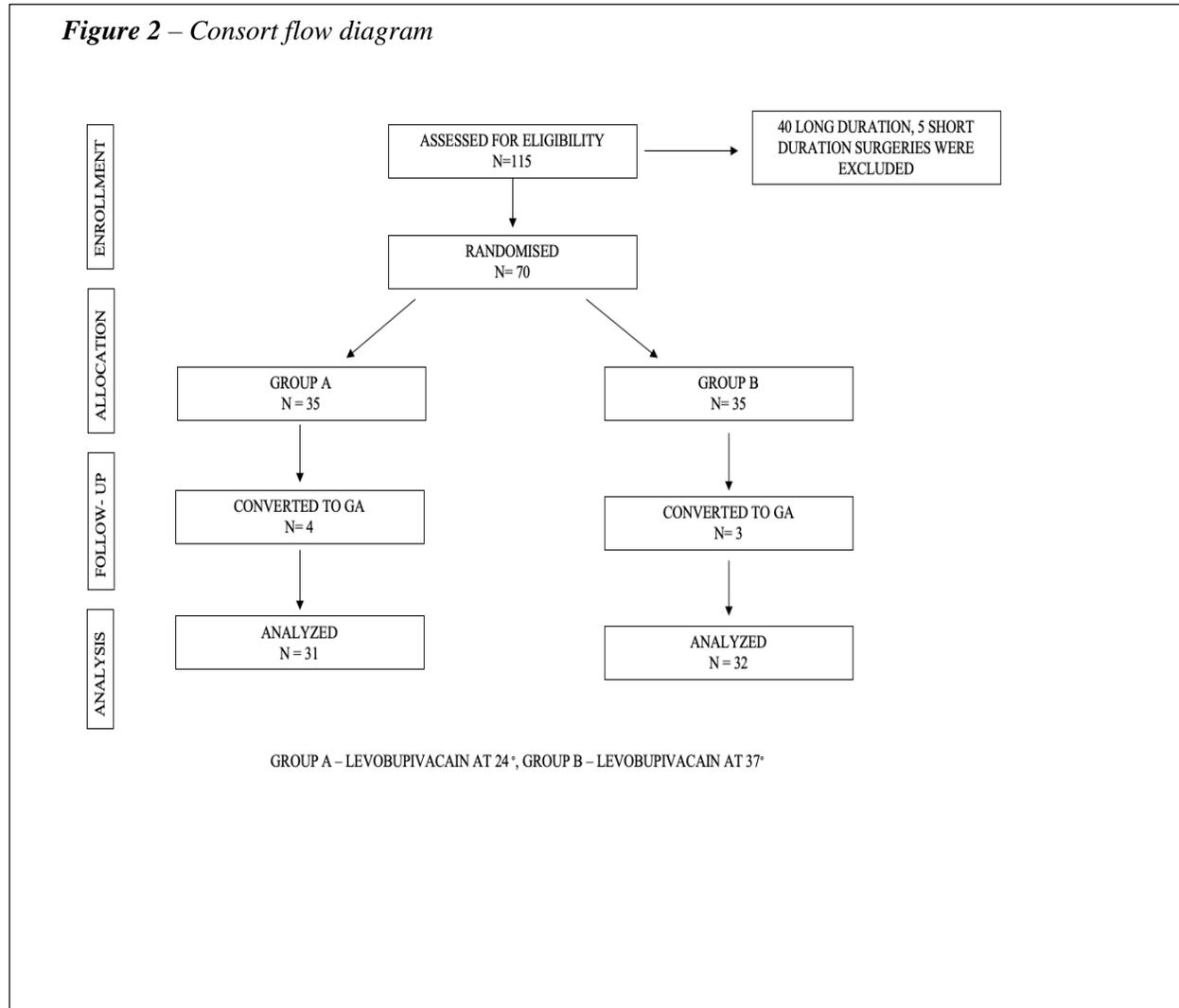
## Results

A total of one hundred and fifteen patients were assessed for eligibility, out of which only 70 patients were included in the study by continuous sampling and allocated into two groups with 35

patients in each group. Seven patients were excluded from the study due to the conversion of spinal anaesthesia into general anaesthesia due to prolongation of surgical duration. Conclusively, a total of Sixty-three patients were analysed with 31 patients in group A and 32 patients in group B (Figure 2). The descriptive characteristics of the patients are shown in Table 1 and all the values were comparable between the two groups (Table 1).

The time of onset of T10 sensory blockade was found to be  $2.7 \pm 2.9$  min in group B, which was earlier to that of group A  $4.8 \pm 4.5$  min with a p value of 0.005. No significant difference was found in both groups in terms of time to two-segment regression. The duration of analgesia was  $155.5 \pm 25.9$  min in group B and  $140.9 \pm 31.9$  min in group A with a p value of 0.048 (Table 2).

**Figure 2 – Consort flow diagram**



The median maximum sensory block level in group A was T8 with an interquartile range of T6–T10, and in group B, it was T6 with an interquartile range of T4–T10. The difference between the two groups was not statistically significant.

There was no significant difference in the incidence of any of the complications such as bradycardia, shivering or vomiting between the two groups. The number of patients with hypotension episodes in each group at different time points is demonstrated in Figure 4

**Table 1:** Descriptive data of patient characteristics with statistical comparisons.

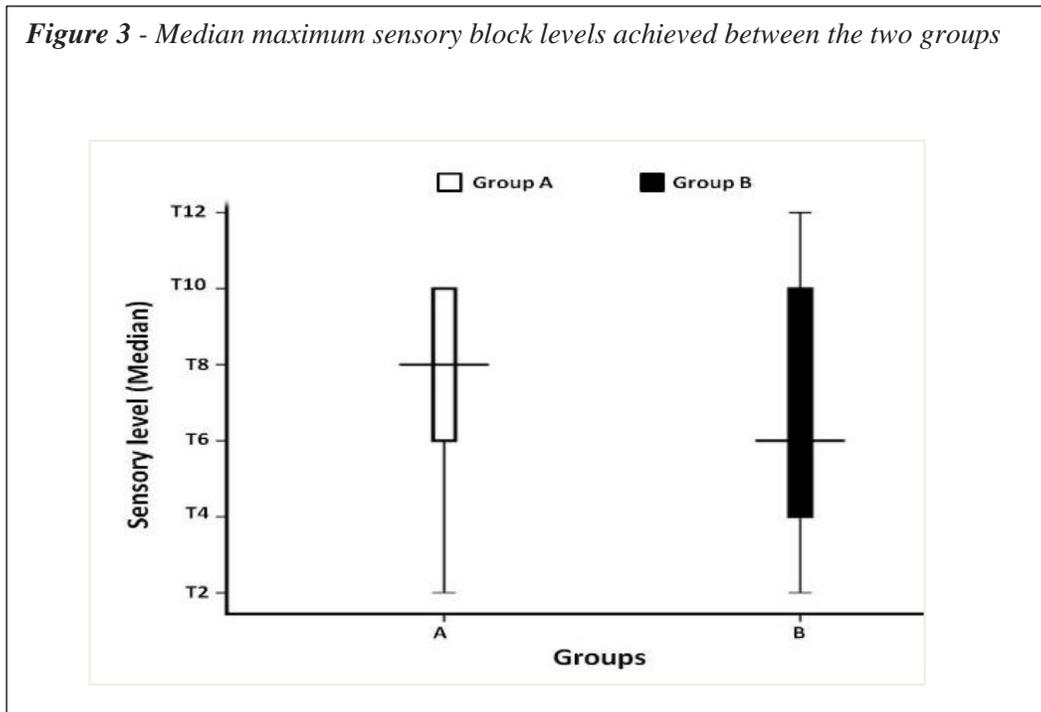
Patient		Group A (n=31)	Group B (n=32)	P value
Age (Years)		40.3±12.1	44.3±11.7	0.72
Gender	Male	13 (41.9%)	16 (50%)	
	Female	18 (58.1%)	16 (50%)	
Height (cm)		157.4±6.5	157.9±4.9	0.16
Weight (Kg)		62.8±13	65.5±11.7	0.33
Surgery duration (min)		57.4 ±34	53.3 ± 28.6	0.45

Values are expressed in mean ± SD; P > 0.05; n= number of patients in each group.

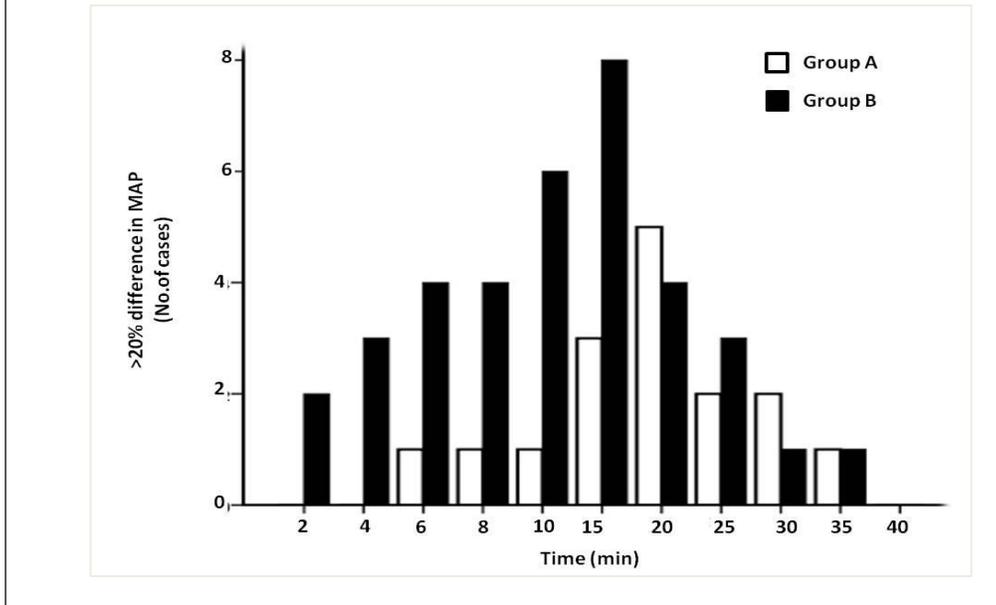
**Table 2:** Sensory and motor block characteristics of the patients in two groups.

Study variables	Group A (n=31)	Group B (n=32)	P value
Time to onset Sensory block (min)	4.8±4.5	2.7±2.9	0.005
Analgesia duration (min)	140.9±31.9	155.5±25.9	0.048
Two segments Regression time (min)	92.7±27.3	99.6±19.8	0.068
Time to onset Motor block (min)	9.1±3.4	9.5±3.0	0.84
Duration of motor block (min)	159.14±29.4	153.2±34.4	0.44

Values are expressed in mean ± SD; n= number of patients in each group



**Figure 4** - Number of patients with hypotension episodes in each group



**Discussion**

This study was conducted to compare the effect of injecting Levobupivacaine at two different temperatures, 25 C and 37 C. There are many factors, which determine the intrathecal drug spread such as concentration of the drug, its volume, drug baricity, density and temperature.<sup>9</sup> Invitro studies demonstrate changes in the density of the local anaesthetic at different temperatures.<sup>10</sup> It has been found that there is a curvilinear reduction in the density with the increased temperature of the local anaesthetic solution.<sup>6</sup> It has been also demonstrated that commercially available plain levobupivacaine is mildly hyperbaric at 23°C and mildly hypobaric at 37°C (1.00419 and 1.00024 respectively). There is lack of in vivo studies demonstrating the clinical effects on distribution of spinal anaesthesia with Levobupivacaine at different temperatures. At 37°C the mean density of CSF is 1.0003g/L with a range of (1.0000- 1.0006± 2SD) g/L. This suggests that variation in all the physiological parameters occur within the fourth place of decimals<sup>5</sup>. In the present study, a rapid sensory onset was noted in the group which received levobupivacaine at 37°C. This could be explained by a change in baricity

associated with an increase in temperature. The increase in temperature causes a reduction in baricity, which, as a result reduces pKa of the drug, increasing the unbound drug form which helps in rapid onset of action.<sup>11</sup> Although, the duration of the sensory blockade was longer in the group which received levobupivacaine at 37°C, a 15 minutes difference between both groups does not have any clinical implications.

In this study, there was a higher level of sensory blockade achieved in group B (median T6 level) when compared to the median T8 level in the group A that is not statistically significant. However, the interquartile range implies the sensory distribution between T4 and T10, which suggests variability in distribution of the spinal anaesthetic drug. It can be explained by the increase in the baricity which in turn causes lowering of pKa and subsequent increase in the unionised form of the drug.<sup>12</sup> However, the variability in drug spread could be due to redistribution of temperature of the injectate on getting in contact with the CSF. Other studies have demonstrated similar findings with bupivacaine and ropivacaine in terms of onset of sensory blockade. Arai et al, explain that the reason

for the onset of sensory blockade being rapid in warmed local anaesthetic could be due to decrease in viscosity.<sup>10</sup> Some researchers have demonstrated that the use of warm lidocaine hastens the onset of action in epidural analgesia and this finding could be due to an increased rate of passive diffusion across non-neural structures or a reduction in pKa, which causes an increase in the non-ionized fraction of local anaesthetic that can cross the neural membranes.<sup>7,13</sup> According to Trabelsi *et al*, heating increases the diffusion capacity of local anaesthetic, thereby resulting in early onset of the action.<sup>14</sup> The duration of sensory blockade and the median highest sensory level has shown comparable results without any significance. Two-segment regression and the motor characteristics of the subarachnoid block were comparable among both groups. There was also no significant difference between the groups in terms of complications. However, the onset of hypotension in the group that received heated levobupivacaine was early when compared to the group that received levobupivacaine at 23°C. This could be explained by variable spread of the heated levobupivacaine, which has caused higher level of drug spread at a faster rate due to the hypobaric nature of the drug.<sup>15</sup> Since Levobupivacaine is very cardio stable, its limitation of comparatively slower onset of action can be clinically minimised by a simple method of warming the drug prior to spinal administration without additional side effects. Limitation of our study was that it was difficult to maintain the drug temperature constant after the ampoule is taken out from the warming device. However, we tried to minimise it by keeping the warming device inside the operation theatre and taking out the ampoule for loading only after obtaining CSF flow in both groups.

### Conclusion

We conclude that warming of intrathecal Levobupivacaine to body temperature (37°C), results in a faster onset of sensory blockade without any added hemodynamic changes and other adverse

effects. This was statistically significant as compared to regular practice of injecting local anaesthetic at room temperature, however the difference of two minutes on onset of sensory block is not of much significance in clinical practice.

### References

1. Morrison SG, Dominguez JJ, Frascarolo P, Reiz S. A comparison of the electrocardiographic cardiotoxic effects of racemic bupivacaine, levobupivacaine, and ropivacaine in anesthetized swine. *Anesth Analg* 2000; **90**:1308–14. <https://pubmed.ncbi.nlm.nih.gov/10825312/>
2. Ben-David B, Frankel R, Arzumov N, Marchevsky Y, Volpin G. Minidose bupivacaine-fentanyl spinal anesthesia for surgical repair of hip fracture in aged. *Anesthesiology* 2000; **92**:6-10. <https://pubmed.ncbi.nlm.nih.gov/10638892/>
3. Bardsley H, Gristwood R, Baker H, Watson N, Nimmo W. A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. *Br J Clin Pharmacol* 1998; **46**:245–9. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1873676/>
4. F. Erdil, S. Bulut, S. Demirbilek, E. Gedik, N. Gulhas, M. O. Ersoy. The effects of intrathecal levobupivacaine and bupivacaine in the elderly. *Anaesthesia*, 2009; **64**:942-946. <https://pubmed.ncbi.nlm.nih.gov/19686477/>
5. Akerman N. Intrathecal drug spread. *Br J Anaesth* 2005; **94**:249.
6. Heller AR, Zimmermann K, Seele K, Rössel T, Koch T, Litz RJ. Modifying the baricity of local anesthetics for spinal anesthesia by temperature adjustment: model calculations. *Anesthesiology* 2006; **105**:346–53. <https://pubmed.ncbi.nlm.nih.gov/16871069/>
7. Fu-Chao Liu, Jiin-Tarng Liou, Yuan-Ji Day, Allen H. Li, Huang-Ping Yu. Effect of Warm Lidocaine on the Sensory Onset of Epidural Anesthesia: A Randomized Trial. *Chang Gung Med J* 2009; **32**:643-9. <https://pubmed.ncbi.nlm.nih.gov/20035644/>

8. Reenu Sarah Kurien, Mousumi Goswami, Sanjay Singh. Comparative evaluation of anesthetic efficacy of warm, buffered and conventional 2% lignocaine for the success of inferior alveolar nerve block (IANB) in mandibular primary molars: A randomized controlled clinical trial. *J Dent Res Dent Clin Dent Prospect* 2018; **12**:102-109. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6076879/>
9. Horlocker TT, Wedel DJ. Density, specific gravity, and baricity of spinal anesthetic solutions at body temperature. *Anesth Analg* 1993; **76**:1015–8. <https://pubmed.ncbi.nlm.nih.gov/8484500/>
10. Ernst EA. In-vitro changes of osmolality and density of spinal anesthetic solutions. *Anesthesiology* 1968; **29**:104–9.
11. Arai Y-CP, Ueda W, Takimoto E, Manabe M. The Influence of Hyperbaric Bupivacaine temperature on the Spread of Spinal Anesthesia: *Anesth Analg* 2006; **102**:272–5. <https://pubmed.ncbi.nlm.nih.gov/16368842/>
12. Kamaya H, Hayes JJ, Ueda I. Dissociation constants of local anesthetics and their temperature dependence. *Anesth Analg* 1983; **62**:1025–30. <https://pubmed.ncbi.nlm.nih.gov/6625205/>
13. Liu F-C, Liou J-T, Li AH, Day Y-J, Yu H-P. The effect of warmed ropivacaine to body temperature on epidural sensory block characteristics. *J Clin Anesth* 2010; **22**:110–4.
14. Trabelsi W, Ben Gabsia A, Lebbi A, Sammoud W, Labbène I, Kchelfi S, et al. Effect of warming bupivacaine 0.5% on ultrasound-guided axillary plexus block. Randomized prospective double blind study. *Orthop Traumatol Surg Res* 2017; **103**:71–5.
15. Burke D, Kennedy S, Bannister J. Spinal anesthesia with 0.5% S(-)-bupivacaine for elective lower limb surgery. *Reg Anesth Pain Med* 1999; **24**:519–23. <https://pubmed.ncbi.nlm.nih.gov/10588555/>