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RESEARCH

Efficacy of premixed versus sequential administration of dexmedetomidine as an adjuvant to intrathecal hyperbaric bupivacaine in lower limb surgery

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Objective: To evaluate the efficacy of intrathecal hyperbaric bupivacaine premixed with dexmeditomidine compared with sequential administration in separate syringes on block characteristics, haemodynamic parameters, side effect profile and postoperative analgesic requirement.
Trial design: This was a prospective, randomised clinical study
Method: Sixty orthopaedic patients scheduled for elective lower limb surgery under spinal anaesthesia were divided into two groups to receive either intrathecal hyperbaric bupivacaine 12.5 mg premixed (Group P) with dexmeditomidine 10 µg (diluted to 0.5 ml with normal saline) or by sequential administration in separate syringes (Group S).
Outcome: Block characteristics, haemodynamic parameters, side effect profile and postoperative analgesic requirement were compared in both groups.
Results: Time to achieve T10 spinal level was significantly less in group S (4.467 + 0.973 min) compared with group P (5.5 + 1.167 min). Similarly, patients in group S achieved Modified Bromage III earlier (6.1 + 1.296 min) than group P (7.5 + 1.333 min), *p*-value 0.0001.
Conclusion: Dexmeditomidine given sequentially in a separate syringe as adjuvant to intrathecal hyperbaric bupivacaine can result in faster onset of both sensory and motor block and prolongs the duration of spinal anaesthesia, minimises clinically significant side effects and reduces the postoperative analgesic requirement.

Keywords: dexmedetomidine, hyperbaric bupivacaine, intrathecal block

Introduction

Due to its lower cost, simpler technique and higher patient acceptance spinal anaesthesia is fast becoming the procedure of choice for lower limb and lower abdominal surgeries. Duration of spinal anaesthesia depends on the local anaesthetic used and is an important limiting factor of this technique. Many adjuvants have been tried with local anaesthetics to increase the duration of effect, to provide stable haemodynamics and to minimise complications. It is common practice to mix adjuvant drugs with hyperbaric local anaesthetic in the same syringe but that can alter the density of local anaesthetic solution influencing spread of the drug in the cerebrospinal fluid.

Various factors that have been shown to influence the intrathecal spread of local anaesthetic are temperature and pH of the drug, baricity and patient position after injection.[1] Studies have already shown that premixing adjuvants with hyperbaric bupivacaine might alter its spread in CSF.[2] Conversely, administering adjuvants sequentially in separate syringes may minimise the change in density and pH of both drugs, preventing any alteration in CSF spread.

Dexmedetomidine, a highly selective α2-adrenoreceptor agonist, has been found to be useful as an intrathecal adjuvant to local anaesthetics. It provides stable haemodynamics and prolongs analgesic effect.[3,4] However, no study was found in the literature comparing premixed with sequential administration of dexmeditomidine with intrathecal local anaesthetic. Therefore the aim of this study was to study the effect of intrathecal administration of hyperbaric bupivacaine premixed with dexmedetomidine compared with sequential administration in separate syringes on block characteristics, haemodynamic parameters, side effect profile and postoperative pain.

Materials and methods

This study was conducted in BPS Government Medical College (FW) after approval by the Institutional Ethics Committee. Sixty orthopaedic patients scheduled for elective lower limb surgery under spinal anaesthesia were enrolled in this study. All the patients were ASA class 1 and 2, aged between 15 and 60 years with no significant comorbidities. Patients with ASA grade higher than 2, age less than 15 years or more than 60 years, anticipated duration of surgery more than 1 hour and history of allergy to dexmeditomidine or bupivacaine were excluded from this study.

Written informed consent was obtained from all patients before starting the study. All patients had undergone preanaesthetic check-up before surgery. Patients were kept nil per os for six hours before surgery. Patients were taken into the preoperative room and vitals were recorded including heart rate, ECG, oxygen saturation and non-invasive blood pressure. Patients were then taken into the operating theatre.

In the operating room, intravenous access was secured with 18G intravenous cannula and monitors were attached. All the patients were randomly divided into two groups with 30 patients in each group using a computer-generated program. Patients in group P received intrathecal hyperbaric bupivacaine 12.5 mg premixed with dexmeditomidine 10 µg (diluted to a volume of 0.5 ml with normal saline). The drugs were mixed together in a single syringe just before intrathecal injection. Those in group S received intrathecal hyperbaric bupivacaine 12.5 mg followed by sequential administration of dexmeditomidine 10 µg (total

volume 0.5 ml with normal saline) in a separate syringe intrathecally. Spinal anaesthesia was administered using a 25G Quincke needle with patients in a sitting position. After spinal anaesthesia all patients were made to lie supine to achieve the desired sensory level. All patients received intravenous Ringer's lactate solution at the rate of 10 ml/kg/h during the intraoperative period.

Haemodynamic parameters, i.e. heart rate, blood pressure and oxygen saturation, were recorded every 2 minutes for the first 10 minutes and every 5 minutes subsequently till completion of surgery. An episode of hypotension was defined as systolic blood pressure below 90 mmHg or a fall in blood pressure by more than 20% of baseline values) and bradycardia as heart rate < 50 beats/min or even higher, if there were associated clinical signs and symptoms. For hypotension, the patient received a rapid infusion of crystalloids (200 ml of normal saline or ringer lactate) and ephedrine 5 mg intravenously if hypotension persisted. For bradycardia, the patient received atropine 0.02 mg/kg intravenously.

The progression of spinal block was assessed using pin-prick every 1 minute until the maximum level was reached. Surgery was started only after sensory level up to T10 or higher was achieved. Time to achieve T10 level as well as maximum height of block was noted and compared. At the same time a modified Bromage scale was used to assess the motor block as: I — no block with full flexion possible at knees and feet; II — partial block, with patient just able to flex knees with full flexion possible at feet; III — almost complete, with patient unable to flex knees but flexion of feet possible; and IV — complete block, i.e. inability to move legs and feet. Time to achieve Bromage III was recorded.

Postoperatively patients were observed for a period of six hours following intrathecal injection in the post-anaesthesia care unit. Time of regression of sensory block two dermatomes below the maximum block height and that of motor block to Bromage I was noted. Also time of demand of first rescue analgesic was also noted. All patients received injection of fentanyl 1.5 mcg/kg on demand if they complained of pain. Requirement for rescue analgesic was assessed in terms of total doses of injections of fentanyl given to each group. Any side effects such as nausea, vomiting, excessive sedation or respiratory depression during the intraoperative period were also noted.

The primary outcome was to study the effect of sequential administration of intrathecal dexmeditomidine on characteristics of spinal block (onset, maximum height of block and duration) compared with when administered premixed in the same syringe. A secondary outcome was to compare clinically significant side effects noticed among patients in both groups as well as postoperative analgesic requirement.

Statistical analysis

Based on similar studies[2] in the past, sample size estimation was done based on time for two-segment regression of spinal block as primary end point. To achieve a level of significance of 0.05 and a power of 80% a sample size of 30 patients was required per group. So, 60 patients in total were considered for this study. Data were entered into a Microsoft Excel® spreadsheet and analysed using Statistical Package for Social Sciences® version 16 (SPSS Inc., Chicago, IL, USA). Qualitative data were expressed as ratio and proportion and analysed using a chi-square test, while quantitative data were analysed with an unpaired t-test. A *p*-value < 0.05 was considered statistically significant.

Results

Thirty patients were studied in each group. Patients in both groups were comparable in terms of age, sex, height, weight and ASA physical status (Table 1). All patients underwent lower limb surgery under spinal anaesthesia and duration of surgery was comparable in both groups with no statically significant difference. There was no incidence of failed spinal block in any patient.

More patients in group P achieved a higher level of intrathecal block than in group S (Table 2). However, time to achieve T10 spinal level was significantly less in group S (4.467 ± 0.973 min) compared with group P (5.5 ± 1.167 min) (*p*-value 0.0004) (see Table 2). Also, patients in group S achieved maximum sensory

Table 1: Comparison of demographic variables of patients

Demographic variables	Group P (*n* = 30)	Group S (*n* = 30)	*p*-value
Age (years)	34.68 + 13.13	34.91 + 11.18	0.944
Sex (M:F)	23:7	24:6	
Weight (kg)	65.86 + 5.32	66.18 + 4.78	0.807
Height (cm)	163.02 + 8.24	161.92 + 6.458	0.571
ASA Status (I/II)	18/12	19/11	
Duration of surgery (minutes)	56.92 + 6.581	58.21 + 5.373	0.409

Table 2: Comparison of sensory and motor characteristics of spinal anaesthesia

Factor	Group P (*n* = 30)	Group S (*n* = 30)	*p*-value
Maximum sensory level achieved T4:T6:T8:T10	3:7:16:4	1:6:14:9	
Time to reach T10 sensory level (minutes)	5.5 + 1.167	4.467 + 0.973	0.0004
Time to reach maximum sensory level (minutes)	11.17 + 1.56	10.37 + 1.474	0.0454
Time for two-segment regression of sensory level (minutes)	119 + 17.291	131 + 14.937	0.0056
Time to achieve Modified Bromage III (minutes)	7.5 + 1.333	6.1 + 1.296	0.0001
Time of regression of motor block to Modified Bromage I (minutes)	129.67 + 18.473	145 + 19.783	0.0030
Total no. of doses of injection of fentanyl used (in first 6 hours)	14	11	

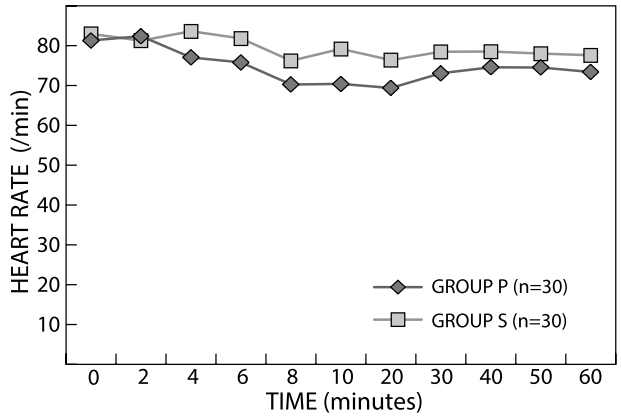

Figure 1: Comparison of mean heart rate in the two groups.

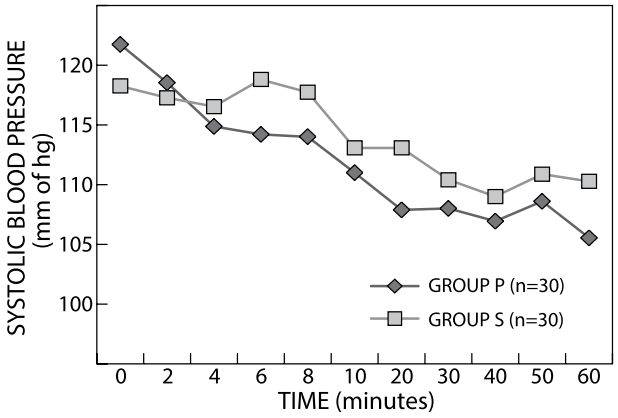

Figure 2: Comparison of systolic blood pressure in the two groups.

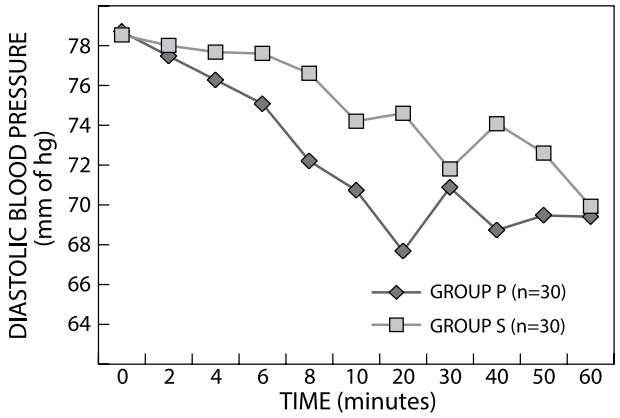

Figure 3: Comparison of diastolic blood pressure in the two groups.

block earlier than those in group P (10.37 ± 1.474 min vs. 11.17 ± 1.56 min, *p*-value 0.0454). Time for two-segment regression of sensory block was significantly longer in group S (131 ± 14.937 min) than group P (119 ± 17.291 min) (*p*-value 0.0056). Similarly, patients in group S achieved Modified Bromage III earlier (6.1 ± 1.296 min) than group P (7.5 ± 1.333 min), *p*-value 0.0001 (see Table 2). Time to regression of motor block to Modified Bromage I was also significantly more in group S (145 ± 19.783 min) than in group P (129.67 ± 18.473).

Haemodynamically, there was no significant difference in the baseline heart rate and blood pressure between two groups (Tables 4, 5 & 6). After spinal injection, though heart rate and blood pressure (both systolic and diastolic) decreased in both groups, the extent of fall (Figures 1, 2 & 3) was more in group S as compared with group P.

Postoperatively, patients in group S required less rescue analgesic than group P (11 doses of injection of fentanyl during the first 6 hours vs. 14 doses) (see Table 2). The incidence of adverse effects was also considerably less in group S compared with group P (Table 3). In group S only 2 patients reported nausea/vomiting, 1 had bradycardia (heart rate < 60/minute) and 2 patients had hypotension (systolic blood pressure < 90 mm hg or 20% below preoperative level) and none reported shivering. In group P, 3 patients reported nausea/vomiting, 5 had bradycardia and 4 had hypotension and one patient reported shivering (see Table 3).

Discussion

Dexmedetomidine is a highly selective alpha-2 adrenoreceptor agonist that acts as a central sympatholytic, blocking the release of noradrenaline by acting on presynaptic terminals. It has been found to be useful in various aspects of anaesthesia and critical care due to its sympatholytic, analgesic and sedative properties.[5–7] It is also emerging as an effective adjuvant with local anaesthetics for both regional[8] and spinal anaesthesia.

Various studies have been done to assess the effect of adding dexmedetomidine to intrathecal local anesthetic.[9–11] Dexmedetomidine has been found to increase the duration of analgesia with minimal side effects. Though the mechanism of this effect is not clear, it is proposed to act by binding to presynaptic C fibres, thus depressing the release of neurotransmitters, and by hyperpolarisation of postsynaptic dorsal horn neurons.[9, 10] It is also shown to reduce the incidence of shivering in the postoperative period and the post-anaesthetic analgesic requirement. Similarly, studies have been done to determine the optimal intrathecal dose of dexmeditomidine.[12–14] These studies have shown that there is a dose-dependent potentiation of effect with dexmeditomidine without any increase in incidence of side effects and an intrathecal dose of 10 mcg improves the onset of block, prolongs duration and thus reduces postoperative analgesic requirement.

However, adding an adjuvant to hyperbaric local anaesthetic might alter its density and thus may influence its spread in the intrathecal space. Various studies have been done in the past to determine the density of cerebrospinal fluid.[15,16] It was found to be 1.00059 ± 0.00020 in men and non-pregnant females.[16] The effect of adding adjuvants to intrathecal local anaesthetics was studied by Imbelloni et al.,[17] who found that addition of adjuvants may alter density of the solution at 37°C, yet the resultant solution remained hyperbaric.

Table 3: Comparison of adverse side effects noted in the two groups

Adverse side effect	Group P (*n* = 30)	Group S (*n* = 30)
Nausea/Vomiting	03	02
Bradycardia	05	01
Hypotension	04	02
Shivering	01	00

Table 4: Comparison of heart rate in the two groups

Time (mins)	Group P (*n* = 30)	Group S (*n* = 30)	*p*-value
0	81.3 + 11.32	82.97 + 10.43	0.556
2	82.37 + 11.86	81.27 + 10.04	0.699
4	77.06 + 12.55	83.6 + 10.76	0.0345
6	75.8 + 9.21	81.8 + 11.16	0.0268
8	70.27 + 9.303	76.2 + 11.83	0.0350
10	70.4 + 11.21	79.2 + 12.49	0.0057
20	69.4 + 7.85	76.4 + 10.78	0.0056
30	73.06 + 8.08	78.47 + 10.77	0.0321
40	74.6 + 8.05	78.53 + 9.88	0.0964
50	74.53 + 7.50	78 + 9.31	0.1176
60	73.4 + 5.36	77.6 + 8.39	0.0245

Table 5: Comparison of systolic blood pressure in the two groups

Time (mins)	Group P (*n* = 30)	Group S (*n* = 30)	*p*-value
0	121.73 + 12.77	118.26 + 11.67	0.2771
2	118.53 + 9.54	117.27 + 9.21	0.6028
4	114.87 + 7.14	116.53 + 9.38	0.4418
6	114.2 + 9.22	118.8 + 11.24	0.0886
8	114.8 + 7.69	117.73 + 12.02	0.265
10	111 + 7.75	113.07 + 9.724	0.3664
20	107.88 + 8.376	113.07 + 8.97	0.0131
30	108 + 8.069	110.4 + 9.792	0.3023
40	106.93 + 7.55	109 + 8.63	0.3276
50	108.6 + 7.069	110.87 + 11.69	0.3673
60	105.53 + 7.943	110.27 + 8.43	0.0291

Table 6: Comparison of diastolic blood pressure in the two groups

Time (mins)	Group P (*n* = 30)	Group S (*n* = 30)	*p*-value
0	78.7 + 9.77	78.53 + 10.22	0.948
2	77.47 + 10.22	78 + 9.307	0.833
4	76.27 + 9.08	77.67 + 9.81	0.568
6	75.07 + 7.216	77.6 + 8.394	0.215
8	72.2 + 8.7	76.6 + 8.601	0.0536
10	70.73 + 9.34	74.2 + 8.49	0.138
20	67.67 + 6.99	74.6 + 8.156	0.0008
30	70.87 + 8.45	71.8 + 8.98	0.679
40	68.73 + 7.99	74.07 + 10.64	0.032
50	69.47 + 8.303	72.6 + 9.16	0.1704
60	69.4 + 7.89	69.93 + 6.89	0.7816

Similarly a study by Desai et al.[18] showed that mixing intrathecal opioids with hyperbaric bupivacaine for intrathecal administration might result in higher opioid requirement in the postoperative period. They postulated that both hyperbaric bupivacaine and opioids (morphine and fentanyl) could produce maximum effect at their original densities and that mixing them alters their densities, affecting spread in the CSF and thus reducing the duration of analgesia. Therefore sequential administration helps to maintain the physical properties of both drugs, resulting in optimal effect.

In this study we compared the effect of adding dexmedetomidine to hyperbaric bupivacaine for intrathecal block as a premixed preparation and when both these drugs are used sequentially in separate syringes. We found that patients in group S achieved both sensory and motor block earlier than those in group P. Though there was no statistically significant difference in the maximum sensory level achieved in both groups, patients in group P tended to achieve a higher level of sensory block. Also, time for two-segment regression of sensory blockage and for motor blockage to regress to Modified Bromage I was significantly greater in group S as compared with group P.

Though in both groups the patients remained calm and cooperative, clinically significant sedation was not seen in any patient. Many studies[8–10] have shown that dexmeditomidine, when used as an intrathecal adjuvant, decreases postoperative analgesic requirement. This analgesic sparing effect was more pronounced in group S as compared with group P as requirement for rescue analgesic was significantly less in group S during the first six hours postoperatively.

Adding dexmeditomidine to spinal local anaesthetic has been shown to cause bradycardia and hypotension due to the sympatholytic effect of alpha 2 adrenoreceptor agonists.[19] In a study Al-Mustafa et al. showed that addition of dexmeditomidine to bupivacaine leads to a dose-dependent yet insignificant decrease in mean arterial pressure.[1] No significant hypotension or bradycardia was noted in our study. The reason for this may be the lower level of spinal block achieved for this study and small dose of intrathecal dexmeditomidine used. Similar findings were reported by Mahendru et al.[20] who showed alpha 2 adrenoreceptor agonists did not have much effect as near maximal sympatholysis was already achieved by local anaesthetics.

Though this study improves our understanding of using dexmedetomidine as an intrathecal adjuvant, it had certain limitations. First, the patients included in this study were all healthy individuals with no significant comorbidities. Thus the effect of intrathecal dexmeditomidine on patients with significant cardiovascular problems remains to be studied. Second, only patients undergoing elective lower limb surgery of less than one-hour duration were considered for this study. Therefore the amount of intrathecal block required for surgery was never high enough to produce clinically significant bradycardia or hypotension. So, the relative potentiation of this side effect by dexmedetomidine given sequentially and in premixed form remains to be seen. Hence further studies are required with a higher number of patients, and those with cardiovascular compromise, or undergoing more complex lower limb or lower abdominal procedures, to establish the benefits of one technique over another.

Conclusion

In conclusion, dexmeditomidine given sequentially in a separate syringe as adjuvant to intrathecal hyperbaric bupivacaine can result in faster onset of both sensory and motor block and prolongs the duration of spinal anaesthesia, minimises clinically significant side effects and reduces the postoperative analgesic requirement as compared with when used in premixed form in the same syringe in patients undergoing elective lower limb surgery.

Notes

(1) Mixing adjuvant drugs with hyperbaric local anaesthetic in the same syringe may alter the density of local anaesthetic, influencing spread of the drug in the cerebrospinal fluid.

(2) Administering adjuvants sequentially in separate syringes may minimise the changes in densities and pH preventing any alteration in CSF spread.

Conflict of interest – None declared.

References

1. Greene NM. Distribution of local anaesthetic solutions within the subarachnoid space. Anaesth Analg. 1985;64:715–30.
2. Sachan P, Kumar N, Sharma JP. Efficacy of premixed versus sequential administration of clonidine as an adjuvant to hyperbaric bupivacaine intrathecally in cesarean section. Anesth Essays Res. 2014;8:20–5.
3. Al-Mustafa MM, Abu-Halaweh SA, Aloweidi AS, et al. Effect of dexmedetomidine added to spinal bupivacaine for urological procedure. Saudi Med J. 2009;30:365–70.
4. Kanazi GE, Aouad MT, Jabbour-Khoury SI, et al. Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. Acta Anesthesiol Scand. 2006;50:222–7.
5. Venn RM, Bradshaw CJ, Spencer R, et al. Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. Anaesthesia. 1999;54:1136–42.
6. Jaakola ML, Salonen M, Lehtinen R, et al. The analgesic action of dexmedetomidine—a novel α2-adrenoceptor agonist—in healthy volunteers. Pain. 1991; 46:281–5.
7. Murthy TV, Singh R. Alpha 2 adrenoceptor agonist-dexmedetomidine role in anaesthesia and intensive care: a clinical review. J Anaesth Clin Pharmacol. 2009;25: 267–72.
8. Abdallah FW, Brull R. Facilitatory effects of perineural dexmedetomidine on neuraxial and peripheral nerve block: a systematic review and meta-analysis. Br J Anaesth. 2013;110:915–25.
9. Al Ghanem SM, Massad IM, Al-Mustafa MM, et al. Effect of adding dexmedetomidine versus fentanyl to intrathecal bupivacaine on spinal block characteristics in gynecological procedures: a double blind controlled study. Am J Appl Sci. 2009;6:882–7.
10. Kanazi GE, Aouad MT, Jabbour-Khoury SI, et al. Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. Acta Anaesthesiol Scand. 2006;50:222–7.
11. Abdelhamid SA, El-lakany MH. Intrathecal dexmedetomidine: useful or not? J Anesth Clin Res. 2013;4:351. doi: 10.4172/2155-6148.1000351
12. Hala EA, Eid MD, Mohamed A, et al. Dose-related prolongation of hyperbaric bupivacaine spinal anesthesia by dexmedetomidine. Ain Shams J Anesthesiol. 2011;4:83–95.
13. Singh AK, Singh Y, Jain G, et al. Comparison of two different doses of intrathecal dexmedetomidine as adjuvant with isobaric ropivacaine in lower abdominal surgery. Anesth Essays Res. 2015;9:343–7.
14. Das A, Halder S, Chattopadhyay S, et al. Effect of two different doses of dexmedetomidine as adjuvant in bupivacaine induced subarachnoid block for elective abdominal hysterectomy operations: a prospective, double-blind, randomized controlled study. Oman Med J. 2015 Jul;30(4):257–63. doi: 10.5001/omj.2015.52
15. Levin E, Muravchick S, Gold MI. Density of normal human cerebrospinal fluid and tetracaine solutions. Anesth Analg. 1981 Nov;60(11):814–7.
16. Lui ACP, Polis TZ, Cicutti NJ. Densities of cerebrospinal fluid and spinal anaesthetic solutions in surgical patients at body temperature. Can J Anaesth. 1998;45(4):297–303.
17. Imbelloni LE, Moreira AD, Gaspar FC, et al. Assessment of the densities of local anaesthetics and their combination with adjuvants. An experimental study. Rev Bras Anaesthesiol. 2009;59:154–65.
18. Desai S, Lim Y, Tan CH, et al. A randomised controlled trial of hyperbaric bupivacaine with opioids, injected as either a mixture or sequentially, for spinal anaesthesia for caesarean section. Anaesth Intensive Care. 2010;38:280–4.
19. Eisenach JC, De Kock Marc, Klimscha W. α2-adrenergic agonists for regional anesthesia. Anesthesiology. 1996;85:655–74.
20. Mahendru V, Tewari A, Katyal S, et al. A comparison of intrathecal dexmedetomidine, clonidine, and fentanyl as adjuvants to hyperbaric bupivacaine for lower limb surgery: a double blind controlled study. J Anaesthesiol Clin Pharmacol. 2013;29:496–502.

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