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Effects of intrathecal dexmedetomidine coadministered with hyperbaric bupivacaine in the lower abdominal surgery: Results of a double-blind, randomized, and controlled trial between two different doses

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ABSTRACT

Background: Although various adjuvants have been added to local anesthetic agents to potentiate its effect, dexmedetomidine is a relatively new drug with only a fewer studies. **Aims and Objectives:** The present study has been conducted to compare the efficacy of intrathecal hyperbaric bupivacaine alone with dexmedetomidine of two different doses as adjuvants in spinal anesthesia for the lower abdominal surgery. **Materials and Methods:** This was a double-blinded, randomized, and controlled trial. Total 120 patients of American Society of Anesthesiologists physical status I and II, 70 male and 50 female, aged between 20 and 60 years, were randomized into three groups receiving 15 mg 0.5% hyperbaric bupivacaine with normal saline, 4 μg (microgram) dexmedetomidine, and 2 μg dexmedetomidine, respectively, administered intrathecally. **Results:** There was significant difference among all three groups with regard to the onset of sensory block and time to reach the highest level of sensory block. Time to reach T10 dermatome, time to reach Bromage 3 motor block, the mean regression time to S_1 dermatome level, the mean regression time to reach Bromage 0, and time to first requirement of rescue analgesia – all these variables showed significance when 4 μg dexmedetomidine additive group was compared with 2 μg dexmedetomidine additive group and bupivacaine alone group. **Conclusion:** In our double-blinded, randomized, and controlled trial, 4 μg intrathecal dexmedetomidine coadministered with 0.5% hyperbaric bupivacaine showed superior efficacy. Further, larger trials are needed to confirm our findings.

Key words: Dexmedetomidine; Bupivacaine; Intrathecal route; Lower abdominal surgery

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INTRODUCTION

Lower abdominal surgeries may be performed under general or regional anesthesia, but regional anesthesia is the preferred mode in most of cases as it avoids the risks and complications associated with general anesthesia. Regional anesthesia techniques may be central or peripheral. The central techniques include neuraxial blockade (e.g., spinal and epidural anesthesia) whereas the peripheral techniques may be plexus blocks (e.g., celiac plexus blocks which is mainly used for relieving chronic abdominal pain in pancreatic cancer patients rather than surgery) and single nerve blocks (e.g., obturator or popliteal nerve blocks). Regional anesthesia allows patients to remain awake during surgical procedures resulting in reduced side-effects as well as analgesic effects extending into immediate post-

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operative period. Spinal anesthesia is the most liked regional anesthesia technique today with several advantages such as rapid onset, superior blockade, less failure rates, and cost-effectiveness.

In recent years, use of intrathecal adjuvants during spinal anesthesia has gained popularity with the aim of prolonging the duration of block, increasing the density of block as well as increasing the success rate and patient satisfaction. Adequate pain management is essential to facilitate rehabilitation and accelerate functional recovery, enabling patients to return to their normal activity more quickly. Requirement of an effective and adequate intraoperative and post-operative analgesia along with better recovery profile has led to the consideration of adding adjuvants through intrathecal routes.

Dexmedetomidine is a potent alpha2-adrenoceptor (α2) agonist with 8 times higher affinity for the α2 than clonidine producing dose-dependent sedation, anxiolysis, and analgesia without respiratory depression.[1] α2-agonists are known to reduce anesthetic requirements and afford hemodynamic stability during intraoperative period.[2] Administration of dexmedetomidine through an intrathecal or epidural route provides post-operative analgesia without heavy sedation. This effect is due to the sparing of supraspinal central nervous system sites from excessive drug exposure resulting in robust analgesia without respiratory depression.[3] Dexmedetomidine produces a predictable hemodynamic decline (dose-dependent decrease in arterial blood pressure and heart rate) in post-surgical patients coinciding with reductions in plasma catecholamines.[4] Kanazi et al., found that 3 μg (microgram) dexmedetomidine and 30 μg clonidine are equipotent intrathecally when added to 0.5% hyperbaric bupivacaine in patients undergoing urology procedures.[5] They also found that dexmedetomidine and clonidine produce significantly rapid onset and longer duration of sensory and motor blockade than bupivacaine alone without serious side effects.[5]

Bupivacaine is the most widely used local anesthetic agent for spinal anesthesia providing adequate anesthesia and analgesia for intermediate to long duration surgeries.[6] Hyperbaric bupivacaine is more predictable for sensory block level and more effective for surgical procedures with the lower abdominal approach.[7] Till date, the literature search reveals only a few studies comparing anesthetic potency and hemodynamic effects of intrathecally administered bupivacaine alone versus bupivacaine with dexmedetomidine as adjuvants in India.

Aims and objectives

The present study was designed in a prospective, randomized, and double-blind fashion to compare the effects of intrathecal bupivacaine alone and bupivacaine with dexmedetomidine as adjunct for patients undergoing lower abdominal surgery using hyperbaric preparations. The secondary objective was to study the side effects associated with these drugs.

MATERIALS AND METHODS

After approval from the Institutional Ethical Committee and obtaining written informed consent of the patients, the study was conducted in Nilratan Sircar Medical College and Hospital, a tertiary care medical college hospital in Eastern India. Total 120 patients of American Society of Anesthesiologists (ASA) physical status I and II of both sexes, aged between 20 and 60 years and scheduled for elective lower abdominal and lower extremity surgeries under spinal anesthesia, were enrolled in this study. Power calculations suggested that a minimum of 16 subjects per group were required to detect 30 min difference in mean duration of sensory anesthesia between groups (taking Type I or α error of 5%, Type II or β error of 20% and inter group standard deviation [SD] of 30 min, as shown in a previous study by Malinovsky et al.).[8] To be on a safer side, 40 patients were included in each group (n=40).

Patients undergoing emergency surgery; having severe systematic disorders such as Stage-2 hypertension, diabetes, musculoskeletal, and neurological disease; those with history of drug and alcohol abuse; having previous abdominal surgery; allergic to amide local anesthetics, and those having body weight more than 30% of the ideal weight were excluded from the study. Patients having contraindication to spinal anesthesia and those with inadequate block (defined as sensory block $<T_8$ segment) and failure of spinal anesthesia (need for intraoperative analgesia within first 30 min) were also excluded from the study.

Patients were admitted 1 day before the scheduled surgery and were examined and interviewed. Whole procedure was explained to the patients. On arrival in the operation theater, monitors were attached and baseline parameters such as heart rate (HR), non-invasive blood pressure (NIBP), oxygen saturation (SpO_2), electrocardiogram (ECG), and temperature were recorded.

Immediately before anesthesia, patients were randomly divided into three equal groups (n=40) using sealed envelopes, as chosen by the patients, containing computer generated random numbers.

The study groups were:-

i. Group A: Received 0.5% hyperbaric bupivacaine 15 mg (i.e., 3 ml) with normal saline (NS) [Control group]

ii. Group B: Received 0.5% hyperbaric bupivacaine 15 mg (i.e., 3 ml) with 4 μg dexmedetomidine (Dex)
iii. Group C: Received 0.5% hyperbaric bupivacaine 15 mg (i.e., 3 ml) with 2 μg dexmedetomidine.

Insulin syringes were used to add pre-determined quantity of inj. dexmedetomidine and total volume of the study drugs was adjusted to 3.5 ml after diluting with preservative free normal saline.

All patients were preloaded with 10 ml/Kg of Ringer's Lactate infusion and no pre-medications were used. Lumbar puncture was performed in sitting position at L3-L4 level through a midline approach using a 25-gauge Quincke spinal needle. After correct needle placement was identified (by free flow of cerebrospinal fluid) and confirmed (by aspiration), 3.5 ml of the study drug was injected at a rate of 0.2 ml/s.[9] Drugs were drawn in similar syringes by a person, not involved in the study, as per random number allocated to the particular patient. Patients and the anesthesiologist administering the drugs were thus blinded to the study preparation.

Vital signs such as HR, NIBP, SpO_2, ECG, and temperature were recorded intraoperatively at 5 min interval for initial 20 min, thereafter at 10 min interval up to 1 h, then at 30 min interval until the end of surgery and in post-operative period, vital signs were recorded at every 30 min interval until the administration of rescue analgesia (inj. diclofenac aqueous 75 mg intramuscularly).

The level of sensory block was evaluated by pinprick method using 20-gauge hypodermic needle. The test was performed every 5 min till loss of discrimination to pin prick for the first 15 min and thereafter every 10 min after operation until full recovery. Bilaterally, T_{12}, T_{10}, T_8, $T_{6,}$ or higher (T_4) dermatomes were checked by pin prick using forehead as baseline point for normal sensation.

Motor blockade was assessed using a modified Bromage scale (0= no motor block; 1= hip blocked; 2 = hip and knee blocked; and 3 = hip, knee, and ankle blocked). The time to reach maximum Bromage score (from spinal injection until Bromage 3 score) was taken as the onset time of motor block and was recorded every 5 min after injection of study drug for initial 15 min. The time to reach T10 dermatome sensory block, peak sensory level, and Bromage 3 motor block were recorded before surgery. The regression time for sensory and motor block was recorded in post-anesthesia care unit (PACU). All durations were calculated considering the time of spinal injection as time zero. Patients were discharged from PACU after sensory regression to S1 dermatome and motor block regression to Bromage 0. Other criteria for post-anesthesia discharge of patients to the ward were stable hemodynamics, absence of pain, vomiting, or obvious bleeding. Assessment of pain postoperatively in PACU was done using visual analog pain scale between 0 and 10 (0 = no pain and 10 = most severe pain). Duration of analgesia was taken as the time from intrathecal injection to the time when patient first complained of pain and required supplemental analgesics. Intraoperative nausea, vomiting, pruritus, and sedation were also recorded.

Hypotension was defined as arterial pressure lower than 25% of baseline and treated with injection phenylephrine intravenously in 100 μg increments. Bradycardia was defined as heart rate <50/min and treated with injection atropine intravenously in 0.6 mg increments. Hypoxia was defined as a decrease in SpO_2 to <90% and treated with supplemental oxygen through a Hudson type polymask keeping fraction of inspired oxygen at 0.3 with a flow of 4 l min.

Statistical analysis

Data were expressed as mean and SD (mean ± SD). Normality of the distribution in each group was checked by the Shapiro–Wilk normality test. The homogeneity in three groups of mean and SD was analyzed using SPSS software version 18.0 (SPSS Inc., Chicago, Illinois, USA). Intergroup comparisons were done using one-way analysis of variance (ANOVA). *Post hoc* Tukey test was followed where ANOVA values were significant. Categorical data were compared using Chi-square test. $P<0.05$ was considered as statistically "significant" ($P<0.05$) (Figure 1).

RESULTS

There were no significant differences between the three groups with regard to demographic data such as age, sex, body weight, and ASA physical status (Table 1).

Comparison of three groups with regard to the block variables is shown in Table 2. There was significant difference among all three groups with regard to the onset of sensory block and time to reach the highest level of sensory block. Time to reach T10 dermatome, time to reach Bromage 3 motor block, the mean regression time to S_1 dermatome level, the mean regression time to reach Bromage 0, and time to first requirement of rescue analgesia – all these variables showed significance between Group A and Group B and between Group B and Group C, but not between Group A and Group C. Intraoperative mean heart rates, systolic blood pressure, and diastolic blood pressure (DBP) among the three groups across various time periods were not significant (Figures 2-4).

Intraoperative mean Ramsay sedation scores were significant among all the three groups (Table 3). However, they were

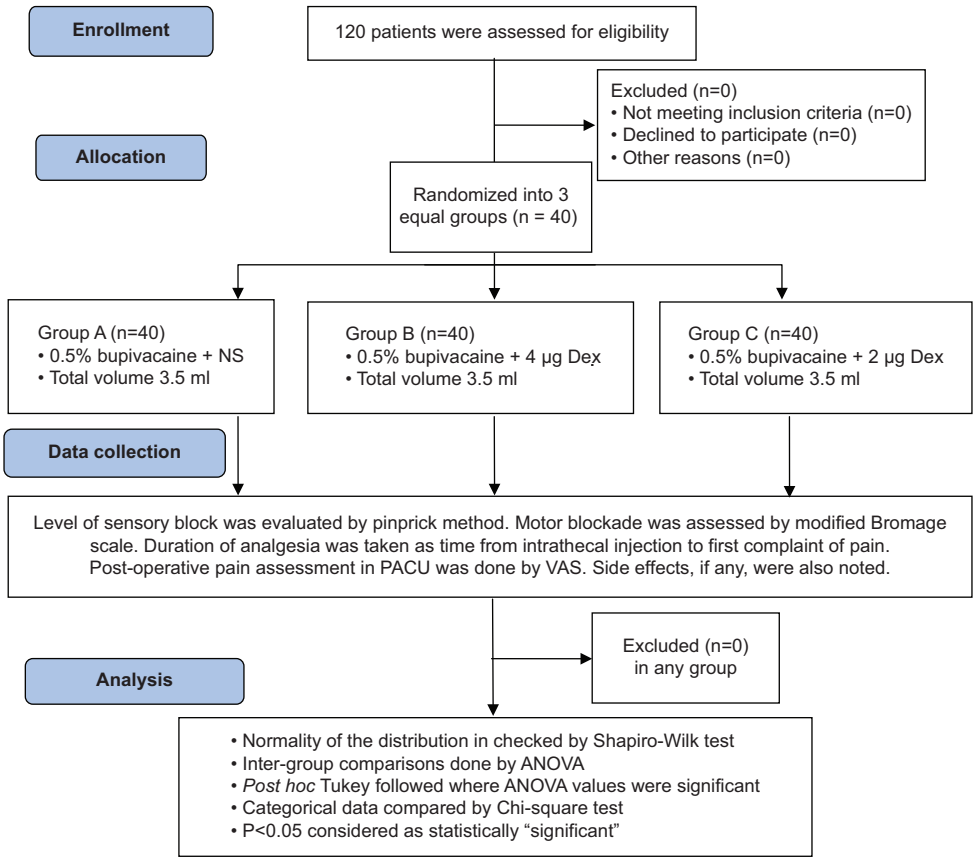

Figure 1: The CONSORT flow diagram of the study design

Table 1: Demographic profile (Mean±SD)

Demographic profile	Group A	Group B	Group C	P-value
Age (years)	35.18±10.853	43.10±8.918	43.25±10.347	0.65
Sex (M:F)	22:18	25:15	23:17	0.72
Weight (kg)	52.38±7.788	62.55±9.687	63.10±10.275	0.87
ASA-PS (I:II)	23:17	28:12	24:16	0.481

ASA-PS: American Society of Anesthesiologists physical status

Table 2: Comparison of three groups with regard to block variables (Mean±SD)

Block variables (min)	Group A	Group B	Group C	P-value
Time to reach T10	4.688±0.914	2.253±0.69*	4.72±0.54†	<0.001
Time to peak sensory	9.683±1.06	5.34±0.69*	8.45±0.51*†	<0.001
Time to Bromage 3	6.878±1.96	2.83±0.697*	6.39±0.54†	<0.001
Regression to S1	202.066±9.36	227.76±7.29*	205.38±6.79†	<0.001
Regression to Bromage 0	185.22±19.47	196.96±5.99*	185.15±8.09†	<0.001
Time to rescue analgesia	224.037±14.64	253.20±9.70*	218.47±5.91†	<0.001

Symbols represent a significant difference (P<0.05) compared with the control group A (*) or between group B and C (†), as determined using a one-way ANOVA with a *post hoc* Tukey test

comparable with regard to side effects profile, namely, nausea/vomiting, hypotension, and bradycardia (Table 4).

DISCUSSION

The lower abdominal surgeries are often performed under spinal anesthesia. The advantages of having an awake patient, minimal cost, and rapid patient turnover have made this method popular worldwide. The main disadvantages of this technique are complaint of intraoperative visceral pain, limited duration of action, and lack of long lasting post-operative analgesia. Hence, additives are often used to prolong the duration and density of subarachnoid block. Local anesthetic agents with dexmedetomidine demonstrate significant synergy and provide excellent analgesia with the lower drug requirements.

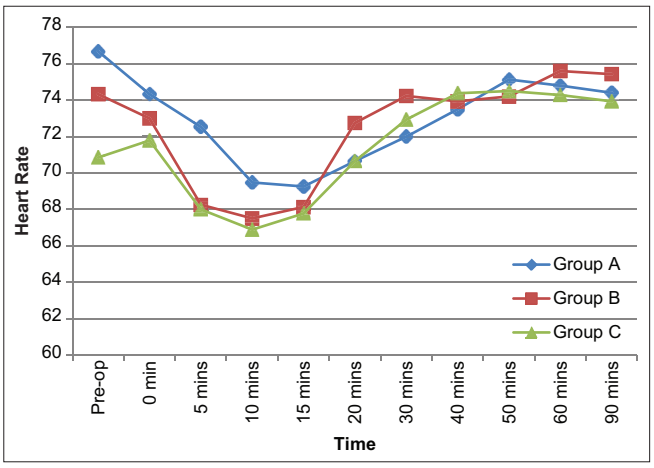

Figure 2: Comparison of intraoperative mean heart rates (beats/min)

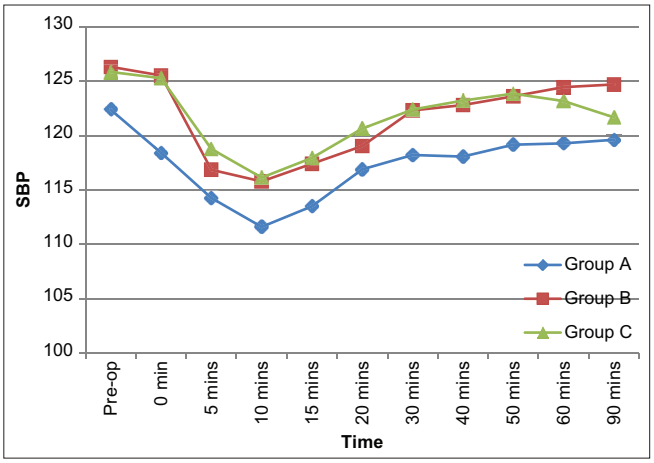

Figure 3: Comparison of intraoperative mean systolic blood pressure (mm Hg)

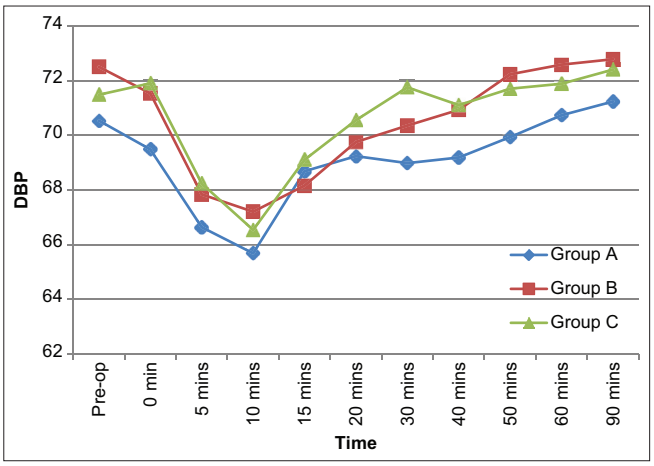

Figure 4: Comparison of intraoperative mean diastolic blood pressure (mm Hg)

Dexmedetomidine is a highly selective alpha-2 adrenoreceptor agonist approved as intravenous sedative and coanalgesic drug. Intrathecal dexmedetomidine coadministered with bupivacaine prolongs the sensory block by depressing the release of C-fibers transmitters and by hyperpolarization of post-synaptic dorsal horn neurons. Motor block prolongation by α-2 agonists may result from binding these agonists to motor neurons in the dorsal horn of the spinal cord. Intrathecal α-2 agonists have also been found to have antinociceptive action for both somatic and visceral pain.[10]

Kanazi et al., found that 3 μg dexmedetomidine when coadministered with hyperbaric bupivacaine intrathecally produce significant faster and prolonged sensory and motor blockade than bupivacaine alone without serious adverse effects.[5] Based on these findings, in the present study, we have used 4 μg and 2 μg (two different doses) of dexmedetomidine for supplementation of spinal bupivacaine (15 mg) and compared its effects with intrathecal bupivacaine (15 mg) alone, regarding subarachnoid block characteristics, intraoperative hemodynamic response, analgesia, sedation, and adverse effects.

First, we compared spinal block characteristics and noticed a significant difference among all three groups in time to reach the highest level of sensory block. Time to reach T10 dermatome, time to reach Bromage 3 motor block, the mean regression time to S1 dermatome, the mean regression time to reach Bromage 0, and time to first requirement of rescue analgesia – all these variables showed significance between moderate dose dexmedetomidine group (Group B) and others, but control group (Group A) and low dose dexmedetomidine group (Group C) were comparable.

FA Ibrahim concluded that intrathecal 5 μg dexmedetomidine produces more prolonged sensory and motor block when added to 2 ml of 0.5% hyperbaric bupivacaine.[11] Xia et al., opined the same with intrathecal 5 μg dexmedetomidine but they used 0.75% hyperbaric bupivacaine instead of 0.5%.[12] Esmaoğlu et al., also reported that sensory and motor blocks were significantly faster and regression of sensory block to S1 and motor block to Bromage 0 was significantly longer when 3 μg dexmedetomidine were coadministered with 15 mg levobupivacaine intrathecally.[13]

Gupta et al., found significantly longer sensory and motor blockade when intrathecal 5 μg dexmedetomidine were coadministered with 12.5 mg hyperbaric bupivacaine, instead of 25 μg fentanyl.[14] Mahendru et al., also obtained similar findings.[15]

Dobrucali et al., obtained shorter onset time to sensory and motor blockade in group receiving intrathecal dexmedetomidine, but, in contrary to our study, it was not significant statistically.[16] It is possibly due to use of smaller dose of intrathecal dexmedetomidine (3 μg).

Table 3: Comparison of intraoperative mean Ramsay sedation score

	Group A	Group B	Group C	P-value
Ramsay sedation score	1.9±0.49	2.48±0.51*	1.43±0.50*†	<0.001

Symbols represent a significant difference (P<0.05) compared with the control Group A (*) or between Group B and C (†), as determined using a one-way ANOVA with a *post hoc* Tukey test

Table 4: Comparison of three groups with regard to side effects

Side effects (no. of patients)	Group A	Group B	Group C	P-value
Nausea/vomiting (present: Absent)	10: 30	7: 33	10: 30	0.324
Hypotension (present: Absent)	9: 31	12: 28	12: 28	0.449
Bradycardia (present: Absent)	13: 27	15: 25	13: 27	0.166

However, motor block duration was significantly longer and peak level of sensory block was significantly higher in dexmedetomidine group, same as our study.

Gupta et al., found reduced demand for rescue analgesia in the group receiving dexmedetomidine as adjuvant to hyperbaric bupivacaine.[14] However, in our study, this difference was significant only in moderate dose dexmedetomidine group (Group B) while low dose dexmedetomidine (Group C) and control group (Group A) were comparable in this regard. This is probably because we used smaller doses (4 μg and 2 μg only) where Gupta et al., used larger dose (5 μg) of dexmedetomidine.

No patients required additional analgesics intraoperatively. The intraoperative mean sedation score (as assessed by Ramsay sedation score) was significantly higher in moderate dose dexmedetomidine group (Group B) than other two groups. Furthermore, Group B patients spent maximum time before requirement of rescue analgesia, which was statistically significant in comparison to other groups.

Dobrucali et al., did not find statistically significant mean sedation score in dexmedetomidine group. This difference may be due to the smaller amount of bupivacaine and dexmedetomidine used in their study (11.25 mg bupivacaine and 3 μg dexmedetomidine).[16]

In this study, we found no statistically significant difference in intraoperative mean heart rate, systolic and DBP among the three groups. Similar kind of result was reported by FA Ibrahim who conducted a study to evaluate the effect of adding dexmedetomidine to intrathecal hyperbaric bupivacaine for post-operative analgesia in patients undergoing inguinal hernia repair.[11] Esmaoğlu et al., and Dobrucali et al., also obtained similar findings.[13,16]

There was no statistically significant difference with respect to the adverse effects such as nausea/vomiting, hypotension, and bradycardia among the three groups. Esmaoğlu et al., also got similar kind of results.[13]

Limitations of the study

There were several limitations of this study such as small sample size, single-center design, and selected study population (pediatric, elderly, and ASA III-IV patients were excluded from the study). Furthermore, we did not use relatively higher doses of intrathecal dexmedetomidine like 10 μg or 15 μg and did not follow-up postoperatively for a longer duration. Further large scale multicentric clinical studies with higher doses of intrathecal dexmedetomidine and longer period of post-operative follow-up can be performed to develop a more reliable and clinically efficient regime of dexmedetomidine as an additive to spinal anesthesia without any side effects.

CONCLUSION

In our double-blind, randomized, and controlled trial, 4 μg intrathecal dexmedetomidine coadministered with 0.5% hyperbaric bupivacaine showed superior efficacy when compared with placebo or smaller dose (2 μg intrathecal dexmedetomidine). We recommend routine use of 4 μg dexmedetomidine as an additive to spinal anesthesia with 0.5% hyperbaric bupivacaine. Further, larger trials with higher doses and longer follow-up are needed to confirm our findings and better delineate the clinically efficient regime of intrathecal dexmedetomidine.

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RH, MM- Plan of study; **RH, MM, KM-** Preparation of the initial draft; **KM, SM-** Contribution to the manuscript; **MM-** Statistical analysis; and **RH-** Review and final preparation of the manuscript.

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