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Effects of intrathecal dexmedetomidine versus intravenous dexmedetomidine as a pre-medication on clinical profile of bupivacaine spinal anaesthesia in Lower abdominal surgeries: A RCT

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Abstract
Dexmedetomidine is a highly selective α2-adrenoceptor agonist which produces dose-dependent sedation and analgesia without respiratory depression. It prolongs the duration of local anaesthetics by different routes of administration. This study was aimed to compare the effect of intrathecal (IT) versus intravenous (IV) dexmedetomidine on bupivacaine spinal anaesthesia in patients undergoing lower abdominal surgery. This prospective double-blinded randomized controlled study was conducted on 60 patients randomly divided equally into 2 groups. Group A (IT group) (n=30) received 3ml of 0.5% hyperbaric bupivacaine and 10µg of dexmedetomidine intrathecally and Group B (IV group) (n=30) received premedication with IV dexmedetomidine 0.5µg/kg and then 3ml of 0.5% hyperbaric bupivacaine plus 0.1ml of normal saline intrathecally. We observed that in bupivacaine spinal anaesthesia, dexmedetomidine, when administered intrathecally, has greater augmentation to sensory and motor block, more hemodynamic stability, better analgesic properties, and fewer overall side effects as compared to premedication with IV dexmedetomidine.

Keywords: Bupivacaine, dexmedetomidine, intravenous, intrathecal, lower abdominal surgery, spinal anaesthesia

1. Introduction
Spinal anaesthesia is a type of regional anaesthesia which involves injection of a local anaesthetic drug into the subarachnoid space and is commonly used for procedures involving the lower abdomen, perineum, and lower limbs. It has several advantages such as the ease of administration, low cost, small dose of local anaesthetic, rapid onset of action, dense motor block and avoidance of the potential complications related to general anaesthesia [1-3]. It produces surgical anaesthesia and analgesia with minimal physiological disturbances.
Bupivacaine 0.5% (H) is the most widely used local anaesthetic for spinal anaesthesia. Various adjuvants such as phenylephrine, epinephrine, ketamine, clonidine, magnesium sulphate, neostigmine, opioids, etc. have been tried through oral, intravenous and intrathecal route to prolong the duration of action of bupivacaine [4, 5].
Dexmedetomidine is a highly selective α2-adrenoceptor agonist (α2: α1 activity-1620:1) which produces dose-dependent sedation and analgesia without respiratory depression [6-9]. It has been reported to prolong the duration of local anaesthetics by different routes of administration [10, 11]. Various studies have shown that the use of dexmedetomidine intravenously (IV) and intrathecally (IT) has prolonged the duration of spinal anaesthesia and enhanced the post-operative analgesia [10, 12]. Kanaji *et al*. have reported that when dexmedetomidine was added to IT bupivacaine, it resulted in prolongation of the duration of spinal anaesthesia [5]. Dexmedetomidine also lengthened the duration of spinal anaesthesia when it was given intravenously before spinal anaesthesia [13] or as a loading dose followed by continuous infusion during surgery [14].
The aim of this study was to compare the effect of intrathecal (IT) versus intravenous (IV) administration of dexmedetomidine on bupivacaine spinal anaesthesia in patients undergoing lower abdominal surgery.

2. Method and Materials

2.1 Patients

After approval from the Institutional Ethical Committee and after obtaining written informed consent of patients, this prospective double-blinded randomized controlled study was conducted over a period of one year (Jan-Dec 2020) on a total of 60 patients classified as American Society of Anesthesiologists (ASA) I or II, of either sex, aged 18-60 years, and scheduled for lower abdominal surgery (duration of surgery more than 30 mins and less than 150 mins) under spinal anaesthesia. The sample size was taken as per convenience. Exclusion criteria were patients with known allergy to any of the test drugs, any contraindication to spinal anaesthesia, obese patients (body mass index >30), patient height >180 cm or <150 cm, pregnant patients, patients belonging to ASA III or IV, patients on beta-blockers, patients with any conduction abnormalities or patients with any neurological deficit.

Patients were assigned randomly to two groups on the basis of envelope technique:

1. Group A (IT group) (n=30) received 3 ml of 0.5% hyperbaric bupivacaine and 10 µg of dexmedetomidine intrathecally.
2. Group B (IV group) (n=30) received premedication with IV dexmedetomidine 0.5 µg/kg by infusion pump over 10 min as a single dose. After 5 mins, 3 ml of 0.5% hyperbaric bupivacaine and 0.1 ml of normal saline were given intrathecally.

2.2 Anaesthesia technique

Pre-anaesthetic evaluation including full assessment of history, clinical examination, and investigations was conducted preoperatively for all patients. All patients were kept nil per oral overnight. In the operating room, baseline vital signs such as blood pressure (BP), heart rate (HR), oxygen saturation by pulse oximetry (SpO_2) and respiratory rate (RR) were recorded. Patients were preloaded with Ringer's lactate solution 500ml after IV insertion of 18G IV cannula. The IV drug regimen was started according to the group to which patients were assigned.

All equipments for spinal blockade were made ready for use, and all the necessary medications were drawn up prior to positioning of patient for spinal anaesthesia, to reduce the amount of time taken to perform the block.

Under a sterile technique, spinal anaesthesia was performed with the patient in left lateral position with 25G Quincke needle in L3-L4 intervertebral space using midline approach. The time of spinal injection was considered time zero (T0). Oxygen (4 l/min) was supplied by a face mask throughout the surgical procedure. Monitoring included continuous ECG, non-invasive blood pressure, pulse oximetry and HR.

2.3 Assessment of parameters

After successful spinal anaesthesia, the vital signs were recorded at 2, 5, and every 5 min in the operation room and every 15 min in the PACU.

Sensory blockade was assessed by pin prick method in mid-axillary line from T0 to every 2 mins for the first 10 mins and then every 15 mins during surgery and post operatively [15].

The onset time, time required to reach loss of sensation at the level of T10 dermatome, time to reach highest sensory level, time for two segment regression and time required for regression of level to L1 were noted.

Motor block was assessed using the modified Bromage scale [16] from T0 to every 2 mins for the first 10 mins and then every 15 mins after surgery in PACU.

Bromage 0: The patient is able to move the hip, knee, and ankle.

Bromage 1: The patient is unable to move the hip but able to move the knee and ankle;

Bromage 2: The patient is unable to move the hip and knee but able to move the ankle; and

Bromage 3: The patient is unable to move the hip, knee, and ankle.

The time to reach Bromage 3 motor block was recorded before surgery and the regression time to Bromage 0 was recorded after surgery.

The level of sedation was evaluated every 15 mins intraoperatively and postoperatively using Ramsey level of sedation scale [17]:

1. Patient is anxious, agitated, or restless.
2. Patient is cooperative, oriented and tranquil alert.
3. Patient responds to commands.
4. Patient is asleep, but with brisk response to light glabellar tap or loud auditory stimulus,
5. Patient is asleep, with sluggish response to light glabellar tap or loud auditory stimulus.
6. Patient is asleep, with no response.

Intraoperative complications like hypotension, bradycardia, or hypoxia were noted. Hypotension was defined as more than 25% decrease in mean arterial pressure (MAP) from the baseline and was treated with fluid boluses and IV Mephentermine 6 mg bolus. Bradycardia was defined as HR <50 beats/min and treated with IV Atropine 0.6 mg. Hypoxia was defined as oxygen saturation value below 90% and was treated with O2 face mask 6 L/min.

Postoperatively, pain was assessed using visual analog scale (VAS) ranging from 0 to 10 (0 = no pain, 10 = the most severe pain) initially every hourly for 2 h, then every 2 hourly for next 8 h, then every 4 hourly till 24 h. Total duration of analgesia was defined as the time from administration of subarachnoid block until first complains of pain (VAS >4). Diclofenac sodium 75 mg intramuscularly was used as rescue analgesic. The development of any side effects including nausea, vomiting, headache, itching, shivering, respiratory depression, or cardiovascular events was noted and treated accordingly.

2.4 Statistical analysis

The data collected was tabulated and analysed using SPSS (version 21.0; SPSS Inc., Chicago, IL, USA). Results were expressed as means and SDs, or numbers and percentages. Statistical analyses were performed using Student's t-test for parametric data and Chi-square test for non-parametric data. $p< 0.05$ was considered statistically significant and $p< 0.001$ was considered as highly statistically significant.

3. Results

3.1 Demographic data

The demographic characteristics, duration of surgery, and ASA physical status were comparable in both the patient groups and were statistically insignificant (p>0.05) (Table 1).

Table 1: Demographic data

Parameters	Group A (IT group) (n=30)	Group B (IV group) (n=30)	p-value
Age (years)	47.06±8.95	50.33±6.83	0.11
Gender (male/female)	18/12	15/15	0.43
Weight (kg)	53.00±8.46	53.40±7.23	0.85
Height (cm)	154.10±13.77	152.83±13.83	0.72
ASA status (I/II)	21/9	15/15	0.11
Duration of surgery (mins)	96.33±15.08	94.17±18.53	0.62

3.2 Vital signs: Preoperative heart rate, systolic blood pressure, and mean blood pressure in both groups were similar (*P*> 0.05). Blood pressure values during the first 90 min (Fig. 2) and heart rate values during the first 60 min were statistically significantly lower in the IV group than in the IT group (*P*< 0.05). At all other times, there were no significant differences between the MAP and HR values of the two groups. (p>0.05) (Fig 1 and 2). SpO_2 levels were comparable between both groups throughout the study (*P*> 0.05).

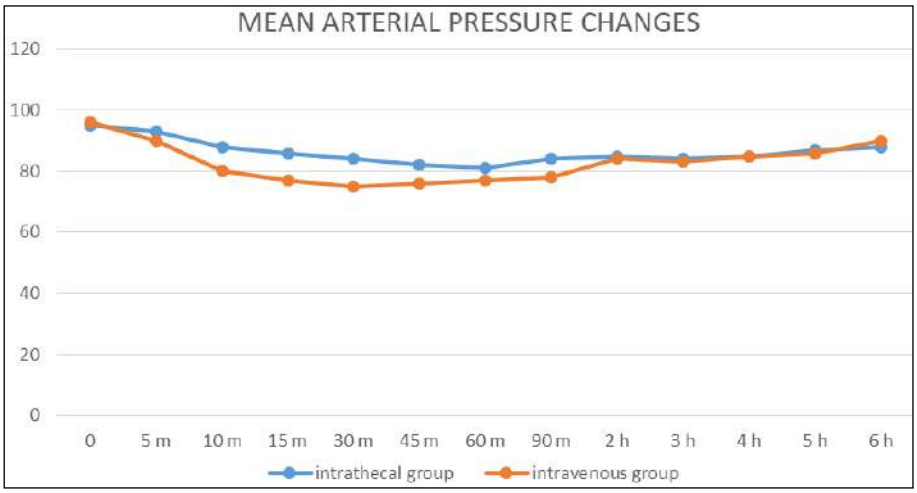

Fig 1: Mean arterial pressure changes between the two groups (mmHg)

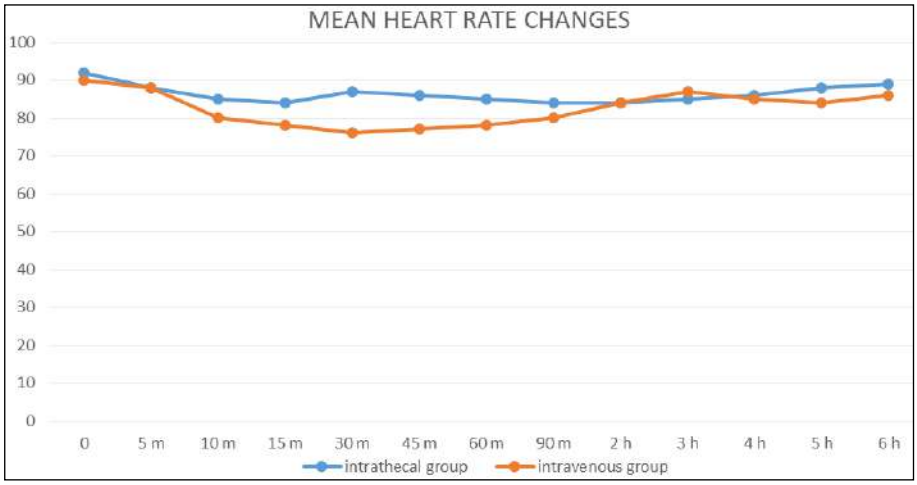

Fig 2: Mean heart rate (HR) changes between groups (beats/min)

3.3 Spinal block characteristics

Group A (IT group) had a statistically significant earlier sensory and motor onset. The time to reach T10 sensory block, time from injection to highest sensory level and time to reach Bromage 3 motor block were significantly shorter in the IT group (*p*< 0.001). Whereas, the two segment regression time, regression time to L1 dermatome, and regression time to Bromage 0 was prolonged in the IT group (*p*< 0.001) (Table 2).

Table 2: Spinal block characteristics

Parameters	Group A (IT group) (n=30)	Group B (IV group) (n=30)	p-value
Onset of sensory blockade (in Mins)	3.53 ± 1.20	5.60 ± 1.22	< 0.0000001
Time to reach T10 sensory level (in Mins)	4.23 ± 0.40	6.10 ± 0.43	< 0.0000001
Time to attain highest sensory level (in Mins)	18.38 ± 0.52	21.97 ± 0.25	< 0.0000001
Time for two-segment regression (in Mins)	124.03 ± 11.26	97.60 ± 15.63	< 0.0000001
Regression time to L1 (in Mins)	288.33 ± 16.91	204.21 ± 14.09	< 0.0000001
Onset of motor blockade (in Mins)	4.22 ± 1.50	6.40 ± 1.32	0.000000149
Time to reach mod. Bromage 3 (in Mins)	7.07 ± 1.36	8.60 ± 1.50	0.0001
Regression time to mod. Bromage 0 (in Mins)	298.66 ± 23.02	203.10 ± 20.60	< 0.0000001

3.4 Analgesia, sedation, and adverse effects

Compared with group B (IV group), group A (IT group)

showed a significantly longer time to the use of rescue analgesia ($p< 0.001$). Also, the intensity of pain was significantly less in group A as compared to group B ($p< 0.001$). The sedation score was higher in the IV group than the IT group, but this was statistically insignificant (p>0.05). The IT group had fewer overall side effects as compared with the IV group, which was statistically not significant (p>0.05) (Table 3).

Table 3: Analgesia, sedation and adverse effects

Parameters	Group A (IT group) (n=30)	Group B (IV group) (n=30)	P-value
Time of rescue analgesia (min)	401.47±45.82	228.67±34.10	<0.001
Sedation score	2.3±0.42	2.6±0.74	0.283
VAS score over 8 h	0.86±0.49	1.55±0.82	<0.001
Hypotension	2 (6.6)	5 (16.5)	0.0285
Bradycardia	5 (16.7)	7 (23.3)	0.519
Shivering	0	0	-
Respiratory depression	0	0	-
Nausea and vomiting	0	0	-

4. Discussion

Many recent studies have suggested dexmedetomidine to be a suitable adjuvant to spinal anaesthesia due to its more selective α-2A receptor action [10-12]. At the spinal level, dexmedetomidine acts on neurons of the superficial dorsal horn, especially lamina II [18]. It also acts at the locus ceruleus to produce sedation and analgesia [18]. This supra spinal action is likely to prolong the spinal anaesthesia after intravenous dexmedetomidine. Hence, in our study, we have compared the effect of dexmedetomidine given by two different routes: IT and IV as pre-medication on bupivacaine spinal anesthesia. We observed that administration of dexmedetomidine intrathecally enhanced the anesthetic properties of bupivacaine more as compared to premedication with intravenous dexmedetomidine.

Several studies have reported that administration of dexmedetomidine intravenously [12, 19, 20] or intrathecally [5, 21] has fastened the onset of sensory block and prolonged the duration of sensory and motor block.

In our study, the IT group had a statistically significant earlier sensory and motor blockade onset. The time to reach T10 sensory block, time from injection to highest sensory level and time to reach Bromage 3 motor block were significantly shorter whereas, the two segment regression time, regression time to L1 dermatome, and regression time to Bromage 0 was significantly prolonged in the IT group (Table 2). These findings are in consistency with the results of previous studies [22, 23].

It has been reported that dexmedetomidine as an adjuvant to local anesthetics prolongs the duration of both motor and sensory blockade produced by single injection neuraxial and peripheral nerve blockade [24, 25]. The mechanism is suggested to be an additive or synergistic effect by which IT [5] or IV [13] dexmedetomidine prolongs the motor and sensory blockade of the bupivacaine. IV dexmedetomidine acts through supraspinal action [26], whereas intrathecally it depresses the release of C-fibers transmitters through binding to presynaptic C fibers and by hyperpolarization of postsynaptic dorsal horn neurons [27].

The potentiating mechanism of motor block by dexmedetomidine is not well understood, but it is suggested to be an additive or a synergistic effect to the local anesthetics [28, 29], interference with neuromuscular activity, or by binding of α2 agonists to motor neurons in the dorsal horn [30]. Yaksh [31] has shown that the intrathecal α2 adrenoceptor agonists can cause a dose‑dependent decrease in motor strength in animals. Another proposed mechanism was that it might be caused by direct impairment of excitatory amino acid release from spinal interneurons [31].

The α2 agonists act at three different sites such as brain and brainstem, spinal cord, and in peripheral tissues to induce analgesia. The results of our study regarding the time of initiation to rescue analgesia and VAS score indicated that IT dexmedetomidine augmented the analgesic properties of bupivacaine as compared to IV dexmedetomidine (Table 3). This suggests that the analgesic effect of α2 agonists may occur mainly at a spinal level. Due to its high lipophilicity, dexmedetomidine is rapidly absorbed into the cerebrospinal fluid and binds to the spinal cord α2 adrenoceptor. At the spinal cord level, stimulation of α2 receptors results in analgesia by different suggested mechanisms such as activation of the descending medullospinal noradrenergic pathways, reduction of the spinal sympathetic outflow at presynaptic ganglionic sites, interaction between opioids and α2 agonists at the spinal cord level, and inhibition of release of substance P in the nociceptive pathway [23, 32]. It has been shown that IT administration of dexmedetomidine exerts potent antinociceptive effects in animals [28, 33].

With respect to hemodynamics, the initial HR and MAP values after drug administration were significantly lower with the IV group as compared to the IT group (Fig. 1 and 2). This is likely to be due to the pharmacological action of dexmedetomidine. The use of α2 agonists is most commonly associated with side effects such as bradycardia and hypotension, which is in agreement with our result. Both the side effects were more frequent in the IV group than the IT group. However, these differences were not statistically significant as in previous studies [23, 34].

The sedation score was higher in the IV group than the IT group, but this was statistically insignificant (p>0.05). (Table 3) This may be explained on the basis that administration of α2 agonist by an intrathecal or an epidural route provides an analgesic effect without severe sedation. This might be because of the sparing of supraspinal CNS sites from excessive drug exposure which results in robust analgesia without heavy sedation [35].

Shivering was absent in both groups in our study. (Table 3) The antishivering property of the α2 adrenergic agents has been showed in studies by Maroof *et al.* [36] and Affifi *et al.* [23]. Respiratory depression was not reported in either group and this finding is in accordance with results of other studies [23, 37]. After spinal anesthesia, the incidence of nausea/vomiting has been reported between 0 and 18% in previous studies [23, 38]. In contrast, no patient in our study developed nausea/vomiting.

Although this study adds to the current knowledge on dexmedetomidine, it has some limitations. The inclusion of a control group using bupivacaine only for spinal anesthesia would have added greater power to the study. Further, results of this study cannot be generalized to different types of patients, surgeries, or older age groups as the study focused on a smaller, specified group of patients conducted in a single institution.

5. Conclusion

In bupivacaine spinal anaesthesia for lower abdominal

surgeries, dexmedetomidine, when administered intrathecally, has greater augmentation to sensory and motor block, more hemodynamic stability, better analgesic properties, and fewer overall side effects as compared to premedication with IV dexmedetomidine.

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