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Intrathecal Dexmeditomedine as an Adjuvant with Bupivacaine for Spinal Anesthesia in Infra Umbilical Surgeries

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Abstract

Introduction: For lower abdominal and lower limb surgeries the neuraxial blockade is the preferred mode of anesthesia. In recent years, use of intrathecal adjuvants like dexmedetomidine has gained popularity with the aim of prolonging the duration of the block, better success rate, patient satisfaction, decreased resource utilization compared with general anesthesia and faster recovery and adequate postoperative pain management. The present study was aimed to evaluate the role of dexmedetomidine when added to heavy bupivacaine 0.5% intrathecally. *Material and Methods:* A double-blinded randomized controlled trial conducted on 76 patients undergoing infra-umbilical surgery, during the period from 1st of January 2016 till December 2016. Patients were randomly divided into one of two groups. The first group (A) received the drug (Dexmedetomidine) with Bupivacaine while the second group (B) received Bupivacaine plus saline. *Results*: The mean SBP was lower among group (A) 132.9 ± 11.0 mmHg compared to group (B) 143.0 ± 10.3 mmHg and mean DBP was significantly lower among group (A) 78.7 ± 11.1mmHg compared to group (B) 82.3 ± 12.1mmHg at all recorded timing intra-operatively. The mean time to reach T8 sensory level was 3.8±1.0 min and mean time to Bromage 3, was 11.9±1.8 min that is less than group B, 4.2±1.2 min and 13.1±2.2 min respectively. Analgesia requirements were significantly lowered among group (A) as compared to group (B).The most frequent complications observed among the group (A) were sedation 15(39.47%), bradycardia 12 (31.57%) and hypotension 18 (47.36%). *Conclusion*: It was concluded that adding Dexmedetomidine along with local anesthetic provides adequate sensory and motor block, reduces intraoperative and postoperative analgesic requirements, and reduces post-op complications with no sedation or neurologic complications.

Keywords: Intrathecal; Dexmedetomidine; Spinal Anesthesia; Adjuvants.

Introduction

Lower abdominal and lower limb surgeries may be performed under local, regional (spinal or epidural) or general anesthesia, but the neuraxial blockade is the preferred mode of anesthesia. Spinal block is still the first choice because of its rapid onset, superior blockade, low risk of infection as from catheter *in situ*, less failure rates, and cost-effectiveness, but has the drawbacks of shorter duration of the block and lack of postoperative analgesia. In recent years, use of intrathecal adjuvants has gained popularity with the aim of prolonging the duration of the block, better success rate, patient satisfaction, decreased resource utilization compared with general anesthesia and

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faster recovery. Adequate pain management is essential to facilitate rehabilitation and accelerate functional recovery, enabling patients to return to their normal activity more quickly. The quality of the spinal anesthesia has been reported to be improved by the addition of opioids (fentanyl, sufentanil) and other drugs [dexmedetomidine, clonidine], but no drug to inhibit nociception is without associated adverse effects [1,2].

α_2-Adrenegic mechanisms of analgesia have been exploited for more than 100 yr. Cocaine, the first spinal anesthetic, produces analgesia primarily by its local anesthetic action, but also inhibits norepinephrine re-uptake, and spinal cocaine produces analgesia, in part, by enhancing noradrenergic stimulation of α_2-adrenoceptors [3].

Intrathecal α_2-agonists are used as adjuvant drugs to local anesthetics. They potentiate the effect of local anesthetics and allow a decrease in the required doses [4].

Dexmedetomidine is an *S*-enantiomer of medetomidine with a higher specificity for α2-adrenoreceptor (α2: α1, 1620: 1) compared to clonidine (α2: α1, 220: 1). It has been investigated as the anxiolytic, sympatholytic, and analgesic properties related to α2-adrenoceptor binding, and it is now being used as a co-analgesic drug. As an adjuvant, the neuraxial administration is the appropriate route to dexmedetomidine, because the analgesic effect of α2-agonists mostly occurs at the spinal level, and dexmedetomidine's high lipophilicity facilitates rapid absorption into the cerebrospinal fluid and binding to the spinal cord α2-adrenoreceptor. Intrathecally-administered dexmedetomidine has been shown to exert potent antinociceptive effects in animals. A few studies, using 10–15 mg of bupivacaine, dexmedetomidine (3–15 μg) prolonged the block duration of local anesthetics with a low-rate of side effects. Those studies, however, showed too high a block level (even up to T2) followed by a prolonged regression time [5].

A number of adjuvants have been used to prolong the postoperative analgesia. Dexmedetomidine is a highly selective α2-adrenergic agonist which has been used for premedication and as an adjunct to general anesthesia. It reduces opioid and inhalational anesthetics requirements [6].

It provides stable hemodynamic condition, good quality of intra-operative analgesia and prolonged postoperative analgesia with minimal side effects. Based on earlier human studies, it is hypothesized that intrathecal Dexmedetomidine would produce more postoperative analgesic effect with hyperbaric bupivacaine in spinal anesthesia with minimal side effects [2].

In the present study, the aim was to evaluate the role of Dexmedetomidine when added to heavy Bupivacaine 0.5% intrathecally among patients subjected to infra-umbilical surgeries.

Materials and Methods

A double-blinded randomized controlled trial was started after the approval of the Ethical Committee of the Medical Research Institute. Written informed consent was obtained from all study participants. 76 patients presenting to infra-umbilical surgery, during the period from 1st of January 2016 till December 2016 were included in the study.

Inclusion criteria were, patients with American Society of Anesthesiologists (ASA) physical status I or II, of either sex, aged between 18 to 60 years, presenting for lower abdominal surgeries and lower limb surgeries. Exclusion criteria were patient allergic to any of the drugs used and/ or suffering from neurologic diseases, coagulopathy, cardiac diseases, and other contraindications for regional/spinal anesthesia.

Patients were randomly divided into one of two groups. The first group (A) received the drug (Dexmedetomidine) under investigation while the second group (B) received Bupivacaine. All patients were preloaded with Ringer's solution 500 ML. They were monitored with automated noninvasive blood pressure, pulse oximetry, and electrocardiogram. Patients received no premedication during the 24 hours prior to the study. Following patient positioning, in the sitting / lateral position, a 25 G spinal needle is introduced through L4-L5 interspaces under strict aseptic precautions. Group (A) patients received 3.5 ml volume of 0.5% hyperbaric Bupivacaine and 5 μg Dexmedetomidine in 0.5 ml of preservative-free normal saline intrathecally. Meanwhile, Group (B) received normal saline added to the heavy Bupivacaine 0.5% which served as a placebo. Medications were prepared by another colleague so that both patient and investigator were blinded. Intrathecal injection in either group was given over approximately 10 seconds. Immediately after completion of the injection, patients were made to lie supine. Oxygen (2 L/min) was applied to each patient via face mask/Nasal prongs. Patients were monitored intra-operatively for their mean blood pressure and pulse every 5 minutes for the first 30 minutes, then every 10 minutes thereafter till the end

of surgery. Patients were assessed for time to reach T-8 sensory level (every 2 minutes) using the loss of pin prick sensation, and loss of motor functions indicated by time to reach Bromage 3, using Modified Bromage Scale.

Moreover, the assessment was done for 2-segment regression, first time to require analgesia, and total analgesic consumption of intravenous pentazocine over 24 hours. Also, patients were assessed intra-operatively for the occurrence of shivering, hypotension, bradycardia, nausea, vomiting, purities, sedation, and any other side-effects.

Hypotension was defined as a decrease of mean blood pressure by more than 30% from baseline or a fall of systolic blood pressure below 90 mmHg and was treated with 3 to 5 mg of inj. Mephentermine and IV fluids as required. Meanwhile, Bradycardia was defined as heart rate<60/min.

The following parameters will be observed and recorded.

1. The onset of sensory and motor blockade.
2. The maximum level of sensory and motor blockade attained and the time taken for the same.
3. Sensory blockade was tested using pinprick method with a blunt 27G hypodermic needle every 15 seconds till the onset of sensory blockade and thereafter at 2mins intervals till the maximum level of sensory blockade is achieved and subsequently at 5 minutes interval during first 30 minutes, then at 15 minutes intervals between 30 and 120 minutes, and thereafter at 30 minutes intervals until complete recovery.
4. The quality of motor blockade was being assessed by modified Bromage scale
5. Time for two segments sensory regression time.
6. The total duration of sensory and motor blockade.
7. Sedation score will be assessed every 15 minutes intraoperatively and hourly in the postoperative period for first 6 hours using *Ramsay sedation score [7].*
8. Postoperative pain will be assessed using Visual analogue scale (VAS) (0 – 10) at 30 minutes, hourly for the next 6 hours, and 2 hourly till 24 hours and time to first rescue analgesic request will be recorded.
9. *The onset of sensory blockade:* is defined as the time taken for the completion of the injection of the study drug till the subject does not feel the pin prick at T8 level.
10. *The quality of motor blockade:* is assessed according to modified Bromage scale. Modified Bromage scale:
11. *Duration of two segments sensory regression:* is defined as the time taken from the maximum level of sensory block attained till the sensation has regressed by 2 segments.
12. *Duration of motor blockade*: is the time taken from the time of injection till the subject attains complete motor recovery, Bromage-0.
13. *Duration of sensory blockade*: is the time taken from the time of injection till the subject feels sensation at S1.
14. *Sedation* is assessed using Ramsay sedation score: 1 = anxious and agitated, 2 = cooperative and tranquil, 3 = drowsy but responds to commands, 4 = asleep but responds to tactile stimulation, 5 = asleep and no response
15. *Duration of pain relief* was defined as the time from spinal injection to the first request of analgesics (VAS > 5) which consisted of injection Diclofenac 75mg with a maximum daily dose of 150mg.

Adverse Effects

Subjects will be monitored for the occurrence of adverse events after spinal injection like nausea, vomiting, desaturation, hypotension, bradycardia, excessive sedation and others.

Observations

Values are presented as the mean±S.D. Group A: Dexmedetomidine, Group B: saline group.

As regards personal characteristics, mean age of group (A) patients was 35.5 ± 12.3 years compared to 36.8 ± 13.6 years among group (B) patients. Male patients constituted 68% among the group (A) and 65% among the group (B). Moreover, patients of both groups had nearly equal mean weight; 70.4 ± 8.8 kg among the group (A) and 73.9±7.5 kg among the group (B).

Mean Systolic blood pressure assessed intra-operatively showed significantly lower results among group (A) 132.9 ± 11.0 mmHg compared to group (B) 143.0 ± 10.3 mmHg and mean diastolic blood pressure assessed intra-operatively showed significantly lower results among group (A) 78.7 ± 11.1mmHg compared to group (B) 82.3 ± 12.1mmHg at all recorded timing intra-operatively. Similarly, the assessed heart rate intra-operatively showed significantly slower mean among the group (A) 73.5 ± 12.0 compared to group (B) 77.2 ± 11.2 at all recorded timing intra-operatively.

Similarly, mean surgical time was 60.2 ± 6.1 minutes and 58.9±10.4 minutes respectively. No significant

differences were observed between both groups regarding any of these variables.

Concerning block characteristics, the mean time to reach T8 sensory level was 3.8±1.0 min and mean time to Bromage 3, was 11.9±1.8 min that is less than group B, 4.2±1.2 min and 13.1±2.2 min respectively, While the mean 2-segment regression time was significantly longer among group (A) patients (115.3 ± 15.8 minutes) compared to group (B), (85.3±9.9 minutes); P<0.0001.

Analgesia requirements were significantly lowered among group (A) as compared to group (B) where a longer time was recorded to need the first analgesia (360 ± 20.0 minutes, 180.0 ± 15.1 minutes respectively) and lower total analgesic consumption in 24 hours (8.0±1.5 mg, 15.8±2.2 mg respectively); (P<0.0001) .

Table 1: Distribution of patients according to their demographic data. (Values are the means ± standard deviations)

	Group A	Group B	*p* Value
Age (years)	35.5 ± 12.3	36.8 ± 13.6	P>0.001
Gender (M/F)	26/12	24/14	P>0.001
Weight (kg)	70.4 ± 8.8	73.9 ± 7.5	P>0.001
Height (cm)	152±5.3	154± 4.8	P>0.001
Duration of operation (min)	60.2 ± 6.1	58.9 ± 10.4	P>0.001
Baseline SBP	132.9 ± 11.0	143.0 ± 10.3	P>0.001
Baseline DBP	78.7 ± 11.1	82.3 ± 12.1	P>0.001
Baseline HR	73.5 ± 12.0	77.2 ± 11.2	P>0.001
Total	38	38	76

Values are presented as the mean±S.D. Group A: Dexmedetomidine, Group B: saline group

Table 2: Distribution of patients according to the results: Regression times in minutes

	Group A	Group B	*p* Value
Onset of sensory block(min)	3.8±1.0	4.2±1.2	0.52
Time to achieve max. block	11.9±1.8	13.1±2.2	0.48
Time to regression of 2-sensory dermatomes (min)	115.3 ± 15.8	85.3 ± 9.9	P<0.001
Time for rescue analgesia(min)	360 ± 20.0	180.0 ± 15.1	P<0.001
Highest pain score on VAS	3.8±1.8	7.2±1.1	P<0.001
Total	38	38	76

(Values are the means ± standard deviations.)

Table 3: Distribution of patients according to the side effects

	Group A	Group B	*p* Value
Hypotension	18(47.36%)	8(21.05%)	0.24
Sedation	15(39.47%)	8(21.05%)	0.134
Bradycardia	12(31.57%)	4(10.4%)	0.04
Nausea	11(28.94%)	4(10.4%)	0.08
Respiratory depression	2(5.2%)	1(2.6%)	1
Shivering	0	4(10.4%)	0.12
Total	38	38	76

The occurrence of complications was comparable among group (A) patients (30%) relation to group (B) patients (32.1%). The most frequent complications observed among the group (A) were sedation 15(39.47%), bradycardia 12 (31.57%) and hypotension 18 (47.36%). Meanwhile, the most frequent complications noticed among the group (B) were sedation 8(21.05%) and hypotension 12(31.57%). No significant differences were observed between both groups regarding any of the encountered complications except for shivering which was significantly more frequent in group (B) and bradycardia which was observed more among the group (A).

Discussion

Local anesthetics are commonly used for intrathecal anesthesia, but the major problem is the relatively short duration of action, thus early analgesic intervention is needed in the postoperative period. Dexmedetomidine (DXM) is a highly selective α_2 adrenergic receptor agonist with a relatively high ratio of α_2/α_1 activity (1600:1) compared to clonidine (220:1). DXM has been safely used as an adjuvant for the subarachnoid block in urological, orthopedic and lower abdominal surgical procedures.

Administration of a α2-agonist via an intrathecal or epidural route provides an analgesic effect in postoperative pain without severe sedation. This effect is due to the sparing of supraspinal CNS sites from excessive drug exposure, resulting in robust analgesia without heavy sedation. At spinal cord level, activation of both α2-C and α2-ARs, in the neurons of superficial dorsal horn especially lamina II directly reduces pain transmission, by suppressing the release of pro-nociceptive transmitter, substance P and glutamate from primary afferent terminals, and by hyperpolarizing spinal interneuron's via G-protein-mediated activation of potassium channels.

In our study, we aimed to evaluate the role of Dexmedetomidine added to heavy bupivacaine 0.5% intrathecally for infra-umbilical surgeries.

In our study, Concerning block characteristics, the mean time to reach T8 sensory level was 3.8±1.0 min and mean time to Bromage 3, was 11.9±1.8 min that is less than group B, 4.2±1.2 min and 13.1±2.2 min respectively, While the mean 2-segment regression time was significantly longer among group (A) patients (115.3 ± 15.8 minutes) compared to group (B), (85.3 ± 9.9 minutes); P<0.0001.

Analgesia requirements were significantly lowered among group (A) as compared to group (B) where a longer time was recorded to need the first analgesia (360 ± 20.0 minutes, 180.0 ± 15.1 minutes respectively) and lower total analgesic consumption in 24 hours (8.0 ± 1.5 mg, 15.8 ± 2.2 mg respectively); (P<0.0001) .

Similar to our results, Ogan et al (2012) [8] showed an earlier significant peak sensory block in the Dexmedetomidine group compared to the other group. Shukla et al (2011) [1] also showed that the onset time to reach peak sensory level was shorter in Dexmedetomidine group as compared with the control group. Shukla et al (2011) [1] showed that there was a significant difference with the time to Bromage 3. Ogan et al (2012) [8] also showed a significant reduction in the time to reach Bromage 1, compared to control group. As regards the 2-segment regression, it ranged from 80-120 minutes in group me with a mean of 100.3±20.8 minutes. Gupta et al (2011) [6] showed a mean of 125.6 ± 16.5 minutes by adding 5 μg Dexmedetomidine intrathecally to ropivacaine. Eid et al (2011) [9] showed a prolongation of 2-segment regression time in her study after adding 10 μg Dexmedetomidine to bupivacaine. Moreover, her study showed a dose-dependent increase of 2 segment regression time by increasing the dose from 10 μg to 15 μg of intrathecal Dexmedetomidine (103±28.7 minutes, 200.6±30.9 minutes respectively).

As regards the first time to require analgesia, and total analgesic consumption of pentazocine in 24 hours, group A showed a significant increase in time to first analgesic dose (360 ± 20.0, versus 180±15.1 in the control group), and a significant decrease in the total analgesic consumption. In agreement with our results, Eid et al (2011) [9] showed a significantly longer time to first analgesic request compared to control group. Ashraf et al (2012) [10] also showed a significantly longer time to first analgesic request (3.30±0.87 hours) compared to control group (0.23±0.11 hours).

In a study by Pratek Koolwal (2015) [11] they found that Dexmedetomidine significantly prolonged time to two segment regression, sensory regression, regression of motor block to modified Bromage 0 and time to first rescue analgesic. In addition, it significantly decreased postoperative pain scores. Similarly Rachna Joshi et al (2013) [12], observed in their study that patients receiving bupivacaine alone intrathecally had a mean time of onset of motor block of 5.2±0.8 minute, which is faster than patients receiving bupivacaine with dexmedetomidine 5 μg (8.45±1.0 minute).The total duration of motor block was found to be 341.80 ± 41.71 min in the study group of dexmedetomidine 10 μg compared to study group B having 282.03 ± 28.03minutes and control group of bupivacaine alone having a mean value of 188.73 ± 18.64 min and this difference was statistically significant (p = <0.001). Also Sisinti Sanjeeb Patro (2016) [13] found that onset of sensory block was 129.33±14.8 seconds in Group II as compared to 208.33±19.18 seconds in Group I with total duration of sensory block as 317.70±16.16 minutes in Group II and 188±11.86 minutes in Group I. Similarly, onset of motor block was 226.33±31.86 minutes and 320.33±29.81 minutes, with total duration of motor block as 286.33±15.15 minutes and 166.5±12.11 minutes in Group II and in Group I respectively. Duration of analgesia was 333.6±20.67 minutes with Dexmedetomidine but 193.67±7.06 minutes in bupivacaine alone group. These findings are similar to the studies by Al-Mustafa MM(2009) [14] and Veena Chatrath (2015) [15].

The occurrence of complications was comparable among group (A) patients (30%) relation to group (B) patients (32.1%). The most frequent complications observed among the group (A) were sedation 15(39.47%), bradycardia 12 (31.57%) and hypotension 18 (47.36%). Meanwhile, the most frequent complications noticed among the group (B) were sedation 8 (21.05%) and hypotension 12 (31.57%). No significant differences were observed between both groups regarding any of the

encountered complications except for shivering which was significantly more frequent in the group (B) and bradycardia which was observed more among the group (A).

As regards the intraoperative side effects, shivering occurred in 2 patients in the group I, and in 12 patients in group II. An explanation of the decreased incidence of shivering in the Dexmedetomidine group is the decrease shivering threshold by 2 degrees. In agreement with our results, Usta et al (2011) [16] stated in their study that intravenously administered Dexmedetomidine infusion inhibited shivering under spinal anesthesia. Karaman et al (2013) [17] showed that intravenous loading dose followed by infusion of Dexmedetomidine decreased the incidence of shivering compared to placebo. Moreover, the intensity of shivering in the 3 observed cases was lower in the Dexmedetomidine group than in the placebo group (P>0.05).

Bradycardia occurred in 8 cases compared to none of the study patients in the control group. Bradycardia in the Dexmedetomidine group is believed to be due to postsynaptic activation of central alpha 2 adrenoceptors (α2-ARs) results in a sympatholytic effect, leading to hypotension and bradycardia, an effect judiciously used to attenuate the stress response of surgery. Dexmedetomidine evokes a biphasic blood pressure response: A short hypertensive phase and subsequent hypotension. The two phases are considered to be mediated by two different α2-AR subtypes: the α-2B AR is responsible for the initial hypertensive phase, whereas hypotension is mediated by the α2A-AR. The initial response lasts for 5 to 10 minutes and is followed by a decrease in blood pressure of approximately 10% to 20% below baseline and a stabilization of the heart rate, also below baseline values; both of these effects are caused by the inhibition of the central sympathetic outflow overriding the direct stimulating effects.

In our study, 18(47.36%)patients developed hypotension starting from 20 minutes following the spinal injection in group A, versus 8 (21.05%) in group B with insignificant differences between the two groups. However, it responded well to intravenous Mephentermine and fluid. Kanazi et al (2006) [4] showed an insignificant effect of Dexmedetomidine on mean blood pressure when added to intrathecal bupivacaine.

Nausea with or without vomiting was associated with the hypotensive episodes. This may be explained by the fact that increased vagal activity after sympathetic block causes increased peristalsis of the gastrointestinal tract, which leads to nausea.

In agreement with our results, Abdelhamid SA (2013) [2] showed that occurrence of complications was significantly less encountered among the group (D) patients (32.3%) I relation to group (P) patients (58.1%), P=0.041. The most frequent complications observed among the group (D) were bradycardia (25.8%) and hypotension (25.8%). Meanwhile, the most frequent complications noticed among the group (P) were vomiting (41.9%) and hypotension (19.4%). No significant differences were observed between both groups regarding any of the encountered complications except for shivering which was significantly more frequent in the group (P) and bradycardia which was observed only among the group (P). However, sedation was absent in both studied groups.In a similar study, Safiya I. Shaikh et al (2014) [18] concluded that addition of dexmedetomidine to hyperbaric bupivacaine intrathecally produces a rapid onset of sensory and motor block prolongs the sensory and motor block and the time to first analgesic requirement significantly in a dose-dependent manner together with stable hemodynamic parameters, and minimal side effects. Dexmedetomidine seems to be an attractive adjuvant to spinal bupivacaine especially in surgical procedures of long duration as an alternative to epidural or prolonged general anesthetics and can preclude intravenous anesthetics. Similar results were found by Solanki SL (2013) [19].

Conclusion

It was concluded that adding Dexmedetomidine along with Local anesthetic provides adequate sensory and motor block, reduces intraoperative and postoperative analgesic requirements, reduces post-op complications with no sedation or neurologic complications.

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