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Research Article

A comparative study of two doses of intrathecal dexmedetomidine 10 mcg and 15 mcg as adjuvants to 0.5% hyperbaric bupivacaine for abdominal hysterectomy: a randomized, prospective, double blind study

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ABSTRACT

Background: Neuraxial adjuvants have been used with local anaesthetics to avoid intraoperative pain, prolong the duration of anaesthesia, and avoid side effects and to provide adequate postoperative analgesia. Dexmedetomidine, a highly selective α2-agonist drug, is being routinely used nowadays as a neuraxial adjuvant. The aim of this study was to compare two doses of dexmedetomidine in terms of efficacy in prolonging the subarachnoid block as well as safety.
Methods: In this prospective, randomized, double-blind, controlled study on 90 ASA I/II patients undergoing elective abdominal hysterectomy patients were randomly allocated to one of the three groups of 30 each, to receive subarachnoid block with 3.4 ml of 0.5% hyperbaric Bupivacaine along with either normal saline (S) or dexmedetomidine 10 µg (D 10) or dexmedetomidine 15 µg (D 15) and onset and duration of motor and sensory block were monitored along with two segment regression times, postoperative VAS scores and analgesic requirements and occurrence of any untoward effects.
Results: Dexmedetomidine significantly decreased the onset times of sensory and motor blocks, prolonged time to two segment regressions, prolonged regression of motor and sensory blocks and time to first rescue analgesic in postoperative period. There was reduction in requirement of analgesics in both the dexmedetomidine groups. Effects were more pronounced in D 15 group than D 10 group. All three group patients were stable haemodynamically with only an insignificant number of patients having bradycardia and hypotension in the D 15 group.
Conclusions: Thus dexmedetomidine prolongs the 0.5% hyperbaric Bupivacaine spinal anaesthesia duration. Prolongation of anaesthesia is in a dose dependent manner and groups are comparable in terms of safety profiles.

Keywords: Intrathecal dexmedetomidine, Neuraxial adjuvants, Hyperbaric Bupivacaine, Abdominal hysterectomy

INTRODUCTION

Fear of uncontrolled postsurgical pain is a major concern of patients undergoing abdominal surgery. In an attempt to prevent occurrence of somatic and visceral pain in the intra-operative period and a to provide prolonged analgesia in the post-operative period, numerous neuraxial adjuvants are being used including NMDA antagonists (ketamine, magnesium), GABA agonists (midazolam) and adrenergic agonists (adrenaline), COX-inhibitors (ketorolac) and Ach-esterase inhibitor (neostigmine). Though innumerable, each additive has certain specific disadvantage which limits their use in subarachnoid block.

Striebel et al stressed upon the effect of α2 adrenergic agonist, Clonidine, on prolongation of analgesia and motor blockade when administered with local anaesthetic intrathecally.[1] Kanazi et al compared low doses of intrathecal clonidine and dexmedetomidine (3µg versus 30 µg) and concluded that the two drugs had equal effect on prolongation of motor and sensory block in these

respective doses. With a α2: α1 selectivity ratio 8 times higher than clonidine, dexmedetomidine is a better sedative and analgesic as compared to clonidine.[2]

Though a number of studies have been conducted on use of intrathecal dexmedetomidine in various doses, very few studies have used dexmedetomidine in the dose of 15 µg. Thus this prospective, randomized, double-blind, placebo-controlled study was conducted on 90 ASA I/II patients posted for elective abdominal hysterectomies to study and compare the effects of intrathecal dexmedetomidine 10 µg and 15 µg as an additive with hyperbaric 0.5% bupivacaine on:

- Onset, maximum level and total duration of sensory block
- Onset, time to total motor block and total duration of motor block
- Two segment regression time of sensory block
- Time to first request of analgesic
- Total post-operative analgesic requirement in first 24 hours
- Any untoward side effects observed.

METHODS

After getting approval from the institutional ethical committee and written informed consent from patients, this study was conducted in a tertiary care medical college hospital.

90 ASA I/II patients of either sex, in age group 30-60 years, weight 40-70 kg, height 150-170 cm and scheduled for elective abdominal hysterectomies were included in the study. A written informed consent was obtained from each patient. Patients were excluded from the study if they had ischaemic heart disease, hypertension, hypovolaemia, any contraindication for spinal anaesthesia or allergy to study drugs or if they were unwilling to participate in the study.

Sample size of 30 patients per group was derived using Cohen's formula. We assumed α error of 0.05 and power of study 80%. Mean and standard deviation were calculated for all the quantitative variables using graph-pad prism statistical software. These 90 patients were randomly allocated using a computer generated randomization table into one of the following three groups:

Group S- patients were administered intrathecal injection of 3.4 ml of 0.5 % bupivacaine (heavy) + 0.5 ml 0.9% normal saline.

Group D 10- patients were administered intrathecal injection of 3.4 ml of 0.5 % bupivacaine (heavy) + 10 ug dexmedetomidine (0.5 ml).

Group D 15 - patients were administered intrathecal injection of 3.4 ml of 0.5 % bupivacaine (heavy) + 15 ug dexmedetomidine (0.5 ml).

We used injection dexmedetomidine (DEXTOMID* 50 µg/ ml), manufactured by NEON laboratories, India as the intrathecal adjuvant in all the patients in both dexmedetomidine groups. Appropriate investigations were done in all the 90 patients. All the patients in all the three groups received tablet diazepam 5mg and tablet ranitidine 150 mg on the night prior to surgery and were kept nil by mouth overnight.

On the day of surgery, all the necessary monitors including 5- lead electrocardiography, pulse oximetry probe and non-invasive blood pressure cuff were attached to the patients. Baseline vitals of the patient were noted. After taking a wide bore IV cannula, preloading was done with 250 ml of Ringer Lactate. The drug to be used for subarachnoid block was prepared by an anesthesiologists not participating in the study. Under all aseptic precautions a midline lumbar puncture was performed with 23G Quincke needle at L3 - L4 interspace with patient in sitting position. Thereafter the patient was placed in supine position. After intrathecal drug injection, hemodynamics was monitored every 2 minutes for first 10 minutes, every 5 minutes for next 30 minutes and then for every 15 minutes till the procedure was completed.

Occurrence of nausea, vomiting, pruritus and respiratory depression were recorded throughout the study duration. Hypotension (defined as a decrease in systolic blood pressure > 30% of the baseline value or systolic blood pressure < 90 mm Hg) was treated with intravenous boluses of 3 mg mephentermine. Bradycardia defined as a heart rate of < 50 beat/min will be treated with boluses of 0.6 mg atropine. Respiratory depression (RR< 8 or SpO2 < 95%) was treated with oxygen supplementation and respiratory support if required. Any other untoward side effect, if any, was noted.

Onset of sensory blockade

Onset of analgesia was determined by the lack of appreciation of pinprick sensation at L1 dermatome level.

Onset and duration of motor blockade

Onset and duration of motor blockade was be assessed by modified Bromage score.

Duration of analgesia

Time of intrathecal drug administration to the first request of supplemetal analgesia. Patients were explained about Visual analogue scale preoperatively, if and when VAS score was more than 3, Inj. diclofenac 75 mg. IV infusion was administered as rescue analgesic.

Hemodynamic changes

Heart rate, respiratory rate, systolic and diastolic blood pressure, ECG, oxygen saturation, Urine output were monitored.

Level of sedation

Was assessed by Ramsay sedation score.

Table 1: Modified Bromage scale.

0	**Patient able to move the hip, knee, ankle**
1	Patient unable to move hip but able to move knee and ankle
2	Patient unable to move hip and knee but able to move ankle
3	Patient unable to move hip, knee and ankle.

Table 2: Ramsay sedation score[3]

1	**Patient anxious, agitated and restless**
2	Patient cooperative oriented and tranquil
3	Patient responds to command only
4	Patient exhibit brisk response to light glabellar tap or loud auditory stimulus
5	Patient exhibit sluggish response to light glabellar tap or loud auditory stimulus
6	Patient exhibits no response

Visual analogue scale

- 0-Absoultely no pain intensity
- 1-Negligible pain
- 2-Very very minimal pain
- 3-Very minimal pain
- 4-Minimal pain
- 5-Pain requiring relief
- 6-Pain with little distress
- 7-Severe pain
- 8-Very severe pain
- 9-Very very severe pain
- 10-Unimaginable pain

An intra-group comparison was made using paired Student's t-test and comparison between two groups at a time (inter-group comparison) was done using the unpaired t-test, ANOVA and Chi-squre test. P<0.05 was considered statistically significant.

RESULTS

The patients in the three groups were statistically comparable with respect to age, weight, height, sex and operative time (Table 3).

When we compared the onset of sensory block by testing pin-prick at dermatomal level L1, patients in group D15 had a mean onset time of 1.98±0.41 minutes while those in group D 10 had a mean of 2.34±0.33 minutes and that in saline group was 4.19±0.96 minutes. The pair wise analysis revealed that the difference between saline group and Dexmed-10 as well as saline group and Dexmed-15 were significant (p<0.001), while the difference between two dexmedetomidine groups was statistically insignificant (Table 4).

Table 3: Comparison of demographic data between two groups.

Characteristic	Group S (n = 30)	Group D 10 (n = 30)	Group D 15 (n = 30)	'p'
AGE (years)				
Mean±SD	31.13±10.70	31.8±11	31.10±10	0.43 (NS)
Sex				
Male	15 (50%)	12 (40%)	15 (50%)	0.87 (NS)
Female	15 (50%)	18 (60%)	15 (50%)	
Weight (kg)				
Mean±SD	46±6.15	45.9±6.1	45.8±6.1	0.11 (NS)
Height (cm)				
Mean±SD	152.7±21.54	156.4±5.21	155±6.32	0.35 (NS)
ASA status				
I	30 (100%)	30 (100%)	30 (100%)	1 (NS)
Duration of anaesthesia (min)	74.66±30.9	89.67±34.69	88.32±30.2	0.08 (NS)

M-mean, SD-standard deviation, NS-Not significant.

Comparison of maximum sensory levels across three groups showed highly significant difference (p<0.001) across the three groups as majority (26) patients in group D15 achieved level T4, 12 patients in group D10 achieved level T6 and only 2 patients in saline group reached level T6.

Table 2: Comparison of sensory block characteristics among the groups.

Parameters	Group S	Group D 10	Group D 15	P-value*
Onset sensory (min) (Mean±SD)	4.19±0.96	2.34±0.33	1.98±0.41	< 0.0001 (HS)
Max sensory (No.)				
T2	0	0	2	< 0.0001 (HS)†
T4	0	0	26	
T6	2	12	2	
T8	16	18	0	
T10	12	0	0	
Time to max sensory(min) (Mean±SD)	7.12±0.77	5.5±0.85	4.41±0.39	< 0.0001 (HS)
Two seg. reg. sensory(min) (Mean±SD)	62.5±10.65	122±18.78	137±16.48	< 0.0001 (HS)
Total duration of sensory block (min) (Mean±SD)	158.5±21.1	341±16.89	386±19.36	< 0.0001 (HS)

*Obtained by using one way ANOVA and † obtained using Chi-square test; HS: Highly-Significant.

Table 3: Comparison of motor block characteristics and postoperative analgesic requirements in three groups.

Parameters (minutes)	S	D 10	D 15	P-value*
Onset motor (Mean±SD)	9.62±1.19	4.47±0.59	3.858±0.40	< 0.0001 (HS)
Total motor (Mean±SD)	125.5±22.68	223±22.54	246.5±25.64	< 0.0001 (HS)
TFA (Mean±SD)	171.17±18.41	362.5±18.93	401.5±19.7	< 0.0001 (HS)
TAR (Mean±SD)	315±39.72	147.5±28.88	119.17±31.95	< 0.0001 (HS)

TFA- time to first request for analgesic, TAR- total analgesic requirement, HS-Highly significant.

Table 4: Comparison of complications in three groups.

Type	Placebo	Dexmed 10	Clonidine 75	*P*-value*
Bradycardia (No.)				0.2005 (NS)
Yes	0	3	3	
No	30	27	27	
Hypertension (No.)				0.4843 (NS)
Yes	2	5	4	
No	28	25	26	
RSS (No.)				0.0006 (S)
1	21	5	10	
2	9	13	13	
3	0	10	6	
4	0	2	1	

*Obtained by using Chi-square test; HS: Highly-Significant; S: Significant; NS: Non-Significant.

Table 5: Comparison of postoperative VAS scores in the three groups.

VAS score	S	D10	D15	P-value*
Min [Mean (Median)]	2.13 (2)	0.07 (0)	0.03 (0)	< 0.0001 (HS)
Max [Mean (Median)]	5.33 (5)	2.23 (2)	2.07 (2)	< 0.0001 (HS)

When time to reach maximum sensory level (T-max sensory) was compared, dexmedetomidine group patients reached peak level significantly faster as compared to saline group and on comparing between the two study groups, difference was statistically significant.

Similarly Table 4 also shows that the 2 segment regression times for sensory analgesia were significantly higher in dexmedetomidine groups and on intergroup comparison D15 had a still significantly higher time of 137±16.48 minutes than D10 group of 122±18.78 minutes.

The total sensory analgesia duration was 386±19.36 minutes in the D 15 group, 341±16.89 minutes in the D 10 group and 158.5±21.1 minutes in the saline group. On statistical analysis, these were also significantly higher in dexmedetomidine groups. Thus dexmedetomididne prolonged the sensory blockade of spinal anaesthesia with 0.5% hyperbaric Bupivacaine. A dose of 15 micrograms

of dexmedetomidine prolonged the sensory block significantly more than 10 micrograms.

The D15 patients had their motor onset 3.858±0.40 minutes which was much faster as compared to D10 (4.47±0.59 min) patients and these two groups were much faster as compared to saline group (9.62±1.19 min). Difference between the groups was statistically highly significant.

Similarly the mean total motor block duration was prolonged in both the dexmedetomidine groups and the difference was highly significant (Table 5).

TFA- time to first request of analgesic, TAR- total analgesic requirement

Post-operative time to first request of analgesic was faster in saline group (171.17±18.41 min) indicating early wean-off of sensory blockade whereas it was delayed in dexmedetomidine groups indicating a good prolonged postoperative analgesia.

Total analgesic requirement was significantly less in dexmedetomidine groups, more so in the D15 group. The difference of means between Dexmed10 and Dexmed15 was significant, and the difference of these groups from placebo was highly significant (Table 5).

Intra-operative haemodynamics

The mean intraoperative haemodynamics did not differ significantly among the three groups. The mean intraoperative heart rates among groups S, D10 and D15 were 72.23±8.41, 70.23±10.20 and 69.28±8.86 respectively. On analysing, the difference was found to be statistically insignificant. Similarly the mean intraoperative MAP (mean arterial pressure) values among the three groups S, D10 and D15 were 79.22±9.01, 75.50±9.48 and 74.28±8.41 respectively. On comparing, the difference was statistically insignificant. The respiratory rates and Oxygen saturation were similar in all three groups.

Table 6 shows that the distribution of patients with bradycardia across three groups was significantly different as per Chi-Square test. Thus significant number of patients in both dexmedetomidine groups had bradycardia when compared with saline group but when the two dexmedetomidine groups were compared, difference was statistically insignificant.

The number of patients having hypotension was 2, 5 and 8 in groups S, D10 and D15 respectively. With a p value >0.05, difference was insignificant statistically.

As compared to saline group, more number of patients in both dexmedetomidine groups remained sedated and the p value was <0.0001. But on comparing the two study groups the difference was insignificant.

Table 7 shows that the minimum VAS scores, across three groups differed highly significantly as indicated by Kruskal-Wallis test with p-value <0.0001. The pair wise analysis using Wilcoxon rank sum test revealed that the difference between saline and each of the other two groups was significant, while two dexmedetomidine groups did not show statistically significant difference.

Similarly, the maximum VAS scores, across three groups differed highly significantly as indicated by Kruskal-Wallis test with p-value <0.0001. The pair wise analysis using Wilcoxon rank sum test revealed that the difference between saline and each of the other two groups was significant, while two dexmedetomidine groups did not show statistically significant difference.

DISCUSSION

Local anaesthetics are commonly used for subarachnoid block in total abdominal hysterectomies, but the major problem is their relatively short duration of action, thus early analgesic intervention is needed in the postoperative period. A number of adjuvants, such as clonidine and midazolam, and others have been studied to prolong the effect of spinal anaesthesia.[4,5]

Mohamed et al studied the effect of addition of dexmedetomidine in spinal anaesthesia for major abdominal cancer surgery.[6] Dexmedetomidine, an imidazole compound, is the pharmacologically active dextroisomer of medetomidine that displays specific and selective α2-adrenoceptor agonism. Activation of the receptors in the brain and spinal cord inhibits neuronal firing and results in sympatholytic effect, causing hypotension, bradycardia, sedation, and analgesia.[6] Kanazi et al used a small intrathecal dose of dexmedetomidine (3 μg), in combination with bupivacaine on humans for spinal anesthesia.[2] Results showed a shorter onset of motor block and a prolongation in the duration of motor and sensory block with hemodynamic stability and lack of sedation. Shukla et al compared the effects of addition of 10 μg dexmedetomidine and magnesium sulphate and concluded that dexmedetomidine addition led to faster onset and prolonged duration of block as compared to magnesium sulphate and normal saline.[7] Though there are multiple such studies comparing dexmedetomidine in low doses with other adjuvants, very few researchers have used a higher dose of dexmedetomidine i.e. 15 μg. So we decided to compare two doses of intrathecal dexmedetomidine in our study.

In our study, all the three groups were comparable in terms of demographic parameters and baseline vitals. Patients were randomly allocated to either receive 10 or 15 μg of dexmedetomidine intrathecally by a non-participating anaesthesiologist and results were compared and also compared with normal saline which was the control group.

The onset of sensory block was significantly faster in both dexmedetomidine groups when compared with saline but it was not significantly different among the two dexmedetomidine groups. Sherif A Abdelhamid et al in their study comparing intrathecal dexmedetomidine 5 µg and saline also found that onset of the sensory block was earlier in dexmedetomidine group, compared to saline group.[8] It ranged 7.7±1.5, and was significantly earlier than control group. Similar findings have been documented by Ogan et al and Shukla et al.[7,9] When the maximum sensory level reached was comared, 26 patients in D15 reached T4 level while none of the patients in either saline or D10 group reached that level. This finding was statistically highly significant with $p<0.0001$. Thus D15 dose has to be used cautiously in haemodynamically unstable patients. The regression times of sensory analgesia and total duration of sensory block were also significantly more in both study groups and more so in the D15 group. These findings correlate with the findings of Hala et al who also compared these two doses of dexmedetomidine.[10] Eid et al showed a prolongation of 2-segment regression time in her study after adding 10 µg dexmedetomidine to bupivacaine.[11] 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). The α2-adrenoceptor agonists act by binding to pre-synaptic C-fibers and post-synaptic dorsal horn neurons. Intrathecal α2-adrenoceptor agonists produce analgesia by depressing the release of C-fiber transmitters and by hyperpolarization of post-synaptic dorsal horn neurons. This antinociceptive effect may explain the prolongation of the sensory block when added to spinal anaesthetics.

In our study onset of motor and total duration of motor block was also significantly more in the dexmedetomidine groups. These findings were similar to those of Shukla et al and Hala et al.[8,10]

As regards the time to first request of analgesic, total analgesic requirement (TAR) and postoperative VAS scores were concerned, dexmedetomidine significantly prolonged the time to first request of analgesic and reduced the TAR as compared to saline but the dose of 15 µg did not have any distinct advantage over dose of 10 µg in terms of prolonging of analgesia. These findings correlate with the findings of Hala et al.

As far as haemodynamics were concerned, though we did face bradycardia in 6 patients of D15 group and 3 patients of D10 group, it was easily reverted with single dose of IV Atropine 0.6 mg. The incidence of hypotension was comparable between the three groups. The patients in both the dexmedetomidine groups were more sedated than those in the saline group and more so in the D15 group. These findings also were similar to Hala et al.

CONCLUSION

Thus dexmedetomidine in the dose of 15 micrograms when compared with dose of 10 micrograms, did have an advantage of significantly faster sensory and motor onset and prolonged and a higher sensory block as well as prolonged post-operative analgesia, thereby reducing the requirement of analgesics and so it can be used safely as a spinal adjuvant for lower abdominal or lower limb surgeries of long durations. The sedation scores, though higher did have a distinct advantage of absence of respiratory depression. But taking into consideration the incidence of bradycardia, one should use it cautiously in patients with cardiac problems like conduction defects or bradyarrhythmias. Also as this study was conducted on ASA I/ II status patients only, care should be taken while using this drug dose in ASA III/ IV patients.

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