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Comparative Study of Intrathecal Dexmedetomidine versus Fentanyl Combined With Hyperbaric Bupivacaine for Perioperative Analgesia in Elective Lower Limb Orthopaedic Surgeries: A Double Blind Controlled Study

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Abstract: Spinal anaesthesia is the most commonly used technique for lower abdominal surgeries as it is very economical, easy to administer, more rapid return to complete alertness when compared to general anaesthesia, superior postoperative analgesia and patient satisfaction, decreasing both the need for postoperative analgesics and the incidence of postoperative nausea and vomiting and reduced the cost of outpatient surgical procedures by decreasing the necessity of recovery room and subsequent hospital admissions. In recent years, use of intrathecal adjuvant has gained popularity with the aim of prolonging the duration of block, prolonged postoperative pain control, better success rate, patient satisfaction, decreased resource utilization compared with general anaesthesia and faster recovery. The quality of the spinal anaesthesia has been reported to be improved by the addition of opioids (such as morphine, fentanyl and sufentanil) and other drugs (such as clonidine, magnesium sulfate, neostigmine, ketamine and midazolam). Hence, the present study is being undertaken to evaluate and compare the effects of dexmedetomidine and fentanyl as intrathecal adjuvants to bupivacaine. The study population was randomized using random number table generated from computer software. Random intervention assignment slip was placed in serially numbered opaque and sealed envelopes. These envelopes were opened following enrolment of the case. 90 total patients randomly divided into 3 groups (n = 30): Group A: Hyperbaric bupivacaine 15mg + dexmedetomidine 5µg (diluted up to 3.5 ml with preservative-free normal saline) were given intrathecally. Group B: Hyperbaric bupivacaine 15mg + fentanyl 25 µg (diluted up to 3.5 ml with preservative-free normal saline) was given intrathecally. Group C: Hyperbaric bupivacaine 15mg (diluted up to 3.5 ml with preservative-free normal saline) alone was given intrathecally. Dexmedetomidine seems to be a better alternative to fentanyl as additive to intrathecal hyperbaric bupivacaine since it produces more prolonged sensory and motor block with similar kind of haemodynamic stability, better post-operative analgesia and sedation and is associated with less adverse effects. This kind of block may be more suitable for lower limb orthopaedic surgeries of longer duration and Dexmedetomidine produces more prolonged sensory and motor block with similar kind of haemodynamic stability, better post-operative analgesia and sedation and is associated with less adverse effects. Intrathecal does of dexmedetomidine used in the present study need further clinical studies to prove its efficacy and safety and to be considered as the suitable dose of dexmedetomidine for supplementation of spinal local anaesthesia.

Keywords: Intrathecal adjuvant, prolonged sensory and motor block, Post-operative analgesia and sedation.

INTRODUCTION

Spinal anaesthesia with 0.5% hyperbaric bupivacaine is a well-known technique for lower limb orthopaedic surgeries. It is easy to perform, faster onset, effective sensory and motor block, allows patients a more rapid return to complete alertness when compared to general anaesthesia techniques. Regional techniques also provide superior postoperative analgesia and patient satisfaction by decreasing both the need for postoperative analgesics and the incidence of postoperative nausea and vomiting. It may also significantly reduce the cost of outpatient surgical procedures by decreasing the necessity of recovery room and subsequent hospital admissions [1].

However, postoperative pain control is a major problem because spinal anaesthesia using only local anaesthetics is associated with relatively short duration of action, and 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 anesthesia [2,3].

Fentanyl, in recent years, has emerged as an useful intrathecal adjuvant for prolonging the effect of spinal anaesthesia. Pain is often encountered during surgery on the lower abdomen under spinal anaesthesia. Intrathecal fentanyl when added to spinal local anaesthetics reduces significantly visceral and somatic pain and this analgesic effect has been proved by many studies [4-8]. Although it is one of the most widely used intrathecal adjuvant in the present scenario, its intrathecal use has been shown to be associated with side effects like respiratory depression and pruritus [9].

Dexmedetomidine, a new highly selective α2-agonist, is under evaluation as a neuraxial adjuvant as it provides stable hemodynamic conditions, good quality of intraoperative and prolonged postoperative analgesia with minimal side effects [10-13]. Dexmedetomidine has been approved by Food and Drug Administration (FDA) as a short-term sedation agent for mechanically ventilated patients in intensive care units (ICU).It is under evaluation as an intrathecal adjuvant. By virtue of its effect on spinal α-2 receptors, dexmedetomidine mediates its analgesic effects. Dexmedetomidine has been found to prolong analgesia when used as an adjuvant to local anaesthetics for subarachnoid block, lumbar and caudal epidural blocks [14]. Based on earlier human studies, it has been shown that a low dose of 5 µg, dexmedetomidine provides a prolonged anaesthesia and good quality post-operative analgesia when used as an intrathecal adjuvant to bupivacaine with minimal effects on the hemodynamic status of the patient [11-13].

Alpha-2 adrenoceptor agonists have been used in a large number of clinical applications, some with little evidence of efficacy. Anaesthetic and analgesic-sparing effects have been reported, but whether they offer additional benefits to patients requiring routine surgery is yet to be decided. A better understanding of the interactions between alpha-2 adrenoceptor, opioid and cholinergic receptors, as well as local anaesthetic mechanisms, should help to determine the most appropriate and effective combination of their agonists.

Hence, the present study is being undertaken to evaluate and compare the effects of dexmedetomidine and fentanyl as intrathecal adjuvants to hyperbaric bupivacaine.

MATERIALS AND METHODS

This study was carried out at MKCG Medical College & Hospital, BRAHMAPUR, during the year 2015 to 2016 after obtaining approval from the Hospital Ethical Committee and written informed consent from the patients.

Study type: Randomized Controlled Trial.

The study population was randomized using random number table generated from computer software. Random intervention assignment slip was placed in serially numbered opaque and sealed envelopes. These envelopes were opened following enrollment of the case.

Study group: 90 total patients randomly divided into 3 groups (n = 30):

GROUP A: Hyperbaric Bupivacaine 15mg + Dexmedetomidine 5µg (diluted up to 3.5 ml with preservative-free normal saline) administered intrathecally.

Group B: Hyperbaric Bupivacaine 15mg + Fentanyl 25 µg (diluted up to 3.5 ml with preservative-free normal saline) administered intrathecally.

Group C: Hyperbaric Bupivacaine 15mg (diluted up to 3.5 ml with Preservative-free normal saline) alone administered intrathecally.

All the patients were kept for 6 hrs fasting prior to surgery. Tablet Alprazolam (0.25 mg) was given as a premedication a night prior to surgery. Preloading was done with Ringer lactate solution (10 ml/kg body weight). Routine monitoring including non-invasive blood pressure (NIBP), ECG, heart rate and pulse oximetry was done. All patients received supplemental oxygen via ventimask.

Under proper aseptic conditions, spinal anaesthesia was performed at the level of L3-L4 interspace in sitting position using a midline approach by a 25G Quincke spinal needle. The drug was injected slowly over 10-15 seconds with the bevel of the needle pointing upwards.

The intrathecal drug formula was prepared by a separate anaesthesiologist under strict aseptic conditions. The anaesthesiologist who administered anaesthesia was blinded to the group allocation. After administering anaesthesia the vital signs of the patient were recorded. Vitals were recorded every 2 minutes up to the 10^{th} minute and every 5 minutes thereafter up to 20 minutes. Beyond 20 minutes the vitals were recorded every 20 minutes till the time of discharge from PACU (Post Anaesthesia Care Unit).

The sensory dermatome level was assessed by cold alchohol swab along the mid clavicular line bilaterally.

The motor dermatome level was assessed according to the Bromage Scale.

Outcome measures

Following outcomes were recorded during the study:

- Highest dermatomal level of sensory blockade achieved.
- Time taken to reach the highest dermatomal level of sensory block.
- Time to reach up to bromage 3 motor block.
- Time taken for sensory regression to S2 level.
- Time taken for motor regression to bromage 0.
- Hemodynamic status of the patient.
- Sedation Score.
- Side effects if any.

STATISTICAL ANALYSIS

All the statistical analysis was performed by using SPSS version 22. The variousstatistical tests that were used in this study were analysis of variance (ANOVA) test, Post hoc test (Bonferroni test) and nonparametric tests like Mann whitney U test and kruskalwallis test.

For all statistical analysis p <0.05 was considered statistically significant. Data was compiled and statistical analysis was performed as explained above. The results and interpretations are explained below.

This table shows there is no significant in demographic characteristic between three groups (compared by ANOVA test) (Table-1).

Table-1: Demographic profile

	GROUP C (MEAN±SD)	GROUP A (MEAN±SD)	GROUP B (MEAN±SD)	P VALUE
Age in yrs	39.16±10.12	43.6±10.5	41.63±9.85	0.245
Weight in Kg	66.87±7.20	66±7.82	64.83±7.50	0.577
Height in cm	166.47±6.40	164.43±5.92	163.6±5.62	0.168
Duration of surgery	48±17.84	47.67±15.24	45.17±11.99	0.734

Table-2: shows mean blood pressure in each group and their statistical comparison

Time(min.)	GROUP C		GROUP A		GROUP B		ANOVA
	Mean	Sd	Mean	Sd	Mean	Sd	
Pre op	99.2	6.73	95.06	7.28	97.63	8.24	0.101
2	89.6	7.07	90.26	6.6	93.3	7.7	0.108
4	85.93	7.49	86.96	7.34	88.5	6.31	0.372
6	84.5	5.73	84.4	6.07	84.77	7.27	0.974
8	84.23	3.48	82.17	6.85	82.3	5.66	0.273
10	82.23	3.37	81.17	4.51	80.7	3.98	0.316
15	83.5	4.91	82.4	4.73	83.57	5.06	0.588
20	83.53	4.4	82.33	4.7	84.87	4.97	0.119
40	84.3	4.92	83.47	4.13	87	5.02	0.013
60	85.97	5	85	3.76	88.27	4.91	0.022
80	86.63	5.34	85.67	3.77	89.77	4.82	0.003
100	86.7	5.62	86.37	3.4	90.6	4.94	0.001
120	87.37	5.85	86.73	3.71	90.97	5.46	0.004
140	88	6.38	87.93	3.9	91.53	5.67	0.016
160	88.83	6.86	88.1	4.27	92.2	6.07	0.018
180	89.37	6.78	88.6	4.1	93.13	6.48	0.008
200	89.4	7.58	89.1	3.89	93.37	6.61	0.015
220	90.47	8.21	90.03	4.59	94.23	6.8	0.033
240	90.97	8.26	90.8	5.89	95.17	7.71	0.038
260	91.7	8.67	91.23	5.9	96.07	7.65	0.026
280	92.67	9.38	92.07	5.61	97	8.77	0.041
300	93.27	8.32	92.67	5.3	96.73	7.4	0.063

Fall in mean blood pressure in first 40 minutes was comparable in all three groups and was statistically not significant. After 40 minutes return of mean blood pressure to pre levels was faster in fentanyl group compared to other two groups and found to be statistically significant (Table-2).

Table-3: Time taken for sensory (s2 level) and motor (bromage 0) blockade regression and p values

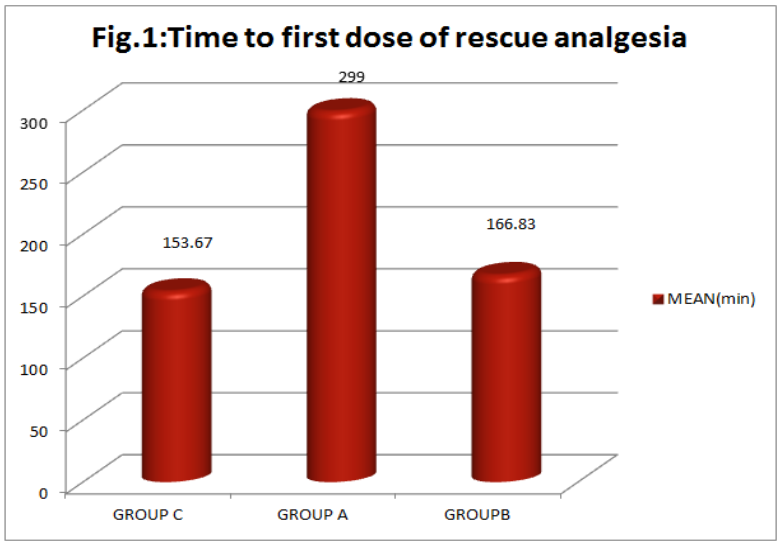
	GROUP C (MEAN±SD)	GROUP A (MEAN±SD)	GROUP B MEAN±SD)	P VALUE
Sensory regression	198.67±32.35	396.67±24.12	190.67±26.12	0.000
Motor regression	140.67±21.32	338±21.24	134±19.76	0.000

There is statistically significant difference between each of three groups with regards to the time taken to recover from sensory and motor blockade. (Compared by ANOVA test) (Table-3).

There is a statistically significant difference between each of three groups with regards to the time for first dose of rescue analgesia (Table-4).

Table-4: shows time to first dose of rescue analgesia and p values in the 3 groups

	GROUP C (MEAN±SD)	GROUP A (MEAN±SD)	GROUP B (MEAN±SD)	P VALUE
Rescue analgesia	153.67±27.88	299±33.92	166.83±20.66	0.000



DISCUSSION

The study was carried out to compare the efficacy of dexmedetomidine (5 µg) with fentanyl (25µg) when added to intrathecal hyperbaric bupivacaine for spinal anaesthesia. Both the drugs were evaluated with regard to sensory and motor blockade (duration and quality), hemodynamic stability and associated adverse effects.

The results of our study show that the supplementation of spinal bupivacaine with 5µg dexmedetomidine significantly prolonged both sensory and motor block compared with intrathecal 25 g fentanyl supplementation. Patients in the groups that received dexmedetomidine and fentanyl had reduced postoperative pain scores and a longer pain free period than those who received spinal bupivacaine (H) alone. No hemodynamic instability or adverse effects were reported in any group.

Demographic details of a patient hold its importance in influencing the characteristics of sub arachnoid block. Various patient characteristics like age, weight, height and sex may affect the intrathecal spread of drug solutions. Our study included 90 patients of ASA grade I or II, between 18-60 years of age, undergoing elective lower limb surgery. The sizes of all the three groups were similar (30 patients each). In our study all the three groups were comparable with respect to age, weight, and height, male: female ratio, ASA I: ASA II ratio. No statistically significant difference was found amongst the three groups. Studies conducted in the past for evaluating efficacy of fentanyl and dexmedetomidine as intrathecal adjuvants also had demographic data comparable for age, gender, height and weight of the patients[8-10], similar to our study.

Time taken to achieve peak level of sensory and motor blockade was compared among all groups. These findings were in concordance with the results of Al Ghanem *et al.* [8]. Whose study was to evaluate the effect of addition of 5 µg dexmedetomidine or 25 µg fentanyl intrathecally to 10 mg isobaric bupivacaine in vaginal hysterectomy and found that the time to reach the maximal sensory block was 19.34 ± 2.87 min. for dexmedetomidine group and 18.39 ± 2.46 min. for fentanyl group? Results were statistically not

significant (p = 0.126). In our study the time taken to achieve the highest dermatomal level of sensory block were 10.4 ± 4.013 minutes in group C, 9.33 ± 3.506 minutes in group A and 10.66 ± 3.651 minutes in group B. The results were comparable and statistically not significant (p=0.346).

Fyneface-Ogan *et al.* [15] and Eid *et al.* [16] in their respective studies to evaluate dexmedetomidine (in different doses) as intrathecal adjuvant found no significant difference in achieving the highest level of sensory block. In our study the highest dermatomal level of sensory blockade achieved were T4 in group C, T4 in group A and T5 in group B. Intergroup analysis showed a statistically significant difference in the highest level of sensory blockade amongst group A and B(p = 0.004). Thus, dexmedetomidine group achieved higher levels of blockade compared to fentanyl group.

All patients in our study demonstrated motor blockade of grade 3 as per bromage scale. Intergroup comparison was found to be statistically insignificant. These findings were consistent with previous studies [8-10].

Al Ghanem *et al.* [8] observed that the onset time of bromage 3 motor block was also not different between dexmedetomidine and fentanyl group; 14.4+6.7 and 14.3+5.7 minutes respectively (p= 0.93). Similarly, in our study the time taken to achieve peak motor blockade was 7.7 ± 2.215 minutes in group C, 8.56 ± 2.635 minutes in group A and 9.06 ± 2.790 minutes in group B. No statistically significant difference was seen amongst all the three groups (p=0.118).

In our study, the time taken for sensory blockade regression to S2 level was 198.66 ± 32.348 minutes in group C, 396.66 ± 24.116 minutes in group A and 190.66 ± 26.120 minutes in group B which is statistically significant (p<0.001). This result correlate with the study done by Al Ghanem *et al.* [8], the time to regression of sensory block to S1 segment was significantly longer in group A (274.8+73.4 min.) than in group B (179.5+47.4 min.) (p < 0.001).

Al Ghanem *et al.* [8] observed that the regression time to reach bromage 0 in dexmedetomidine group (240+64 min) was significantly longer than that for fentanyl group (155+46 min) (p<0.001).In our study, the time taken for motor blockade regression to bromage 0 was 140.66 ± 21.323 minutes in group C, 338 ± 21.237 minutes in group A and 134 ± 19.757 minutes in group B(p=0.000).

Thus, in our study, dexmedetomidine group showed a statistically significant prolongation of both sensory and motor regression when compared to fentanyl and hyperbaric bupivacaine alone group.

In our study the mean duration of surgery was 48 ± 17.840 minutes for group C, 47.66 ± 15.241 minutes for group A and 45.16 ± 11.997 minutes for group B. No statistically significant difference was found amongst the three groups. Al Ghanem *et al.* [8] study had duration of surgery of 51.6 ± 26.8 minutes in dexmedetomidine group and 59.0 ± 25.7 minutes in fentanyl group. Both the group were comparable.

Eid MD *et al.* [17] concluded that 10 µg and 15 µg dexmedetomidine as adjuvant, increased the duration of analgesia provided by spinal bupivacaine, to 240 and 520 minutes respectively. In our study the time to first dose of analgesic requirement was 153.66 ± 27.883 minutes in group C, 299 ± 33.921 minutes in group A and 166 ± 20.656 minutes in group B. Thus, the dexmedetomidine group showed prolongation of analgesia following subarachnoid block which was statistically significant in comparison to other two groups. Our study supports clinical evidence suggesting that α2-adrenergic agonist enhances analgesia when used intrathecally with hyperbaric bupivacaine [18]. In our study fentanyl group also prolonged the duration of analgesia in comparison to hyperbaric bupivacaine alone group but it was not statistically significant.

Al-Mustafa M M *et al.* [9] studied the effect of adding different doses of dexmedetomidine (5µg or 10µg) to bupivacaine (12.5mg) for neuraxial anaesthesia. They observed a maximum sedation score of 2 without pre-medicating their patients with any type of benzodiazepines in both the groups. Eid *et al.* [16] observed that 15 µg intrathecal dose of dexmedetomidine resulted in significantly higher mean sedation score of 4. This can be beneficial for patients undergoing lengthy complex surgeries as an alternative to epidural or prolonged general anesthetics and can preclude the use of IV sedatives. However, such high sedation scores may be harmful in elderly and high risk surgical patients owing to the risk associated with excessive sedation and respiratory depression. In our study, the highest sedation score achieved was 2 in all the three groups. The mean sedation was 1.354 ± 0.073, 1.504 ± 0.095, 1.437 ± 0.083 in groups C, group A and group B respectively. Thus, dexmedetomidine group achieved the highest mean sedation score in comparison to other two groups and was found to be statistically significant.

Eid Md *et al.* [16] found no statistically significant difference in mean heart rate when 10 µg or 15 µg Dexmedetomidine was added to bupivacaine. Similarly, in our study the mean heart rate was comparable in all the three groups and found to be statistically insignificant.

In our study the mean blood pressure in the post-operative period, was found to be slightly lower in dexmedetomidine and heavy bupivacaine alone group when compared to the fentanyl group. This was found to be statistically significant. Kanazi *et al*. [10] noted that dexmedetomidine or clonidine when added to intrathecal bupivacaine did not cause a significant reduction in blood pressure.

The most significant side effects reported about the use of intrathecal α2 adrenoreceptor agonists are bradycardia and hypotension [19].

Fyneface-Ogan *et al.* [20] observed mild hypotension in all their study groups that was corrected with fluid administration. Mild bradycardia was also observed in all the groups. One (3.33%) patient in group B, 2 (6.67%) patients in group BF, and 1 (3.33%) patient in group BD had mild bradycardia that was transient. In our study, hypotension was the commonest side effect observed and was more in bupivacaine alone group but intergroup comparison was statistically not significant($p>0.05$).

Bradycardia was seen in total of 9 patients in our study and was more in dexmedetomidine group (4 patients) compared to fentanyl and bupivacaine (H) alone group each but it was transient and did not require any intervention. There was no statistically significant difference noted amongst the three groups.

Urinary retention was seen in 3 patients in dexmedetomidine group compared to one patient each in the other two groups but it was statistically not significant ($p>0.05$).

Nausea and vomiting was highest in bupivacaine (H) alone group followed by fentanyl group and least in dexmedetomidine group. It was also not statistically significant on analysis ($p>0.05$).

The administration of intrathecal opoids may provide benefits in augmenting intra operative anaesthesia but carries a risk of respiratory depression. Varassi et al[21] demonstrated that intrathecal administration of fentanyl 25 micrograms in non premedicated geriatric patients did not alter respiratory rate, ETCO2, minute ventilation, respiratory drive and ventilator response to CO2. On the contrary, 50µg intrathecal fentanyl can cause an early respiratory depression in geriatric patients. In our study none of the groups showed any effect on respiratory rate or any decrease in O2 saturation.

Pruritis is a common adverse effect in patients receiving opoids. Hunt *et al*. [6] observed a significant increase in the overall incidence of pruritis in patients who received 50µg intrathecal fentanyl compared to the ones who received 25µg fentanyl. In our study, 2 patients from the fentanyl group experienced itching as compared to one patient in the hyperbaric bupivacaine alone group. The dexmedetomidine group was devoid of any incidence of pruritis. Statistically the results were comparable ($p>0.05$).

The α2 adrenergic agents also have antishivering property as observed by Talke *et al*. [22], We observed the incidence of shivering was least in the dexmedetomidine group compared to the other two groups. However, all the groups were statistically comparable ($p>0.05$).

CONCLUSION

In conclusion, dexmedetomidine (5mcg) seems to be a better alternative to fentanyl (25mcg) as additive to intrathecal hyperbaric bupivacaine (15mg) since it produces more prolonged sensory and motor block with similar kind of haemodynamic stability, better post-operative analgesia and sedation and is associated with less adverse effects. This kind of block may be more suitable for lower limb orthopaedic surgeries of longer duration. Intrathecal does of dexmedetomidine used in the present study need further clinical studies to prove its efficacy and safety and to be considered as the suitable dose of dexmedetomidine for supplementation of spinal local anaesthesia.

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