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Intravenous Dexmedetomidine and Butorphanol Prolongs Bupivacaine Sensory Analgesia in Lower Abdominal Surgeries.

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Abstract:
Background:*To compare the effects of intra-thecal bupivacaine alone, with dexmedetomidine and butorphanol administered by intravenous route as adjuvant to intra-thecal bupivacaine separately.*
Methods:*The randomized, double blind comparative study was conducted in 60 patientsbelonging to ASA grade I or II, aged 18-55 years admitted for lower abdominal surgeries under spinal anesthesia. The patients were randomly divided into 3 groups (n=20). All patients were administered 15mg of 0.5% bupivacaine for spinal anesthesia. Group(B) was given spinal anesthesia alone. Group(B+D) was given DXM(1μg/kg) IV, group(B+B) was givenbutorphanol(20μg/kg) IVas an adjuvant to intra-thecal bupivacaine.*
Results:*The mean time to reachmaximum sensory level was highest in Group(B) and least in (B+D).Total duration of analgesia was almost similar in DXM and butorphanol group and least in the control group. No. of rescue analgesic required was significantly lower in DXM group than the rest of the groups. VAS score was highest in the control group(B) while it was almost similar in DXM and butorphanol group.*
Conclusion: *IV dexmedetomidine and butorphanol can prolong the duration of sensory block, time to first analgesic request associated with spinal anesthesia and provide better postoperative analgesia than the group in which no intravenous adjuvants are used.*
Keywords:*spinal anesthesia, dexmedetomidine, butorphanol, bupivacaine.*

I. Introduction

Because of the technical challenges of readily identifying the epidural space and the toxicity associated with the large doses of local anesthetics needed for epidural anesthesia, spinal anesthesiais still dominant form of neuraxial anesthesia.[1] Role of intrathecal DEX and butorphanol in prolonging the spinal analgesia and anesthesia had been very well studied separately. This study was conducted to compare the effects of intrathecal bupivacaine alone, with DXM and butorphanol when administered by intravenous route as adjunct to intrathecal bupivacaine.

II. Material And Methods

After getting approval from Institutional Ethical Committee, the current randomized, double blind, prospective, comparative study was conducted in 60 patients, aged 18-55 of years belonging to ASA grade I or II,scheduled for lower abdominal surgery under spinal anesthesia. An informed consent was taken from all the patients and/or attendants.Patient'srefusals for consent,having contraindication to neuraxial blockade or allergy to study drugs were excluded from the study.A computer-generated randomization list was used to assigned patients into the three groups. The intravenous drug formula was prepared by an anesthetist doctor and was passed on to the doctor who performed the spinal analgesia who was blinded as to which group the patient was allocated.

Group(B): spinal anesthesia with hyperbaric bupivacaine15mg (3ml of 0.5%)+intravenous infusion of 100 ml of NS over 10 min. This served as control group.

Group(B+D): spinal anesthesia with hyperbaric bupivacaine 15mg (3ml of 0.5%)+DXM 1μg/kg infused intravenously in 100 ml of NS over 10 min.

Group(B+B):spinal anesthesia with hyperbaric bupivacaine 15mg (3ml of 0.5%)+ butorphanol 20μg/kg infused intravenously in 100 ml of NS over 10 min.

All patients were pre-medicated, a night before surgery with ranitidine 150 mg and alprazolam 0.25mg orally. In the operation theatre, standard monitoring was attached and all patients were preloaded with 10ml/kg of Ringer Lactate.

Spinal anesthesia was given using aseptic techniques in the sitting position at L_4-L_5 interspace via midline approach using 25-G Quincke needle with3 ml of 0.5% hyperbaric bupivacaine. Patient was thenlaid in supine position and operation table was kept flat with pillow under the head. Immediately after resuming supine position, patients in Group(B) received IV infusion of 100 ml NS, Group(B+D) received IV infusion of DXM diluted in 100 ml NS and Group(B+B) received butorphanol diluted in 100 ml NS. Infusion was given over 15mins in all the groups.

Heart rate, non-invasive arterial blood pressure and SpO_2 were recorded in all three groups preoperatively, intraoperatively and during shifting. Hypotension has been defined as systolic blood pressure <90 mmHg or >30% decrease in baseline values and was treated with fluids boluses and injection mephentermine 6mg IV. Tachycardia has been defined as heart rate >100/min and bradycardia has been defined as heart rate <60/min and was treated with injection atropine 0.6 mg IV.

Sensory block was assessed by response to pin prick in mid-clavicular line bilaterally using a 20-G hypodermic needle every two minutesinterval until the maximal level of sensory anesthesia is achieved and at 5 min interval thereafter. The time to reach the maximum level of sensory block and time for regression of two segments in the maximum block height was noted.

The time for first analgesic requirement postoperatively or the time when the patient perceived pain for the first time following spinal anesthesia was noted. Pain was assessed using VAS (visual analogue scale) hourly for 24 hours.Duration of analgesia was defined as time from administration of subarachnoid block until the first complaint of pain (VAS ≥4). Total number of rescue analgesia given was noted for 24 hours. Rescue analgesia was given with paracetamol 10 mg/kg IV. Complications such as hypotension, bradycardia, nausea, vomiting, shivering, and headache were noted and treated accordingly. An anesthesiologist, who was blinded to the study drug used, documented all the parameters.

Statistical Analysis

Continuous data were summarized as Mean±SD while discrete (categorical) in %. The outcome measures(pulse rate, systolic BP, diastolic BP, SpO_2, sedation score and VAS score) of three groups over the periods(time) were compared by repeated measures two factor (Groups x Periods) analysis of variance (ANOVA).Groups were also compared by one way ANOVA followed by Tukey's post hoc test. The categorical variables were compared by chi-square (χ^2) test. A two-sided (α=2) $p<0.05$ was considered statistically significant. All analyses were performed on SPSS 16.

III. Results

The basic characteristics viz. age, gender, weight, height and ASA grade of the groups at admission were found to be similar [Table 1]. Thus these variables did not affect the outcome of the study.The mean baseline values of PR, SBP, DBP, RR and SpO_2were recorded.The summary of sensory blockade and two segment regression time is depicted in Table 2. Comparing the proportion of sensory blockade level and mean time between the three groups ANOVA revealed significantly different sensory blockade level ($F=4.537, p=0.015$) and time ($p<0.05$), respectively among the groups. Further, Tukey test was not significantly differed ($p>0.05$) within group except B vs. B+D ($p<0.01$). Two segment regression time was 131.65±51.38 min. in group (B), 211.00±58.66 min. in group(B+D) and 181.60±30.61min. In group(B+B), there was significant difference ($F=13.753$, $p<0.001$). Further, Tukeytest also revealed significant ($p<0.01$) difference within groups except (B+D) vs. (B+B) group which did not significantly differ ($p=0.04$).

Pain and analgesic usage summary (Mean±SD) of three groups are depicted in Table 3.The pain levels(VAS score) over 24 hrs. was 2.6 ± 0.197 in group(B), 1.46 ± 0.58 in group(B+D) and 1.38 ± 0.54 in group(B+B), there was significant difference ($F=42.203, p<0.001$)). Patients receiving DEX and butorphanol had lower VAS ($p=0.854$) at all observed time compared to control group.1st Time requirement of analgesic was 193.70±72.86 in group (B), 306.50±57.70 in group (B+D) and 288.00±76.20 in group(B+B), there was significant difference ($p<0.001$). Further, Tukey test also revealed significant ($p<0.05$) difference within groups except (B+D) vs. (B+B) group, which do not differed significantly ($p=0.678$).Use of analgesic was maximum in group receiving only bupivacaine and similar in group(B+D) and (B+B) ($p=0.09$).

The frequency distributions of complications among three groups are summarized in Table 4/Fig. 1. The complications such as hypotension, bradycardia, nausea and shivering were present in all three groups. The intraoperative systolic blood pressure, diastolic blood pressure and heart rate for the study groups are presented in Fig. 2, 3 & 4. Hypotension and shivering were higher in (B) group while bradycardia and nausea was higher in (B+D) group. Comparing the proportion of each complication between the three groups, χ^2 test revealed

similar (p>0.05) proportion of complications among the groups except shivering, which was found significantly (p 0.001) higher in (B) group as compared to both (B+D) and (B+B) groups.

IV. Discussion

Dexmedetomidine (DXM) is a highly selective α_2-adrenoceptor agonist. Small doses of DXM used in combination with bupivacaine in humans for spinal anesthesia has been shown to produce a shorter onset and a prolongation in the duration of sensory block with preserved hemodynamic stability and lack of sedation.[2]DXM has been used for premedication and as an adjunct to general anesthesia.[3],[4],[5]Butorphanol tartrate is a synthetic opioid partial agonist analgesic. Most of the observed behavioral, pharmacological, and therapeutic effects appear due to its lower efficacy agonist actions at μ opioid receptors. Abboud et al. have reported that epidural butorphanol cause dose dependent increase in duration of analgesia for relief of post cesarean pain.[6]There have been studies which observed the effects of various intravenous anesthetic agents on the characterstics of subarachnoid block produced by hyperbaric or isobaric bupivacaine.In one comparative study theintravenous midazolam and DXM have been shown to increase the duration and height of sensory block.[7]In few recent studies DXM has been studied separately as intravenous adjunct to intrathecal bupivacainebut there is no study for intravenous butorphanol as an adjunct to intrathecalbupivacaine. It has been mostly used for post-operative analgesia; its intraoperative role has been studied in our study. Our study not only compared the role of intravenousDXM and butorphanol in lower abdominal surgeries, it also gave us an idea about their individual performance separately.Alpha 2 receptors are found in the peripheral and central nervous systems, platelets, and many other organs, including the liver, pancreas, kidney, and eye. Stimulation of the receptors in the brain and spinal cord inhibits neuronal firing, causing hypotension, bradycardia, sedation, and analgesia.The analgesic effect primarily results from the inhibition of locus ceruleus at the brain stem. In addition, dexmedetomidine infusion may result in increased activation of alpha-2 receptors at the spinal cord resulting in inhibition of nociceptive impulse transmission. Intravenous DXM alone have been shown to increase the duration of sensory and motor block of isobaric bupivacaine.[8,9,10] The dose of DXM used to prolong the effect of intrathecal bupivacaine varies between 0.25 μg/kg to 1 μg/kg. Although, 0.25 μg/kg of intravenous DXM has been found effective in exaggerating the effects of intrathecal bupivacine, we used single bolus of DXM(1μg/kg) as it is recommended loading dose.[11]In most of the studies, DXM infusion used as a loading dose followed by an infusion has been found to prolong the duration of analgesia and motor blockade. Butorphanol, 20-40μg/kg i.v. was comparable or preferable to fentanyl 1-2 μg/kg i.v. as a supplement to balanced anesthesia in most studies.[12]Butorphanol is used in the treatment of moderate to severe pain associated with as orthopedic issues, burns, renal colic, and surgical. Groups receiving butorphanol as a part of balanced anesthesia were reported to be satisfied with their anesthetic experience, require less post-operative analgesiaand also reported postoperative drowsiness and sedation.[13]Due to the extensive hepatic metabolism of butorphanol, oral bioavailability is approximately 5 to 17%. Peak plasma concentrations of 1.5 ng/mL butorphanol occur almost immediately after a single 1mg i.v. administration.

Apparent plasma half-lives of butorphanol were between 6 and 10 hours.[14]Intrathecal butorphanol potentiates bupivacaine-induced sensory spinal block and reduces the analgesic requirement in the early post-operative period without prolonging motor block recovery time.[15]In our study, in all the three groups, the mean time to reach maximum sensory level was highest in control group followed by butorphanol group and DXM group with the least. Thus it is evident that both adjuncts were efficacious in decreasing onset of sensory blockade with DXM more effective. In our study, VAS score was significantly different among all groups. It was highest in the control group than the DXM and butorphanol group. Studies have showed that i.v DXM can prolong time to first analgesic request associated with spinal anesthesia.[16] In butorphanol also the time for requirement of first analgesia was prolonged compared to control group. Similarly, epidural, intravenous, or intramuscular butorphanol can prolong analgesia of other agents and reduce opioid-induced nausea and pruritus.

The analgesic effect of butorphanol is influenced by the route of administration. Onset of analgesia is within a few minutes for intravenous administration and within 15 minutes for intramuscular injection.[17] Both showed almost similar time for requirement of first analgesia. No. of rescue analgesia was significantly lowered in DXM and butorphanol than the control group.DXM also provides intense analgesia during the postoperative period. In one study, by Venn RM et al, the postoperative analgesic requirements were reduced by 50% in cardiac patients and the need for rescue midazolam for sedation was diminished by 80%.[18]In our study as we used loading of 1microgm/kg DXM only and found more prolonged two segment regression time (211.00±58.6min) than the study using continuous infusion.[10] Thus, we found that both the drugs significantly delay sensory emergence.

V. Conclusion

Overall DXM is equipotent to butorphanol in prolongation of sensory analgesia and provide better post operative analgesia than the group in which no intravenous adjuvant is used.

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Table 1: Basic characteristics of three groups.

Characteristics	Group (B) (n=20)	Group (B+D) (n=20)	Group (B+B) (n=20)	p value
Age (yrs)	39.5 ± 12.09	40.75 ± 9.43	44.15 ±10.99	0.477
Sex:Males Females	14 (70%) 6 (30%)	9 (45%) 11 (55%)	12 (60.0%) 8 (40%)	0.282
Height (cm)	157.00 ± 40.51	160.95 ± 8.81	156.90 ±4.53	0.075
Weight (kg)	60.7 ± 6.39	60.8 ± 6.96	61.60 ± 6.90	0.899
ASA I II	15 (75%) 5 (25%)	15 (75%) 5 (20%)	16 (80%) 4 (20%)	0.915

Table 2: Summary of sensory blockade and two segment regression time.

Sensory Blockade	Group (B) (n=20)	Group (B+D) (n=20)	Group (B+B) (n=20)	P Value
Levels: T4 T6 T7 T8 T10	 3 6 1 3 7	 1 10 0 9 0	 1 11 1 7 0	 p<0.05
Time (min)	8.25±3.45	6.10±1.65	6.50±1.64	p<0.05
Two segment regression time (min)	131.65±51.38	211.00±58.66	181.60±30.61	p<0.001

Table 3:Pain and analgesic usage summary (Mean±SD) ofthreegroups.

	Group (B)	Group (B+D)	Group (B+B)	P Value
VAS Score	2.6±0.197	1.46±0.58	1.38±0.54	p<0.001
1st Time requirement of Analgesic (min)	193.70±72.86	306.50±57.70	288.00±76.20	p<0.001
Rescue Analgesia (no.)	3.8±1.20	2.4±0.88	2.55±1.15	p<0.001

Table 4: Frequency distribution of complications of three groups.

Complications	(B) (n=20)	(B+D) (n=20)	(B+B) (n=20)	PValue
Hypotension	3 (15.0%)	1 (5.0%)	1 (5.0%)	0.129
Bradycardia	4 (20.0%)	8 (40.0%)	3 (15.0%)	0.372
Nausea	2 (20.0%)	4 (20.0%)	1 (5.0%)	0.585
Vomiting	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.200
Shivering	6 (30.0%)	1 (5.0%)	2 (10.0%)	0.001

Fig.1: Frequency distribution of Complicationsamong three groups.

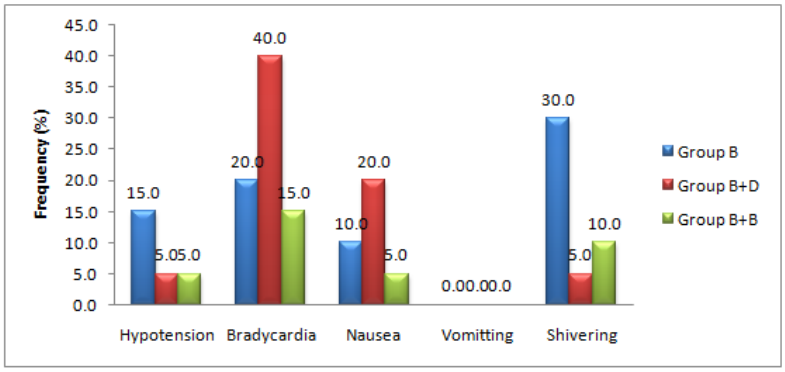

Fig.2: Mean SBP of three groups over the periods.

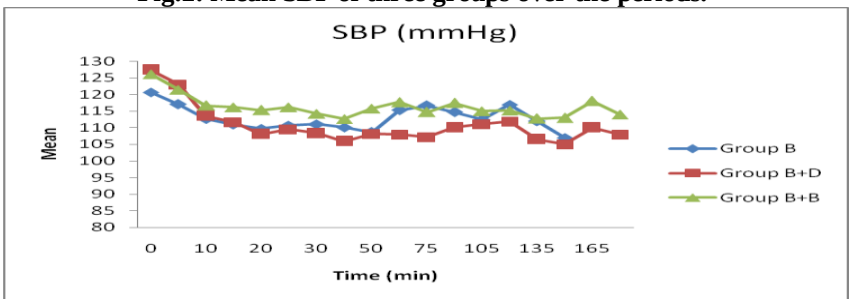

Fig.3: Mean DBP of three groups over the periods.

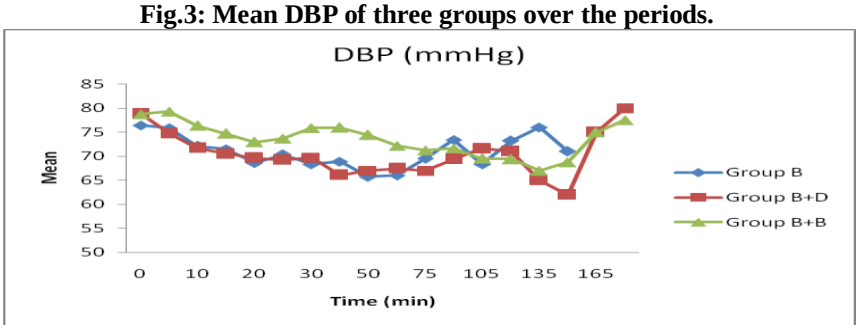

Fig.4: Comparative pulse rate of three groups.