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Comparative Evaluation Among Intrathecal Dexmedetomidine, Clonidine, Midazolam As Adjuvant To Isobaric Ropivacaine In Subarachnoid Block For Lower Limb And Lower Abdominal Surgeries

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Abstract
Background and Objectives: *"Effect of intrathecal dexmedetomidine, clonidine, midazolam as adjuvant to isobaric ropivacaine in subarachnoid block for lower limb and lower abdominal surgeries. The objective was to assess the effect of dexmedetomidine 20 mcg, clonidine 30mcg and midazolam 1mg as an adjunct to isobaric ropivacaine in spinal anesthesia.*
Materials and Methods: *One hundred twenty selected patients were randomized to receive intrathecal 0.75% isobaric ropivacaine 3ml with clonidine 30mcg, dexmedetomidine 20mcg and midazolam 1mg in spinal anesthesia for lower limb & lower abdominal surgeries. Block characteristics, hemodynamic changes, postoperative analgesia and adverse effects were compared.*
Results: *Supplementation of ropivacaine with dexmedetomidine significantly prolong the duration of sensory and motor blockade in intraoperative period as compared to intrathecal ropivacaine with clonidine and intrathecal ropivacaine with midazolam, and hence, provided effective potentiation of analgesia. The haemodynamic parameters and SpO2 were comparable with minimal changes in all the groups*
Conclusion: *We conclude that dexmedetomidine when added to ropivacaine as an adjuvant is superior to clonidine and midazolam.*

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I. Introduction

After lower limb surgeries most patients require parenteral or oral opioids and/or non-steroidal anti-inflammatory drugs (NSAIDs) for analgesia. However, they provide unreliable postoperative analgesia and have more systemic adverse effects. The use of additives in intrathecal or epidural anaesthesia has become popular to optimize postoperative analgesia.

Spinal anaesthesia is a form of neuraxial regional anaesthesia in which local anaesthetic is placed directly in the intrathecal space (subarachnoid space), is a widely used technique providing faster onset with effective and uniformly distributed sensory and motor block. It is the most common anaesthesia technique used to conduct lower limb surgeries and lower abdominal surgeries among all methods.

Dexmedetomidine, 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[1, 2]. Clonidine is an α 2 -agonist that is commonly used for its antihypertensive. In general, clonidine seems to decrease anaesthetic requirements and provides sedation and anxiolysis. Midazolam is used for its sedative, anxiolytic, and amnesic effects [3,4]. Intrathecal midazolam produces antinociception and potentiates the effect of local anaesthetics. Ropivacaine is a long-acting amide local anaesthetic agent. It produces effects similar to other local anaesthetics via reversible inhibition of sodium ion influx in nerve fibres. Ropivacaine has a greater degree of motor sensory differentiation, which is useful when motor blockade is undesirable. It also has high threshold for CNS toxicity than bupivacaine.

After an extensive review of literature, there was no study found ropivacaine with 20mcg dexmedetomidine and there was no study with ropivacaine and midazolam so it has been done in this study.

II. Materials And Methods

After approval from the institutional ethical committee, a written informed consent was obtained from all patients and randomized, double blind, prospective clinical study was carried out on 120 patients. Patients included for the study were the American Society of Anesthesiologists (ASA) physical status Class I or II, of

either sex (18–60 years) presenting for elective lower limb or lower abdominal surgeries. Patients who had contraindications to spinal anaesthesia, allergy to the drug, were excluded from the study groups. On arrival in the operation theatre, after intravenous access patient were pre-loaded with ringer lactate solution infusion with 10mL/kg body weight and monitors for baseline non-invasive blood pressure, electrocardiogram, heart rate and pulse oximetry were connected and parameters were recorded pre operatively. Under all aseptic precaution, at the level of L3–L4 intervertebral space spinal anaesthesia was administered in sitting position using midline approach by 25-gauge Quincke spinal needle. Patients were made supine after the block.

Cases were divided into three equal groups (40 each) by using computer generated randomization table method.

- **Group BC** –received intrathecal isobaric ropivacaine0.75% (3 ml) + clonidine 30μg (0.2ml).
- **Group BD**– received intrathecal isobaric ropivacaine 0.75% (3 ml) + Dexmedetomidine 20μg (0.2ml).
- **Group BM** – received intrathecal isobaric ropivacaine 0.75% (3 ml) + Midazolam 1mg (0.2ml).

The following parameters were observed-

- Onset and duration of sensory blockade
- Onset and duration of motor blockade
- Haemodynamic changes
- Two segment regression
- Duration of analgesia
- Complications/side effect (if any)

Anaesthesiologist who performed the block and did an assessment of the block was different from one who prepared the drugs. The surgeons were blinded to the patient groups.

Sensory and motor block were monitored at 0, 1, 3, 5, 10, 15, 30, 45, 60, 90, 120, 180 minutes. The onset of sensory block was defined as the time between injection of intrathecal anaesthetic agent and the absence of pain at the T10 dermatome assessed by sterile pin prick. The duration of motor block was defined as the time interval between the end of spinal anaesthetic administration and the recovery of complete motor function.

Intra- and post-operatively, pain scores were recorded using visual analog scale (VAS) between 0 and 10 (0 = no pain, 10 = the most severe pain). The duration of analgesia was defined as the period from spinal injection to the first rescue analgesia given in the postoperative period and first rescue analgesia given when VAS >3. All durations were calculated considering the time of spinal injection as time zero. Intraoperative hemodynamic vital parameters of heart rate, respiratory rate, and oxygen saturation of the patient were recorded at 0, 1, 3, 5, 10, 15, 30, 45, 60, 90, 120, 180 minutes.

The rescue analgesia was given in the form of injection Paracetamol (1gm) IV infusion at when VAS >3 and the time of administration will be recorded. All the patients were observed for any side-effects like nausea, vomiting, dryness of mouth, pruritus, respiratory depression, fall in oxygen saturation, hypotension, bradycardia and urinary retention or any other adverse effect and were managed according to clinical protocol in the intra and post operative periods. Hypotension was defined as a fall in systolic blood pressure > 30% of the baseline value or systolic blood pressure <100 mm Hg and was given intravenous boluses of crystalloid fluids and 6 mg ephedrine with Oxygen via venti mask. Bradycardia was defined as a pulse rate of <60 beat/ min and was treated with bolus of 0.6 mg atropine. Nausea/vomiting was treated by giving inj. Ondansetron.

Statical analysis was done using a SPSS 22 version software. Categorical data was represented in the form of frequencies and proportions. Continuous data was represented as mean and standard deviation. Association between the categorical variable were tested using chi square test. Mean difference among the groups were assessed by applying the one-way ANOVA and post –hoc test. 'p' value< 0.05 was considered significant.

III. OBSERVATION AND RESULTS

Demographic Data

Table no. 1: Gender, Age, Height, Weight Distribution (Mean±SD) of the Patients:

The distribution of patients with respect to age, height, weight & gender was comparable in all three groups (p value > 0.05) which was statistically non-significant.

Demographic Data	Group BD	Group BC	Group BM	F Value#	P value
Gender(male/female) (M/F)(n%)	M-20 (50.0) F-20 (50.0)	M-19 (47.5) F-21 (52.5)	M-20 (50) F-20 (50)	0.067	0.967
Age (years)	41.0±11.71	43.10±14.42	43.75±11.87	0.510	0.602
Weight (kg)	65.28±6.40	63.60±6.47	66.63±7.55	1.972	0.114
Height (cm)	172.15±8.48	170.48±8.87	172.73±9.59	0.676	0.510

One way ANOVA test was applied

Table no. 2: American Society of Anaesthesia (ASA) Grade Distribution:
The distribution of patients with respect to ASA grading was comparable in all the groups (p value > 0.05).

ASA Grading	Group BD	Group BC	Group BM	2 Value	P value
	n (%)	n (%)	n (%)		
I	24 (60.0)	26 (65.0)	26 (65.0)	0.287	0.866
II	16 (40.0)	14 (35.0)	14 (35.0)		

Table no. 3: Onset of Sensory Block:
The mean duration of **onset of sensory block** in group BM (3.335±1.07 minutes) and group BD (3.55±1.01 minutes) were shorter when compared to groups BC (3.90±0.98 minutes). The difference of which was statistically significant (p value < 0.05).

Sensory Block	Group BD	Group BC	Group BM	F Value#	P value
Onset (in min) Mean±SD	3.55±1.01	3.90±0.98	3.33±1.07	3.21	0.04

One way ANOVA test was applied

Onset of Sensory Block Pairwise Comparison After Applying the Post Hoc Test				
Sensory Block	**Group BC**	**Group BM**	**Mean Difference**	**P value**
Onset (in min) Mean±SD	3.90±0.98	3.33±1.07	0.575	0.03

Table no. 4: Onset of Motor Blockade:
The mean duration of **onset of motor block** was shortest in group BM (5.43±1.39 minutes) followed by group BD (5.98±1.53 minutes) and longest in group BC (6.83±1.57 minutes). The difference of which was statistically significant (p value < 0.05).

Motor Blockade	Group BD	Group BC	Group BM	F Value#	P value
Onset (in min) Mean±SD	5.98±1.53	6.83±1.57	5.43±1.39	8.87	<0.01

One way ANOVA test was applied

Onset of Motor Blockade Pairwise Comparison After Applying the Post Hoc Test		
Motor Blockade Onset (in min)	**Mean Difference**	**P value**
Group BD vs Group BC	0.850	0.03
Group BC vs Group BM	1.400	<0.01

Table no. 5: Duration of Sensory Block:
The **Mean duration of sensory blockade** is longest in group BD (338.15±17.34 minutes) followed by group BC (312.73±9.3minutes) and shortest in group BM (263.85±18.41minutes). The difference of which was statistically significant (p value < 0.05).

Sensory Block	Group BD	Group BC	Group BM	F Value#	P value
Duration (in min) Mean±SD	338.15±17.34	312.73±9.3	263.85±18.41	235.293	<0.01

One way ANOVA test was applied

Duration of Sensory Block Pairwise Comparison After Applying the Post Hoc Test		
Sensory Block Duration (in min)	**Mean Difference**	**P value**
Group BD vs Group BC	25.42	<0.01
Group BD vs Group BM	74.30	<0.01
Group BC vs Group BM	48.87	<0.01

Table no. 6: Duration of Motor Blockade:
The mean duration of motor blockade is longest in group BD (263.78±41.99 minutes) followed by group BC (255.18±18.67 minutes) and longest in group BM (198.78±20.01). The difference of which is statistically significant (p value < 0.05).

Duration of Motor Blockade	Group BD	Group BC	Group BM	F Value#	P value
Duration (in min) Mean±SD	263.78±41.99	255.18±18.67	198.78±20.01	59.55	<0.01

One way ANOVA test was applied

Duration of Motor Blockade Pairwise Comparison After Applying the Post Hoc Test (Tukey HSD test)		
Motor Block Duration (in min)	**Mean Difference**	**P value**
Group BD vs Group BM	65.00	<0.01
Group BC vs Group BM	56.40	<0.01

Table no. 7: Total Duration of Analgesia:
The **mean duration of analgesia** in group BD was 419.43±11.70 minutes, group BC was 364.43±13.25 minutes and in group BM was 338.60±19 minutes which shows statistically significant prolongation of duration of analgesia in group BD ($p<0.05$) as compared to group BC and group BM.

Total Duration of Analgesia	**Group BD**	**Group BC**	**Group BM**	**F Value#**	**P value**
Duration (in min) Mean±SD	419.43±11.70	364.43±13.25	338.60±19	302.766	<0.01

One way ANOVA test was applied

Total Duration of Analgesia Pairwise Comparison After Applying the Post Hoc Test (Tukey HSD test)		
Total Duration of Analgesia Duration (in min)	**Mean Difference**	**P value**
Group BD vs Group BC	55.00	<0.01
Group BD vs Group BM	80.85	<0.01
Group BC vs Group BM	25.82	<0.01

Table no. 8: Two Segment Regression:
Intra operatively & post operatively difference in two segment regression was observed between all three groups (p value > 0.05) which was statistically not significant.

Two Segment Regression	**Group BD**	**Group BC**	**Group BM**	**F Value#**	**P value**
Mean±SD	147.40±7.02	145.33±6.77	144.15±4.59	2.80	0.06

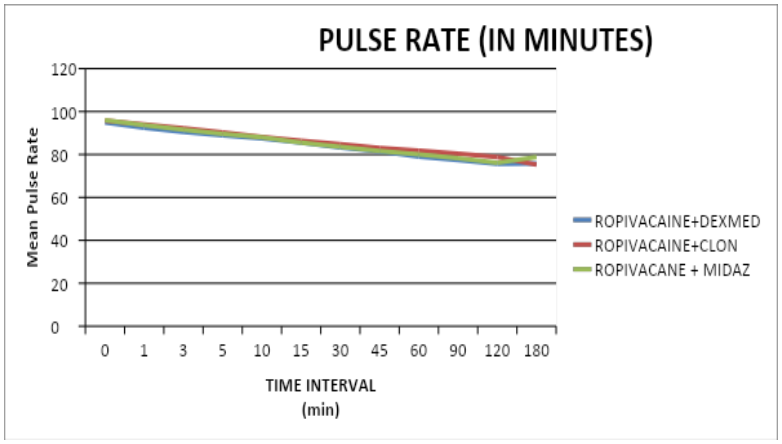
One way ANOVA test was applied

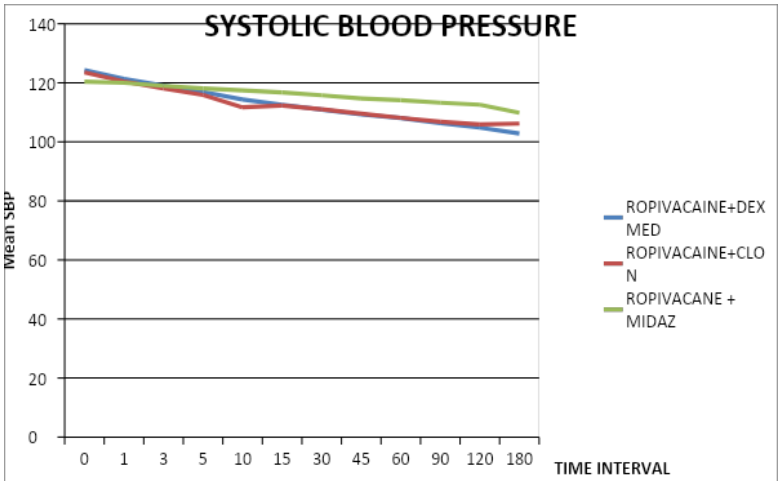
Hemodynamic Parameters

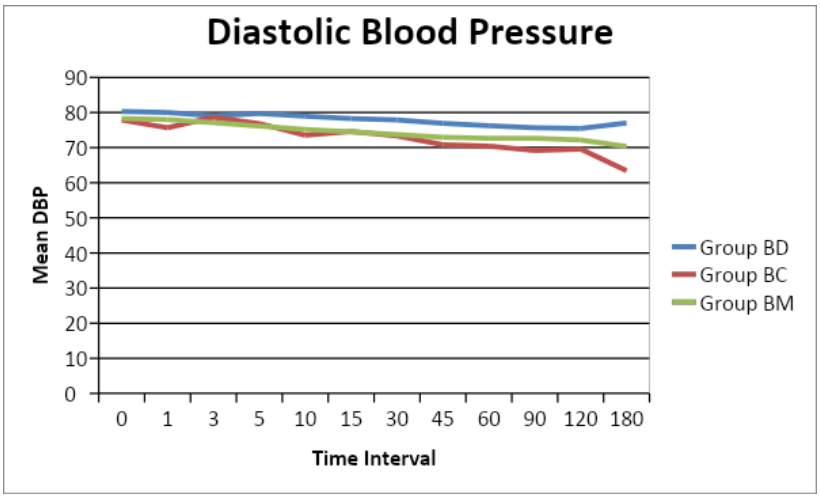
In Hemodynamic parameters the mean SBP distribution for the treatment group BC, BD, BM. It was observed that as the time increases SBP showing a declining trend. At time interval 0 minute, 1 minute, 3 minute, 5 minute, 10 minute, 180 minute there was no significant difference was observed in mean SBP for the three treatment group BD, BC, BM. For the treatment group BC, BD, BM the significant difference for mean SBP was observed at time interval 15-minute, 30 minute, 45 minute, 60 minute, 120 minute.

The mean DBP distribution for the treatment group BC, BD, BM was observed that as the time increases DBP showing a declining trend. At time interval 0 minute, 1 minute, 3 minute, 5 minute, 15 minute, there was no significant difference was observed in mean DBP for the three treatment group BD, BC, BM. For the treatment group BC, BD, BM the significant difference for mean DBP was observed at time interval 10-minute, 30-minute, 45-minute, 60-minute, 90-minute, 120-minute, 180-minute.

However, Pulse Rate and SpO remained within normal limits and were comparable in all three groups (p value>0.05).


PULSE RATE (IN MINUTES)
Mean Pulse Rate
120
100
80
60
40
20
0
0 1 3 5 10 15 30 45 60 90 120 180
TIME INTERVAL
(min)
ROPIVACAINE+DEXMED
ROPIVACAINE+CLON
ROPIVACANE + MIDAZ


SYSTOLIC BLOOD PRESSURE
140
120
100
80
60
40
20
0
0 1 3 5 10 15 30 45 60 90 120 180
TIME INTERVAL
ROPIVACAINE+DEX MED
ROPIVACAINE+CLO N
ROPIVACANE + MIDAZ


Diastolic Blood Pressure
Mean DBP
90
80
70
60
50
40
30
20
10
0
0 1 3 5 10 15 30 45 60 90 120 180
Time Interval
Group BD
Group BC
Group BM

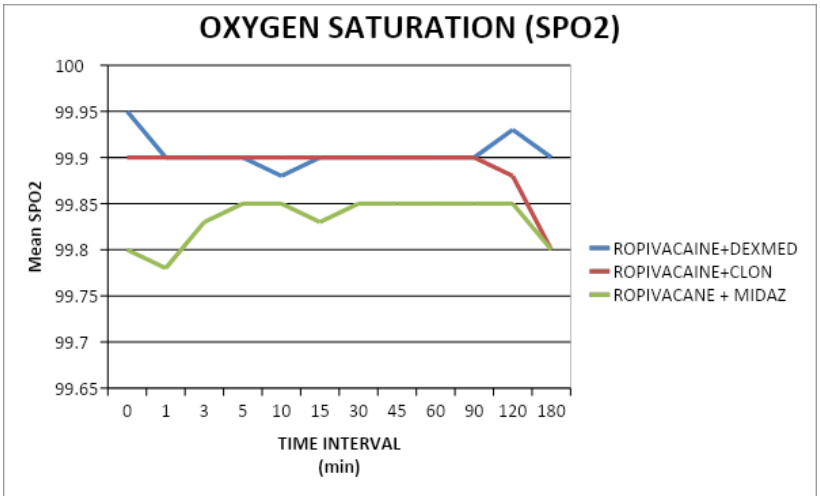


Table no. 9: Post-Operative Complications or Side Effects:

No significant complications were seen in any of the group.

Post operative Complications	**Group BD** N (%)	**Group BC** N (%)	**Group BM** N (%)
Absent N (%)	40 (100)	40 (100)	40 (100)

IV. DISCUSSION

Dexmedetomidine, a 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. [1, 2.] Dexmedetomidine has been approved as a short-term sedative for mechanically ventilated intensive care unit (ICU) patients.

Clonidine is an α 2 -agonist that is commonly used for its antihypertensive. In general, clonidine seems to decrease anesthetic requirements (decreases minimum alveolar concentration) and provides sedation and anxiolysis.

Reported since 1978 as a relatively water-soluble benzodiazepine [3] midazolam is being extensively used both in critical care medicine and operating room. It is used for its sedative, anxiolytic, and amnesic effects [4], but possible use of intrathecal midazolam as an adjuvant is a relatively newer concept in anaesthesia practice. Intrathecal midazolam produces antinociception and potentiates the effect of local anaesthetics.

Al-Mustafa et al.[5](2009) studied effect of dexmedetomidine 5µg and 10 µg with bupivacaine in urological procedures and found that dexmedetomidine prolongs the duration of spinal anaesthesia in a dose-dependent manner.

Mausami neogi et al.[6] (2010) conducted a study in 75 pediatric patients (1-6 years) undergoing elective inguinal herniotomy to assess and compare the potency of clonidine and dexmedetomidine used as adjuvant to ropivacaine for caudal analgesia in pediatric patients and concluded that addition of clonidine or dexmedetomidine with ropivacaine significantly increase the duration of analgesia.

This study shows statistically significant prolongation of mean duration of analgesia in group BD ($p<0.05$) as compared to group BC and group BM. So, dexmedetomidine has maximum duration of prolongation of analgesia.

Rajani Gupta, Jaishi Bogra, Reetu Verma, Monica Kohli, Jitendra kumar Kushwaha, Sanjiv Kumar et al.[7](2011) conducted the study in 60 patients scheduled for lower limb surgery to evaluate the efficacy and safety of intrathecal dexmedetomidine added to ropivacaine. They concluded that the addition of dexmedetomidine to ropivacaine intrathecally brings prolongation in the duration of motor and the sensory block without any serious adverse event.

Vidhi Mahendru, Anurag Tewari, Sunil Katyal, M Rupinder Singh, et al[8] (2013) study showed dexmedetomidine group showed significantly less and delayed requirement of rescue analgesic and concluded that Intrathecal dexmedetomidine is associated with prolonged motor and sensory block, hemodynamic stability, and reduced demand of rescue analgesics in 24 h as compared to clonidine, fentanyl, or levobupivacaine.

In our study also dexmedetomidine showed reduced demand of rescue analgesia as compared to clonidine and midazolam.

Kim and Lee [9] and Bharti et al. [10] found out that intrathecal midazolam also reduces visceral and somatic pain during intra-operative period.

In this study, both dexmedetomidine and midazolam improved the intra operative analgesia, as no patient in either of the study group suffered from visceral or somatic pain intra-operatively and no patient in both the study groups required additional analgesia or general anaesthesia.
In this study no significant hemodynamic instability was seen in any of three patient groups

V. CONCLUSION

We concluded that the supplementation of 3ml of intrathecal 0.75% Ropivacaine with 20µg dexmedetomidine significantly shortens the time of onset and prolonged the duration of sensory and motor blockade in intraoperative period as compared to intrathecal 0.75%. Ropivacaine with 30µg Clonidine and intrathecal 0.75% with 1mg midazolam, and hence provided effective potentiation of analgesia. The hemodynamic parameters and SpO2 were comparable with minimal changes in all the groups. There was no significant difference in two segment regression of dexmedetomidine as compared to other groups. Minimal VAS score with no significant side effects/complications were seen.
So, this study concluded that Dexmedetomidine when added to ropivacaine as adjuvant is superior to clonidine and midazolam.

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