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Original article

COMPARATIVE EVALUATION OF TWO DIFFERENT DOSES OF INTRAVENOUS DEXMEDETOMIDINE INFUSION FOR SEDATION IN PATIENTS UNDERGOING LOWER ABDOMINAL GENERAL SURGICAL PROCEDURES UNDER SPINAL ANESTHESIA

Renuka R

Department of Anesthesiology, Sapthagiri Institute of Medical Sciences and Research Centre, Chikkasandra , Bangalore, India

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Abstract

BACKGROUND: Spinal anesthesia is the most popular regional anesthesia technique for lower abdominal surgeries. The failure of many spinal anesthesia techniques is more due to inadequate sedation and anxiolysis than technically faulty blocks. This study was designed to determine the appropriate dose of intravenous dexmedetomidine maintainance infusion to provide adequate sedation for spinal anesthesia. METHODS: A prospective, randomized, controlled double-blind study was carried out on 75 patients aged 18-60 years with ASA I and ASA II physical status who were scheduled for elective lower abdominal surgery under spinal anesthesia. Before the spinal anesthesia, all study participants were given an initial loading dose of 0.5 μg/kg dexmedetomidine infusion. Participants were randomly divided into three groups for maintenance drug infusion, Group A (to receive dexmedetomidine infusion at 0.2 μg/kg/hr), Group B (to receive dexmedetomidine infusion at 0.4 μg/kg/hr) and Group C to receive an intravenous infusion of normal saline during surgery. The Ramsay Sedation Scale (RSS) score, duration of analgesia, hemodynamic variables and occurrence of adverse events were monitored in all patients. RESULTS: Dexmedetomidine group had increased RSS score in intraoperative period and upto first 30 minutes in postoperative period compared to control group . Time to request for first analgesic was prolonged and incidence of shivering and PONV in postoperative period was less in group B than group A. The hemodynamic parameters, Respiratory parameters were not statistically significant among group A and group B. CONCLUSION: We conclude that intravenous administration of dexmedetomidine0.5 μg/kg loading dose followed by 0.4 μg/kg/hr as maintenance infusion is the optimum dose to produce sedation during spinal anesthesia with an additional advantage of increased duration of analgesia and reduced postoperative sideeffects .

Key words: *Spinal anesthesia , dexmedetomidine , infusions , conscious sedation , hemodynamics, RAMSAY sedation scale.*

Introduction

Spinal anesthesia/Subarachnoid block (SAB) is considered the gold standard method for anesthesia in lower abdominal surgery because it is economical, easy to perform, offers excellent operating conditions, and has a reasonable safety-effectiveness profile. Many spinal and epidural anesthetics have failed more because of insufficient sedation and anxiolysis than because of technically defective blocks [1]. However, patients are often reluctant to stay awake during a procedure, and the need to maintain uncomfortable positioning during long-term surgery can result in spontaneous movements that can interfere with the surgical procedure [2]. Adequate sedation is therefore important if the benefits of spinal anesthesia are to be fully realized. Many drugs have been tried for this purpose, but the limited duration of action with the requirement for intermittent supplementation has shifted towards finding a drug that can induce constant sedation without respiratory depression with minimal possibility of hemodynamic instability.

Dexmedetomidine, a highly selective α 2-adrenergic receptor agonist has proven to be a miracle drug in anesthesia practice due to its organ-pro-

Corresponding author: Renuka R., Department of Anesthesiology, Sapthagiri Institute of Medical Sciences and Research Centre, Chikkasandra , Bangalore, India Mobile phone: 91 8105196837 Email: drmadhumitha9@rediffmail.com

tecting, co-analgesic effect and its ability to sedate, which corresponds to natural sleep [3]. It is increasingly used for sedation outside the operating room due to its wide range of clinical applications. It has also been shown to be coanalgesic when used in conjunction with regional anesthesia, either intravenously or intrathecally, with studies of different dosages being conducted to find the optimal dose. However, there is little literature on the appropriate dose of intravenous dexmedetomidine maintenance infusion to be used during the intraoperative period for the purpose of sedation in surgeries performed under spinal anesthesia with 0.5% hyperbaric bupivacaine. With this in mind, this study was formulated with an aim to determine the safe and effective dose of maintainance demedetomidine infusion for sedation in patients undergoing surgery under spinal anesthesia. The primary objective of the study was to compare Ramsay Sedation Scores and duration of analgesia among the groups .The secondary objective was to evaluate the drug's effect on hemodynamic parameters and any side effects.

Methodology

This prospective, randomized, double-blind clinical study was conducted after receiving approval from the institutional ethics committee over 18 months duration (June 2019-January 2021). The study was carried out in accordance with the Helsinki Declaration. The study included 75 patients with physical status ASA 1 and ASA 2 of both gender, between 18 and 60 years of age with a height of 150 - 170 cm, who were intended for elective general surgery in the lower abdomen. Patients on treatment with adrenergic blockers, calcium channel blockers or with a history of alcohol, opioid or sedative abuse, as well as patients with contraindications for SAB were all excluded from the study. Randomization was done using simple random sampling method and concealment by sealed opaque envelop method performed by an anesthesiologist involved in the study and the study participants were allocated to either Group A(to receive maintainance infusion of Dexmedetomidine at 0.2 µg/kg/hr) , Group B (to receive maintainance infusion of Dexmedetomidine at 0.4 µg/kg/hr) or Group C (to receive normal saline infusion) through out the surgical procedure .The procedure and recording were performed by another investigator who was unaware of the group allocation thus ensuring double blinding.

Written informed consent was obtained from all the participants considered for the study. An 18 G intravenous (IV) cannula was secured and preloaded with 15 ml/kg of Ringer's lactate. A loading dose of 0.5 mcg/kg intravenous Dexmedetomidine infusion was administered to all the study participants over 10 mins duration in the preoperative room. On the operation table multipara monitors were connected and baseline parameters recorded. The SAB method was standardized in all groups by selecting the patient in the seated position for the administration of SAB, L3-L4 interspace, standard midline access using a 25G Quincke's needle. 3 ml of 0.5% hyperbaric bupivacaine (15 mg) was administered intrathecally over a period of 10 seconds duration and immediately after completion of the injection the patients were placed in supine position. Immediately after positioning, the study participants were given the study drug as per the group allocation. Intraoperative maintenance of intravenous administration in all groups was discontinued as soon as the surgeon began suturing the skin.

The time at which the SAB was administered was regarded as time 0 and further durations were calculated from this time. Hemodynamic parameters- heart rate (HR), non invasive mean arterial pressure pressure (MAP and oxygen saturation (SpO2)were determined intraoperatively every 2 min for the first 20 min, then every 5 min until the end of the surgery and postoperatively every 30min for 2 hours and every hour for the next 4 Hours. All the time points were calculated considering time of drug injection in subarachnoid space as the baseline (time 0). The degree of sedation was assessed with the Ramsay Sedation Score (1-Awake : Patient is anxious and agitated, or restless, or both; 2- Awake : Patient is cooperative,oriented, and tranquil; 3- Awake : Patient responds to commands only; 4- Asleep : Patient reacts with a brisk response to a light glabellar tap or a loud auditory stimulus; 5- Asleep : Patient reacts with a sluggish response to a light glabellar tap or a loud auditory stimulus) at an interval of 15 min both intra and postoperatively. Excessive sedation was defined as a score greater than 4/6.

Hypotension (SBP -20% decrease from baseline), bradycardia (heart rate- 20% decrease from baseline) and postoperative complications such as nausea and vomiting, shivering were identified and treated accordingly. The time for the first request for analgesia, which was considered to be the duration of analgesia was noted and an intravenous infusion of 1 g paracetamol was chosen as the rescue analgesic. Tramadol 50 mg was administered intravenously when the patient still complained of pain 30 min after the administration of paracetamol.

STATISTICAL ANALYSIS

In the present study, a descriptive statistical analysis was carried out. Results of continuous measurements are shown as mean, SD and results of categorical measurements in number (%). Chi-square tests and Fisher's exact test were used to determine the significance of study parameters on a categorical scale between two or more groups. The paired t-test was used to determine the significance of study parameters on a continuous scale within the group (intra-group analysis) on metric parameters. The student t-test (two-tailed, independent samples) was used to determine the significance of study parameters on a continuous scale between two groups (intergroup analysis) for metric parameters. The P-value <0.05 was considered significant. A one-way ANOVA analysis was used to compare the significance between dexmedetomidine group (group A and group B) with control group (group C). Post hoc test was used to compare between all three groups. The statistical software SPSS 19 was used to analyze the data.

Results

All 75 patients enrolled in the study have completed the study protocol and are included in the data analysis. There was no spinal anesthesia failure. Thus, each group consisted of 25 patients(Figure1). All groups were similar in terms of demographic characteristics, ASA grading and surgical duration (Table 1).Surgical procedures consisted of abdominal tubectomy, inguinal hernia mesh repair, jabouley's procedure, flap cover, open appendicectomy, tendoachillis repair, perforator ligation, trendelenburg procedure, transabdominal hysterectomy, split skin graft and tuboplasty. The preoperative hemodynamic parameters, respiratory rate and Ramsay sedation score was statistically comparable among the groups (Table 2).

The mean values of hemodynamic parameters (heart rate and blood pressure), respiratory rate, oxygen saturation and RSS were compared between the groups before subarachnoid block, at regular intervals after subarachnoid block and till 6 hours after completion of surgery. Occurrence of any adverse events like hypotension, bradycardia, shivering , PONV were also compared between the groups.

Intraoperative period

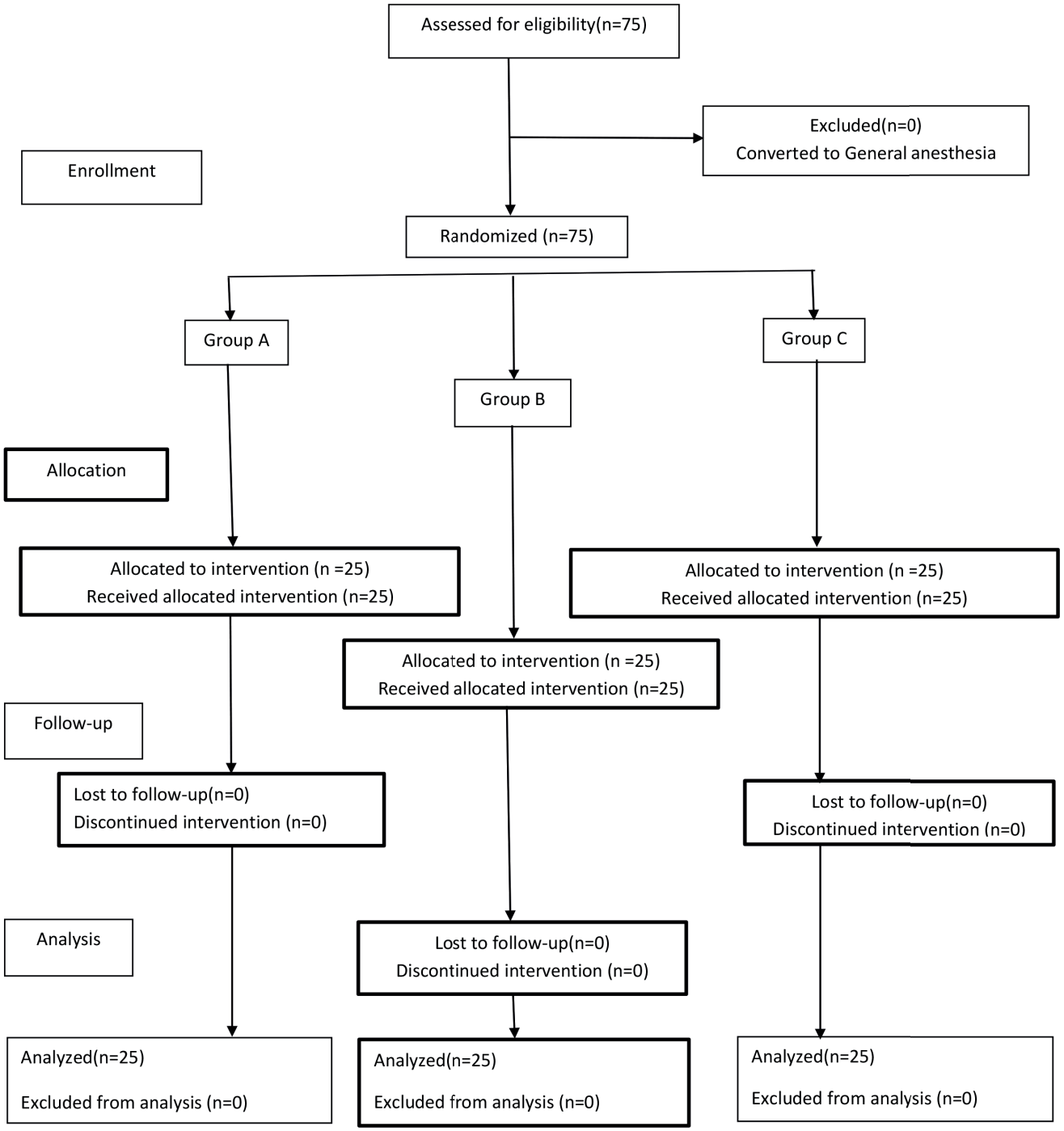
The mean heart rate was significantly lower in the dexmedetomidine group (group A and group B) compared to the control group (group C) with a P value <0.05 for first 60 minutes . When compared between group A and group B it was signifi-

Table 1: Demographic characteristics among the study participants (N=75)

	Group A	**Group B**	**Group C**	**P value ***
Age (Mean ±SD)	38.36±11.54	39.2±9.56	38.72±10.18	0.9571
Gender (Male /Female - %)	60/40	72/28	60/40	0.5940
Weight (Mean(kg) ±SD)	64.2±6.03	66.56±5.73	62.2±7.94	0.073
Height (Mean(cm) ±SD)	157.32±9.10	161.56±4.20	157±8.49	0.066
ASA grading - ASA 1/ ASA 2(%)	96/4	92/8	84/16	0.793
Surgical duration (minutes)	64.2±5.91	66.56±5.61	62.2±7.787	0.0666

*P value from One Way ANOVA test

Figure 1: Consort flow chart



cantly lower in group A compared to group B with a P value 0.017 up to first 10 minutes (Table 3).

The mean arterial pressure was significantly lower in the dexmedetomidine group (group A and group B) compared to the control group (group C) with a P value of 0.043 from 75 minutes onwards and it was found to be significantly lower in group B compared to group A with a p value of 0.047 (Table 3).

There was no clinically significant difference in the respiratory rates and oxygen saturation between the groups during surgery.

Ramsay Sedation Score was significantly higher in dexmedetomidine group (group A and group B)compared to the control group (group C) ($p<<0.001$)from 20 minutes till the end of surgery. The maximum mean sedation score [3.96 + 0.55] was reached 30 min after the start of the dexmedetomidine maintenance infusion (figure 2). How-

Table 2: Pre-operative findings among the study participants (N=75)

	Group A	**Group B**	**Group C**	**P value ***
Heart Rate (beats/min) (Mean ±SD)	77.16±15.15	80.2±12.54	71.4±11.48	0.06
SBP(mm of Hg) (Mean ±SD)	122.92±10.25	120.96±6.42	125.88±10.1	0.16
DBP(mm of Hg) (Mean ±SD)	69.64±9.58	63.72±7.01	68.6±10.42	0.056
MAP(mm of Hg) (Mean ±SD)	87.44±9.35	82.76±5.21	87.68±8.91	0.0574
RR(per min) (Mean ±SD)	16.64±1.96	16.04±2.49	15.64±1.15	0.19
RSS(Mean ±SD)	1.96±0.2	2±0	1.96±0.2	0.60

*P value from One Way ANOVA test

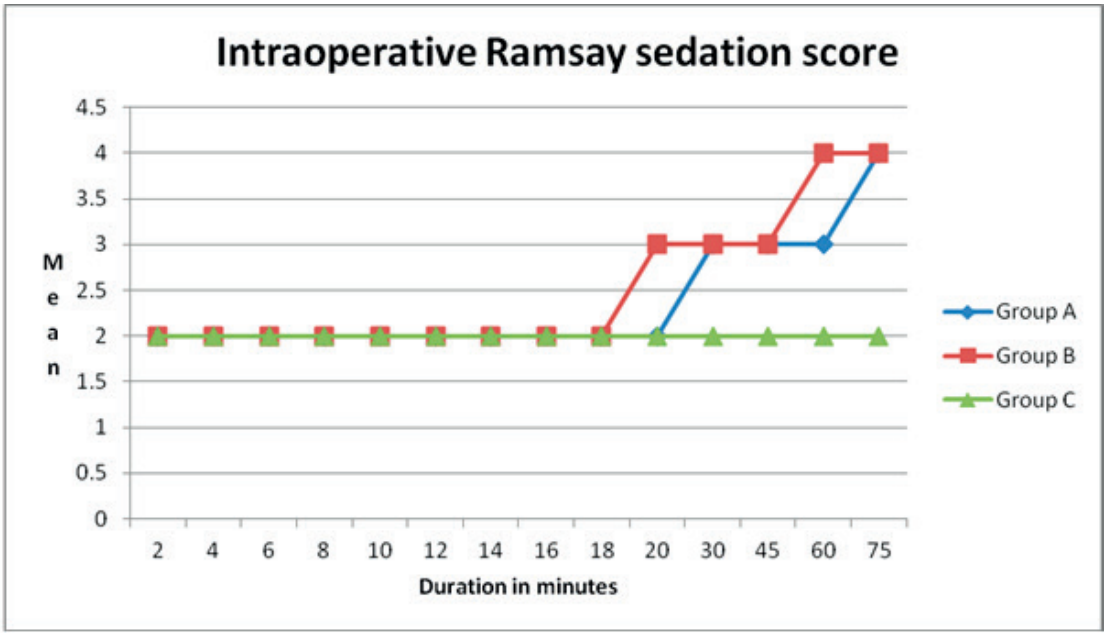
Table 3: Comparison of parameters at different intraoperative time points between the study groups (N=75)

	Group A (Mean ±SD)	**Group B** (Mean ±SD)	**Group C** (Mean ±SD)	ANOVA P value*	P value (Post hoc test)**
2 minutes					
Heart Rate (beats/min)	75.8± 14.05	89.56±12.8	75.68±9.66	**0.0001**	1 vs 2= 0.001 1 vs 3=1.000 2 s3=<0.0001
Mean arterial pressure (mm of Hg)	83±9	81±6	86±9	0.0635	
Oxygen saturation (%)	99±1	98±1	99±1	0.1209	
Respiratory rate (per min)	16±1	16±2	16±1	0.2468	
RSS	2±0	2±0	2±0	0.3729	
10 mins					
Heart Rate (beats/min)	71±11.29	80.08±12.01	70.96±10.45	**0.0063**	1 vs 2= 0.017 1 vs 3=1.000 2 vs 3= 0.017
Mean arterial pressure (mm of Hg)	79±6	78±5	80±8	0.3523	
Oxygen saturation (%)	98±1	98±2	99±1	0.1790	
Respiratory rate (per min)	14±1	14±2	15±2	**0.0146**	1 vs 2=0.909 2 vs 3=0.013 1 vs 3=0.178
RSS	2±0	2±0	2±0	0.3729	
20 mins					
Heart Rate (beats/min)	65.6±7.4	71.52± 10.59	72.72± 8.85	**0.015**	1 vs 2= 0.07 1 vs 3=0.02 2 vs 3= 1.000
Mean arterial pressure (mm of Hg)	74±7	75±6	74±5	0.7851	
Oxygen saturation (%)	98±2	98±1	99±1	**0.0026**	1 vs 2=0.682 1 vs 3=0.069 2 vs 3=0.002
Respiratory rate (per min)	14±2	12±1	15±2	**0.0026**	1 vs 2=0.013 2 vs 3=0.001 1 vs 3=0.006
RSS score	2±1	2±1	2±0	**0.0169**	1 vs 2=0.175 2 vs 3=0.0001 1 vs 3=0.001
30 mins					

Heart Rate (beats/min)	64.04± 6.46	66.4±10.34	73.64± 9.22	0.0008	1 vs 2= 1.000 1 vs 3=0.001 2 vs 3= 0.015
Mean arterial pressure (mm of Hg)	71±17	73±4	74±8	0.5398	
Oxygen saturation (%)	99±1	98±2	99±1	0.0601	
Respiratory rate (per min)	13±1	11±1	15±2	0.0001	1 vs 2=0.001 2 vs 3=0.001 1 vs 3=0.002
RSS score	3±1	3±1	2±0	0.0002	1 vs 2=0.531 2 vs 3=0.001 1 vs 3=0.011
60 mins					
Heart Rate (beats/min)	63.28± 8.21	63.36± 8.01	71.81± 9.95	0.0109	1 vs 2= 1.000 1 vs 3=0.021 2 vs 3= 0.035
Mean arterial pressure (mm of Hg)	56±36	60±38	51±39	0.3854	
Oxygen saturation (%)	98±1	98±1	99±1	0.0501	
Respiratory rate (per min)	12±1	10±1	15±2	0.0001	1 vs 2=0.001 2 vs 3=0.001 1 vs 3=0.001
RSS score	3 ±1	4±1	2±0	0.002	
75 mins					
Heart Rate (beats/min)	61.44±5.34	61.67±14.88	67.88±7.06	0.308	
Mean arterial pressure (mm of Hg)	60±39	56±31	60±39	0.0433	1 vs 2=0.047 1 vs 3=0.225 2 vs 3=1.000
Oxygen saturation (%)	98±1	98±1	99±1	0.6570	
Respiratory rate (per min)	12±1	10±1	14±1	0.001	1 vs 2=0.001 2 vs 3=0.001 1 vs 3=0.001
RSS score	4 ±1	4±0	2±0	0.002	

*P value obtained from One Way ANOVA; **Post Hoc Bonferroni test carried out wherever ANOVA was significant

Figure 2: Intraoperative Ramsay sedation score in the three groups



ever, there was no significance in RSS score was noted between group A and group B.

Postoperative period

The hemodynamic variables ,.respiratory rate and RSS score was monitored till 6 hrs post operatively in all study participants.

The heart rate and mean arterial pressure was significantly lower in Dexmedetomidine group when compared to control group till 6 hrs postoperatively(P<0.05).There was no clinically significant difference in the respiratory rates and oxygen saturation between the groups in the postoperative period.

The Ramsay Sedation Score was significantly higher in Dexmedetomidine group at 15 mins and 30 mins post operatively as compared to control group C (table 4) with p<<0.001. However, no significant difference in sedation scores was observed between the group A and group B in the postoperative period .

The time until the first request for a postoperative analgesic was significantly longer in dexmedetomidine group A [224±42 mins] and group B [315±55 mins] compared to the control group [170±47 mins] (P value < 0.001) as seen in Table 5. When compared among dexmedetomidine groups it was significantly longer in group B compared to group A with p< 0.0001

In our study,three patients in dexmedetomidine group B [12%] had bradycardia compared to the control group (P value 0.102) as depicted in Figure 3.There was no significant difference in the number of patients who needed ephedrine to treat hypotension in both the dexmedetomidine group [32% vs 24%] and the control group [40%] (P value 0.6570). Three patients in dexmedetomidine group A and one patient in group B had postoperative shivering compared to eight patients in the control group (P value 0.032). In the present study, a significantly lower incidence of postoperative nausea and vomiting (PONV) was found in the dexme-

Table 4: Comparison of parameters at different time points in the postoperative period between the study groups (N=75)

	Group A	**Group B**	**Group C**	ANOVA P value*	P value (Post hoc test)**
0 minutes					
Heart Rate (beats/min)	66±7	66±6	73±6	0.0006	1 vs 2=1.000 2 vs 3=0.002 1 vs 3=0.003
Mean arterial pressure (mm of Hg)	80±10	78±10	91±9	0.0166	1 vs 2=0.533 2 vs 3-0.346 1 vs 3=0.017
Respiratory rate (per min)	14±1	13±1	15±1	0.0001	1 vs 2=0.423 2 vs 3=0.001 1 vs 3=0.009
RSS	2±0	2±1	2±0	0.015	1 vs 2=0.361 2 vs 3=0.012 1 vs 3=0.515
15 minutes					
Heart Rate (beats/min)	67±9	66±3	78±12	0.001	1 vs 2=1.000 2 vs 3=0.001 1 vs 3=0.001
Mean arterial pressure (mm of Hg)	79±6	80±4	83±7	0.0566	1 vs 2=1.000 2 vs 3=0.158 1 vs 3=0.085
Oxygen saturation (%)	99±1	99±1	99±1	0.6586	
RSS	2±0	2±1	2±0	0.015	1 vs 2=0.361 2 vs 3=0.012 1 vs 3=0.515

30mins					
Heart Rate (beats/min)	68±9	67±4	78±13	0.001	1 vs 2=1.000 2 vs 3=0.001 1 vs 3=0.001
Mean arterial pressure (mm of Hg)	78±5	78±3	80±5	0.0035	1 vs 2=1.000 2 vs 3=0.007 1 vs 3=0.014
Oxygen saturation (%)	99±1	99±1	98±1	0.0344	
RSS	2±0	2±0	2±0	0.0070	1 vs 2=0.091 2 vs 3=0.007 1 vs 3=1.000
6HRS					
Heart Rate (beats/min)	69±7	64±5	72±9	0.0006	1 vs 2=0.049 2 vs 3=0.001 1 vs 3=0.358
Mean arterial pressure (mm of Hg)	82±7	79±4	82±6	0.0114	1 vs 2=0.310 2 vs 3=0.009 1 vs 3=0.467
Oxygen saturation (%)	98±1	98±2	98±1	0.1989	
RSS score	2±0	2±0	2±0	0.6021	

Figure 3: Distribution of various side effects among three groups

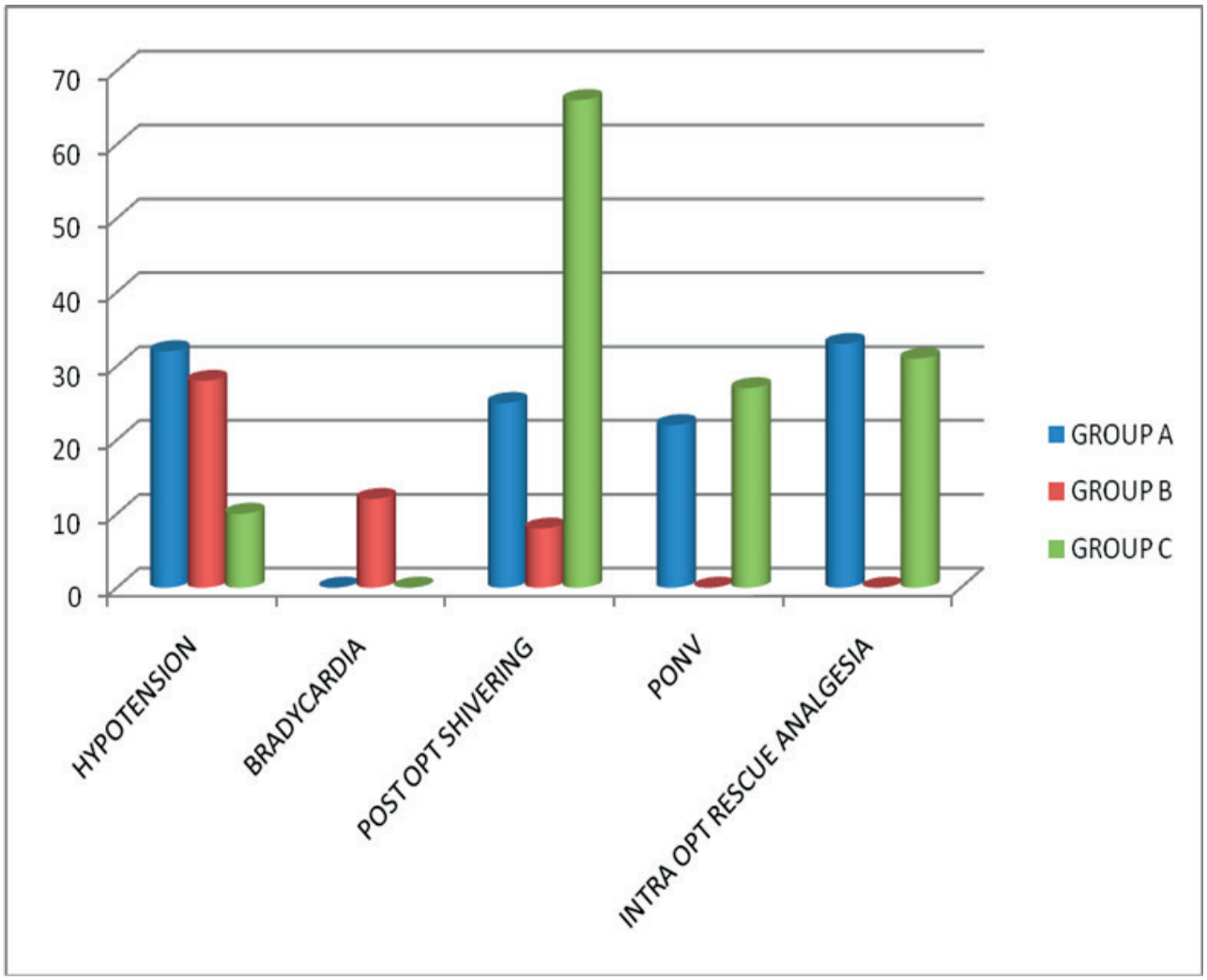


Table 5: Comparison of the time to first rescue analgesia in study participants (N = 75)

Time to first rescue analgesia	Mean (min) ±SD	P value*	P value (Post hoc test) **
Group A	224±42	<0.0001	1 vs 2= <0.0001
Group B	315±55		1 vs 3=0.001
Group C	170±47		2 vs 3= <0.0001

*P value obtained from One Way ANOVA
**Post Hoc Bonferroni test

detomidine group (P value 0.008) as depicted in Figure 3.

Discussion

Dexmedetomidine is the most popular drug used in clinical practice for perioperative and periprocedural applications due to its large safety margins and organ protective effects. It has been shown to be a coanalgesic when given with regional anesthetic techniques because it intensifies the block and prolongs the effect of the local anesthetic.

In this golden era of dexmedetomidine, it reignited traditional sedatives in critically ill patients due to its unique properties of action, such as ability to induce conscious sedation thus providing an access to daily assessment of neurological, cognitive and respiratory functions. Based on its success and benefits in this area, it has been used in many perioperative situations since it was approved by the FDA in 1999 [4-7].

In our study, the intraoperative Ramsay sedation score in the dexmedetomidine group were significantly higher than in the control group and the maximum mean sedation score was reached 30 min after the start of the dexmedetomidine infusion which was similar to the study finding by Jai Song and associates [8, 9]

In the present study , the time until the first request for a postoperative analgesic was significantly longer in dexmedetomidine group A and group B compared to the control group C which was a similar finding to the result of the study by Hong et al., who found a lower postoperative pain intensity and a longer average time until the first request for postoperative analgesia in the dexmedetomidine group compared to the control group[10] . In our study, we also found significantly longer duration of analgesia in group B compared to group A. This primary analgesic effect could be attributed to the inhibitory effect of dexmedetomidine on the release of substance P from the dorsal horn of the spinal cord [11].

In our study, three patients in dexmedetomidine group A and one patient in group B had postoperative shivering as compared to eight patients in the control group which could be attributed to the inhibitory effect of dexmedetomidine on central thermoregulation [12]. Similar results were reported by Tekin et al [13] (0% v/s 30% in dexmedetomidine and control groups, respectively).

In the present study, a significantly lower incidence of postoperative nausea and vomiting was found in the dexmedetomidine groups, which was similar to the study by Massad IM et al., and study finding of other authors [14, 15, 16]

The adverse effects like bradycardia , hypotension observed were transient , had no significant clinical effects and responded well to atropine , IV fluids and ephedrine respectively . the results in our study was comparable to the study by various authors who reported the dose-dependent occurrence of bradycardia and hypotension without significant clinical effects and which were easily manageable [8, 17]

According to the observations of a study by Jai Song and co-workers [7], they suggested a dexmedetomidine loading dose of 1 μg/kg followed by a maintenance infusion of 0.25 μg/kg/hr as the most appropriate dose for continuous administration. But in our study, based on the sedation score and hemodynamic effects, we observed that a loading dose of 0.5 μg/kg followed by a maintenance infusion of 0.4 μg/kg/hr is the most appropriate dose, which is slightly different from their study. This could be due to the reduction in the loading dose of the drug used in our study.

The limitations of our study were we did not evaluate the differences between the groups in terms of total analgesic consumption in the first 24

hours. Our study comprised a relatively small sample size and also the effect on intraoperative block characteristics which if estimated could have added more value to this study.

Conclusion

We conclude that a loading intravenous dose of dexmedetomidine 0.5 μg/kg followed by continuous administration at an infusion rate of 0.4 μg/kg/hr may be an appropriate dose to ensure adequate sedation while reducing the risk of haemodynamic instability. It also has the added benefits of extending post-operative analgesia, preventing post-operative shivering and PONV.

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