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Can Intravenous Dexmedetomidine Prolong Bupivacaine Intrathecal Spinal Anesthesia?

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Abstract

Background and objectives: Different adjuvants have been used to prolong intrathecal spinal anesthesia, with the possible advantages of delayed onset of post-operative pain, delayed and reduced analgesic requirements. The aim of this study was to evaluate the effect ofintravenous dexmedetomidine on prolongation of intrathecal spinal anesthesia, level of sedation, post-operative analgesic requirement.

Methods: Ninety adult patients classified as American Society of Anaesthesiologists physical status (ASA) I or II scheduled for various elective surgical proceduresbelow umbilicus under intrathecal spinal anesthesia were double-blind randomized to one of three groups. Each patient received 0.5% hyperbaric bupivacaine 2.5 ml intrathecal spinal anesthesia.

Group C (control): Patient receiving intravenous normal saline 10 ml over 10 mins (as placebo) 10 minutes before intrathecal spinal anesthesia with 0.5% hyperbaric bupivacaine 2.5 ml and normal saline 10 ml over 10 mins (as placebo) after 30 minutes of spinal anesthesia.

Group D_1: Patient receiving intravenous dexmedetomidine 1 μg/kg over 10 mins, 10 minutes before intrathecal spinal anesthesia.

Group D_2: Patient receiving intravenous dexmedetomidine 1 μg/kg over 10 mins after 30 minutes of intrathecal spinal anesthesia.

Results: Sensory block was higher in group D2 (T-4.1 ± 0.7) than D1 (T-4.5 ± 0.5) and C (T-6.3 ± 0.8). Time for sensory regression of two blocks was 145 ± 32, 142 ± 28 and 94 ± 26 min in group D2, D1 and C respectively. Duration of motor block was similar in all groups. GroupD2 and D1 increased the time to first request for post-operative analgesia by 190.3 ±13.3 and 174 ± 19.5 min whereas in group C 133.40 ±10.4 min. The maximum Ramsay sedation score was greater in the group D1 and D2 than in C.

Conclusion: Intravenous dexmedetomidine prolonged spinal bupivacaine sensory blockade in both the groups. It also provided sedation and additional analgesia.

Keywords: Bupivacaine; Dexmedetomidine; Intravenous; Postoperative pain

Introduction

Spinal anesthesia is a well-known technique used in surgical practice. It may cause some discomfort either by the procedure itself or due to prolonged peri-operative period, requiring simultaneous administration of hypnotic, sedative or amnesic drugs. However, these drugs may affect the ventilation and leads to respiratory depression, with consequent hypoxemia. The duration of Intrathecal Spinal Anesthesia (ISA) with a single bolus dose is also limited.

Various adjuncts like epinephrine, phenylephrine, opioids or clonidine have been used to prolong the spinal anesthesia, with the possible advantages of delayed-onset of postoperative pain and reduced analgesic requirements, but each of these has a unique advantage and disadvantage. Hansen et al. (2004) suggested that intravenous or caudal clonidine, an alpha2-adrenergic agonist, had prolonged the bupivacaine caudal block with minimal adverse effects [1]. Dexmedetomidine highly selective alpha$_2$-adrenergic agonists, better hypnotic, sedative, and analgesic. It has been used safely for general anesthesia, postoperative analgesia and ISA without any respiratory depression [2]. Compared with clonidine, dexmedetomidine is seven to ten times more selective for alpha2-receptors and has a shorter duration of action [3]. It decrease sympathetic tone, attenuate the stress responses to anesthesia and surgery with mild cardiovascular adverse effects [4]. Although a synergistic interaction between ISA dexmedetomidine and bupivacain has been observed in previous studies however, the literature on intravenous dexmedetomidine on the duration of sensory and motor block during ISA is scarce [5,6]. This was aprospective, randomized, and double-blind clinical studybased on assumption that intravenous dexmedetomidine, may prolong the duration of spinal anesthesia induced sedation and post-operative analgesia with minimal effect on cardiovascular and respiratory systems. The purpose of this study was, therefore, to observe prolongation of ISA with intravenous dexmedetomidine and assessment of cardio-respiratory stability, level of sedation, post-operative analgesia using hyperbaric bupivacaine for ISA.

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Material and Methods

This study was undertaken after an institutional approval by the Committee on Human Research and Ethics, written informed consent was obtained from all patients. The study population consisted of 90 patients, who were classified as American Society of Anaesthesiologists (ASA) physical status I or II, male or female adults between the ages of 18-65 years scheduled for various elective surgical procedures below umbilicus under intrathecal spinal anesthesia.

Study design

This study was a prospective, randomized, and double-blinded clinical comparison study. The Sample size for the study was ninety, generated using a sample size calculator. The study participants were randomly divided into three groups by a computer generated randomization table. A study anaesthetist (Person A) prepared study drugs, Person B monitored the heart rate, mean arterial pressure, sensory level, pain (Visual analogue scale) motor block (modified Bromage scale) and level of sedation (Ramsay Sedation Scale) intraoperatively and upto 24 hours after spinal anesthesia. Person C was responsible for study drugs administration (intravenous and intrathecal) to the patients [7-9]. Person A and C were kept constant throughout the study. Person B, C and the patient were kept unaware of the drug injected to enable double-blinding. After randomization and blinding, patients were allocated in one of the following groups.

Group C (control): Patient receiving intravenous normal saline 10 ml (as placebo) over 10 minutes, 10 minutes before ISA with 0.5% hyperbaric bupivacaine 2.5 ml and normal saline 10 ml (as placebo) over 10 minsafter 30 minutes of ISA.

Group D_1: Patient receiving intravenous dexmedetomidine 1 μg/kg in dilution of 10 ml over 10 minutes, 10 minutes before ISA with 0.5% hyperbaric bupivacaine 2.5 ml and normal saline 10 ml (as placebo) over 10 minutes after 30 minutes of ISA.

Group D_2: Patient receiving intravenous normal saline 10 ml (as placebo) over 10 minutes, 10 minutes before ISA with 0.5% hyperbaric bupivacaine 2.5 ml and intravenous dexmedetomidine 1 μg/kg in dilution of 10 ml over 10 minutes after 30 minutes of ISA.

Inclusion criteria

Inclusion criteria for the study were ASA class I or II, age range 18-65 years scheduled for various elective surgical procedures below umbilicus under spinal anesthesia.

Exclusion criteria

Exclusion criteria included Patient refusal, coming for emergency surgeries, use of any opioid or sedative medications in the week prior to surgery, a history of alcohol or drug abuse, known allergy to any of the test drugs, contraindication to spinal anesthesia (as infection at puncture site, pre-existing neurological deficits in the lower extremities, coagulation defects), and cardiovascular, respiratory, neurological, psychological, hepatic, or renal disease, diabetes mellitus, pregnant, patients requiring supplementary analgesia or general anesthesia during surgery and those developed any complications such as hypotension, bradycardia and shock were excluded from this study.

Pre-surgical protocol

The day prior to surgery all patients underwent a pre-anaesthetic evaluation with special consideration to elicit a history of hypertension, dyspnoea, chest pain, cough, wheezing, convulsions, and diabetes mellitus as well as previous anesthetic history and drug sensitivity. Information collected also included weight, nutritional status, and airway assessment by the Mallampatti scoring system. A detailed examination of the respiratory, cardiovascular, and central nervous system was performed in all patients including preoperative routine investigations such as hemoglobin, hematocrit, total lymphocyte count, differential lymphocyte count, platelet count, serum electrolytes, blood group/Rh typing, blood urea nitrogen, serum creatinine, fasting blood sugar, chest radiography, and electrocardiogram. Patients were advised to fast the night prior to surgery, received tablet alprazolam 0.25 mg and tablet ranitidine 150 mg orally on the previous night and day of surgery.

Surgical protocol

On day of surgery procedure were explained to the participants and a written informed consent was obtained from each participant. Intravenous access was secured and infusion of Ringer's lactate solution started. Patients were then shifted to the operating room after which routine non-invasive monitor was applied and vital signs monitored. After preloading the patients with Ringer Lactate 15 ml/kg, patient was put on lateral position and lumbar puncture was performed at L3-4 level with Quincke type point 25 gauge spinal needle and the injection bupivacaine 2.5 ml solution was injected intrathecally over 30 seconds. As per the group allocation injection dexmedetomidine 1 μg/kg or normal saline in dilution of 10 ml in double-blinding was given by infusion pump 10 mins before or 30 mins after ISA intravenous over 10 minutes. Level of sensory loss was assessed by pin-prick test in mid axillary line. Mean arterial pressure, heart rate and oxygen saturation (SpO_2) were monitored regularly and for study purpose before, after dexmedetomidine infusion at 5, 15, 45, 75, 120, and 180 minutes. Any fall in the heart rate below 60 beats per minute was treated with incremental doses of Injection atropine 0.3 mg IV and patients were excluded from the study.

Visual Analogue Scale (VAS)

Postoperative pain was assessed by the patient using the visual analogue scale (VAS; 0=no pain; 10=worst possible pain) at 4, 8, 12, and 24 hour (hr). In addition, the overall 24-hr pain VAS was evaluated by the overall pain impression of the patient for 24 hr postoperatively [7].

Modified bromage scale

Modified Bromage Scale was used to assess motor blockade. Motor blocked assessed every 5, 15, 45, 75, 105, 120 and 180 mins.

Bromage 0, the patient is able to move the hip, knee and ankle;

Bromage 1, the patient is unable to move the hip, but is able to move the knee and ankle;

Bromage 2, the patient is unable to move the hip and knee, but is able to move the ankle;

Bromage 3, the patient is unable to move the hip, knee and ankle.

All durations were calculated considering the time of spinal injection as time zero [8].

Ramsay sedation scale

Ramsay Sedation Scale was used to assess level of sedation in all patients at every 5, 30, 60, 90 and 120 mins.

1-Patient is anxious and agitated or restless, or both.

2-Patient is co-operative, oriented, and tranquil.

3-Patient responds to commands only.

4-Patient exhibits brisk response to light glabellar tap or loud auditory stimulus.

5-Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus.

6- Patient exhibits no response [9].

Duration of effective analgesia was measured from the time of intrathecal drug administration to the patient's first request for analgesia. Patients were also assessed for the side effects like nausea, vomiting, bradycardia and hypotension (systolic arterial pressure below 100 mm Hg, a decrease in the initial systolic arterial pressure of 20% from baseline, or both) [10].

Statistical analysis

Data were analysed using computer statistical software system SPSS® version 16 (Statistical Packages for the Social Sciences, Chicago, IL). Results were expressed as mean and Standard Deviation (SD). Analysis of data between the groups were performed using one-way analysis of variance (ANOVA) followed by the Bonferroni test for post hoc analysis for parametric data or Kruskal-Wallis test for non parametric data. If revealed significant differences, the Mann-Whitney U-test was used to analyze differences between the groups in pairs. Categorical data were analyzed using the Chi-square test. The Sample size for the study was 90 generated using a sample size calculator. Sample size calculation revealed that 30 patients per group were required to detect an increase of the time of a two-dermatome sensory regression by 30 min with a standard deviation of 28 min at an alpha of 0.05 with power of 80%. P values<0.05 were considered to indicate statistical significance.

Results

The demographic characteristics of each group were similar. There were no statistical differences observed with respect to number of patients in each group, age, height, weight, sex ratio or duration of surgery (p>0.05) (Tables 1-8).

No patient reported pruritus. Complete recoveries of sensory and motor functions were observed in all studied patients. At the postoperative follow up visit no neurological deficit was detected in the patients (Figure 1).

Discussion

Spinal anesthesia remains one of the basic techniques in modern anesthesia despite waxing and waning of its popularity over many years since its introduction into clinical practices. Various drugs have been tried in the subarachnoid space along with local anaesthetics with the aim of improving the duration of post-operative analgesia [11].

Our results indicate that intravenous dexmedetomidine given before and 30 minutes after intrathecal administration of bupivacaine prolongs the duration of sensory blockade during spinal anesthesia and increased the maximum upper level of sensory block. In addition, dexmedetomidine had reduced postoperative pain scores and a longer analgesic duration than those who received spinal bupivacaine alone as found by Jung (2013), when dexmedetomidine given 5 min after intrathecal injection of hyperbaric bupivacaine [12]. It also provided sedation throughout the procedure without any haemodynamic instability or increased side effects.

Variables	Group C (n=30)	Group D1 (n=30)	Group D2 (n=30)	p-value
Age (Yrs)	38.14 ± 14.30	36.71 ± 10.6	39.83 ± 13.02	0.64
Height(cms)	156.28 ± 4.77	156.36 ± 4.74	158.68 ± 8.52	0.73
Weight(kg)	59.45 ± 8.53	58.68 ± 8.52	60.9 ± 4.97	0.513
Sex (M:F)	21:09	18:12	19:11	0.79
Duration of surgery (min)	98.36 ± 18	109.83 ± 24	102.61 ± 21	0.618

Data are presented as means ± standard deviation and ratio.
There was no statistically significant difference in distribution of age, height, weight and sex in three groups (p>0.05).

Table 1: Demographic profile of the study groups stratified by treatment.

Parameter	Group C vs. D1	p-value	Group C vs. D2	p-value	Group D1 vs. D2	p-value
HR (per min)	78.5 ± 8.3	0.675	81.9 ± 7.4	0.578	79.2 ± 6.9	0.902
MAP (mmHg)	98.3 ± 5.3	0.098	99.6 ± 4.9	0.463	94.8 ± 4.3	0.324
RR (per min)	11.5 ± 6.8	0.521	12.3 ± 8.1	0.37	11.9 ± 7.4	0.418
SpO_2 (%)	99.8 ± 7.3	0.374	99.4 ± 6.5	0.081	99.1 ± 8.3	0.279

Data are presented as means ± standard deviation, and p-value. ANOVA with repeated measures was used to compare the changes in HR, MAP, RR and SpO_2 values pre-operative.HR-Heart Rate, MAP-Mean Arterial Pressure, RR-Respiratory Rate, SpO_2-Oxygen saturation.
There was no statistically significant difference in pre-operative HR, MAP, RR and SpO_2 in three groups (p>0.05).

Table 2: Comparison of pre-operative vital variables in the study groups.

p-value at time	Group C vs. D1	Group C vs. D2	Group D1 vs. D2
5 mins p-value	0.094	0.029*	0.09
15 mins p-value	0.131	0.012*	0.139
45 mins p-value	0.050*	0.028*	0.575
75 mins p-value	0.113	0.178	0.883
120 mins p-value	0.283	0.178	0.184
180 mins p-value	0.437	0.921	0.355

Data are presented as p-value. ANOVA with repeated measures was used to compare the changes in HR and p-value calculated. Bonferroni's multiple comparison tests were used to make intergroup comparisons.

- Intra-operative heart rate was statistically significant between the Group C vs. D1 at 45 min and Group C vs. D2 at 5, 15 and 45 mins (p<0.05).
- There was no statistical significance in between Group D1 vs. D2 (p>0.05).

Table 3: Comparison of Intra-operative heart rate (HR) in the study groups.

p-value at time	Group C vs. D1	Group C vs. D2	Group D1 vs. D2
5 mins p-value	0.039*	0.024*	0.195
15 mins p-value	0.024*	0.039*	0.737
45 mins p-value	0.007*	0.033*	0.617
75 mins p-value	0.007*	0.013*	0.783
120 mins p-value	0.041*	0.031*	0.893
180 mins p-value	0.303	0.068	0.429

Data are presented as p-value. ANOVA with repeated measures was used to compare the changes in MAP and p-value calculated. Bonferroni's multiple comparison tests were used to make intergroup comparisons.

- Intra-operative mean arterial pressure was statistically significant between Group C vs. D1 and Group C vs. D2 at 5, 15, 45, 75 and 120 mins ($p<0.05$).
- There was no significance in between Group D1 vs. D2 ($p>0.05$).

Table 4: Comparison of Intra-operative mean arterial pressure (MAP) in the study groups.

p-value at time	Group C vs. D1	Group C vs. D2	Group D1 vs. D2
5 mins p-value	0.246	0.194	0.674
15 mins p-value	0.118	0.246	0.665
45 mins p-value	0.37	0.127	0.431
75 mins p-value	0.305	0.108	0.484
120 mins p-value	0.288	0.191	0.766
180 mins p-value	0.164	0.248	0.756

Data are presented as p-value. ANOVA with repeated measures was used to compare the changes in RR and p-value calculated. Bonferroni's multiple comparison tests were used to make intergroup comparisons.

- There was no statistically significant difference in Intra-operative respiratory rate in three groups ($p>0.05$).

Table 5: Comparison of Intra-operative respiratory rate (RR) in the study groups.

p-value at time	Group C vs. D1	Group C vs. D2	Group D1 vs. D2
5 mins p-value	0.29	0.221	0.856
15 mins p-value	0.658	0.856	0.686
45 mins p-value	0.823	0.499	0.446
75 mins p-value	0.336	0.23	0.8
120 mins p-value	0.633	0.446	0.812
180 mins p-value	0.434	0.785	0.291

Data are presented as p-value. ANOVA with repeated measures was used to compare the changes in SpO_2 and p-value calculated. Bonferroni's multiple comparison tests were used to make intergroup comparisons.

- There was no statistically significant difference in Intra-operative SpO_2 in three groups ($p>0.05$).

Table 6: Comparison of Intra-operative oxygen saturation (SpO_2) in the study groups.

Variables	Group C	GroupD1	Group D2
Highest sensory level (thoracic segments)	6.3 ± 0.8*¥	4.5 ± 0.5	4.1 ± 0.7
Time for two-segment regression of sensory block (min)	94 ± 26*¥	142 ± 28	145 ± 32
Time for regression of motor block to Bromage 1 (min)	184 ± 24	195 ± 33	193 ± 27
Time to first request for analgesia (min)	133.40 ± 10.35*¥	174 ± 19.47	190.33 ± 13.25
Overall 24-hr pain VAS	3.8 ± 0.9	3.3 ± 0.6	3 ± 0.5

Data are presented as means ± standard deviationValues are expressed as mean ± standard deviation. * Group C vs. D1 and ¥ Group C vs. D2 with the Mann-Whitney U-test.
VAS = visual analogue scale.

Table 7: Comparison of highest sensory level, sensory and motor regression of spinal anaesthesia and data regarding post-operative analgesia in the study groups.

Jaakola et al. in an evaluation of the analgesic effect of different doses of intravenous dexmedetomidine (0.25, 0.5, and, 1 μg/kg) on ischaemic pain in healthy volunteers and demonstrated moderate analgesia with a ceiling effect at 0.5 μg/ kg [13]. Tezer (2005) concluded that sympathetic responses during laryngoscopy and intubation were effectively reduced by dexmedetomidine 1 μg/kg/hr without any adverse effect [14]. Rapid or bolus intravenous administration of dexmedetomidine produces sudden hypertension and bradycardia until the central sympatholytic effects dominates, resulting decrease in both MAP and HR from baseline [15]. With this in mind, dexmedetomidine was given 1 μg/ kg over 10 min in this study, as rapid administration might cause bradycardia and hypertension or hypotension.

However, there are no clinical data regarding the association of intravenous dexmedetomidine and ISA with bupivacaine. Although this study showed that the intravenous dexmedetomidine prolonged the duration of sensory block of bupivacaine spinal anesthesia and increased the maximum upper levels of sensory block, the underlying mechanism of this effect remains unclear. The supra-spinal, direct analgesic, and/or vasoconstricting actions of dexmedetomidine are suggested to be involved in this mechanism [16].

In Group C the time for first request of analgesia was at 133 mins compared to Group D1 and D2 where the first request of analgesia was at 174 and 190 mins respectively ($p<0.05$). The motor block in Group C was stable during the first 75 mins and started to decrease at 184 mins. In Group D1 and D2 the motor block was stable during the first 75 mins and started to decrease at 195 and 193 mins respectively ($p>0.05$). Compared with the prolongation of the sensory block, the duration of motor block was not affected by dexmedetomidine. It could be explained that conduction of sensory nerve fiber might be more inhibited than

Group	Bradycardia	Hypotension	Nausea	Ramsay sedation score5/6(mean)
Group C	1	2	1	0/0
Group D1	3	4	2	3/0
Group D2	1	3	1	2/0
Total	5	9	4	5

- There were total of five patients presented with bradycardia given injection atropine.
- There were total of nine patients presented with hypotension received injection phenylephrin.
- There were total of four patients presented with nausea.
- The median (range) of the highest Ramsay sedation score was 3 (2-5) in the group D1, 2 (1-4) in the group D2, and 1 (1-2) in the saline group. The maximum Ramsay sedation score was greater in the dexmedetomidine than in the saline group. Excessive sedation was observed in five patients of the dexmedetomidine group D1 (3) and D2 (2) respectively.

Table 8: Observed adverse effects.

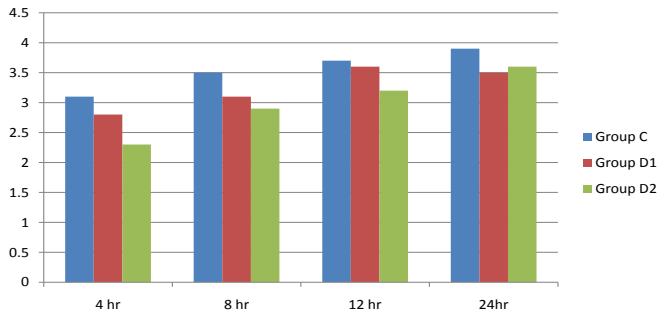

Figure 1: Comparison of Visual Analogue Scale (VAS) scores for the first 24 hours in three groups using Mann-Whitney U-test.24-hr VAS scores were not statistically different among the three groups.

motor nerve fiber at the same concentration of dexmedetomidine, as similarly reported with clonidine [17].

Kunisawa (2011) described dexmedetomidine an alternative to benzodiazepines or propofol for achieving sedation in adults because the incidences of delirium and coma associated with dexmedetomidine are lower than the corresponding incidences associated with benzodiazepines and propofol, although dexmedetomidine administration can cause mild adverse effects such as bradycardia and hypotension [18]. In our study, as in Group C, D1 and D2 incident of bradycardia were 1, 3 and 1 and hypotension were 2, 4 and 3 respectively. In previous studies, it has been shown that dexmedetomidine caused minimal respiratory depression [19]. There was no respiratory depression in any of our study patients. Respiratory parameters (respiratory rate and SpO2) remained within normal limits throughout our procedure. This all might be attributed to sympathetic blockade associated with ISA, slow administration of a low dose, and sufficient preoperative hydration. However, further studies are needed to investigate the efficacy of dexmedetomidine in geriatric patients or medically compromised patient populations.

Although this study adds to the current knowledge on dexmedetomidine, the results should be considered cautiously taking in account the obvious limitations: limitation of our study is that we used the requirement for rescue analgesic rather than the VAS score to assess the prolongation of analgesia with administration of premedication drug. The primary therapeutic end-point of the current study design was to achieve a VAS score of 3, and indeed, 24-hr VAS scores were not statistically different among the three groups. The study was not sufficiently powered to detect significant differences in the secondary outcome variables or adverse effects. The population involved healthy young patients and the effects in older patients are yet to be investigated with cardiovascular co morbidities. Nevertheless, it was concluded within the limitations of the present design that the addition of intravenous dexmedetomidine before spinal block or 30 minutes after spinal block provided better pain relief with delayed-onset of postoperative pain and significantly less analgesic requirements. Intravenous dexmedetomidine 30 minutes after spinal block haemodynamically tolerated better than Intravenous dexmedetomidine before spinal block.

In conclusion, we have shown that a single dose of intravenous dexmedetomidine given as premedication or 30 minutes after spinal block prolonged the duration of sensory blockade of bupivacaine induced ISA. They also provided sedation and additional analgesia without haemodynamic adverse effects.

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