Original Article

Evaluation of low-dose dexmedetomidine and neostigmine with bupivacaine for postoperative analgesia in orthopedic surgeries: A prospective randomized double-blind study

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Abstract

Background and Aims: Neuraxial adjuants to local anesthetics is an effective technique of improving the quality and duration of postoperative analgesia. The safety and efficacy of drugs like dexmedetomidine and neostigmine as epidural medications have been sparsely investigated.

Material and Methods: Combined spinal-epidural anesthesia was performed in 60 American Society of Anesthesiologists I and II patients who required lower limb surgeries of ≤3 h duration. The epidural drug was administered at the end of surgery with patients randomized into three groups. Group I, II and III received 6 ml of 0.25% bupivacaine alone, with 1 ug/kg of neostigmine and with 0.5 ug/kg of dexmedetomidine + 1 ug/kg of neostigmine, respectively. The patients were prescribed 50 mg tramadol intravenous as rescue analgesic. Patients were assessed for hemodynamic parameters, pain scores, duration of analgesia, rescue analgesic requirements and the incidence of side-effects over the next 10 h. Data was analyzed using SPSS® version 17.0 (Chicago, IL, USA). $P < 0.05$ was considered as statistically significant.

Results: Patients in Group III had significantly longer mean duration of analgesia (273.5 min) compared to Group II (176.25 min) and Group I (144 min). There was increased requirement of fluids to maintain blood pressures in Group III. Neostigmine did not cause significant incidence of gastrointestinal side effects.

Conclusions: Epidurally administered dexmedetomidine and neostigmine exhibit synergism in analgesic action. The incidence of drug-related side-effects was low in our study.

Key words: Adjuvant, dexmedetomidine, epidural, neostigmine

Introduction

Regional analgesia techniques reduce neuroendocrine stress response, thromboembolic phenomenon and requirement of parenteral analgesics in the postoperative period.[1] The duration of effective analgesia is dependent on the dose and concentration of local anesthetics. Higher the volume and concentration, greater will be the incidence of local anesthetic systemic toxicity. Opioids as additives extend postoperative pain relief along with improving the quality of analgesia, but they result in urinary retention, sedation and pruritis.[2] Nonopioids such as clonidine, ketamine, neostigmine, tramadol, midazolam and dexmedetomidine have been evaluated as epidural adjuvants.[3]

Epidural neostigmine has been researched in doses ranging from 1 to 10 ug/kg.[4] The major drawback with neostigmine is a high incidence of nausea and vomiting. Dexmedetomidine as epidural adjuvant (1-2 ug/kg) exhibited good sensory analgesia in clinical trials. However, there have been conflicting evidence regarding drug-induced bradycardia and hypotension.[5]

Because of the adverse effects, neostigmine and dexmedetomidine are not frequently used as neuraxial adjuvants by anesthesiologists. The effects are dose-dependent,

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and hence we presumed that combining the two drugs at low doses can effectively potentiate the analgesia without increasing the incidence of side-effects.

The present study was conceptualized to study the combined analgesic profile of dexmedetomidine with neostigmine compared to neostigmine alone. The analgesic synergism was evaluated for adverse effects and hemodynamics.

Material and Methods

Sixty patients undergoing lower limb procedures, mainly hemiarthroplasty, dynamic hip screw, interlocking nail femur/tibia and malleolar fixation, between 18 and 50 years of age and American Society of Anaesthesiologists (ASA) physical Status I and II were selected for the study. The study was approved by Institute Ethics Committee. The enrolled patients were explained about postoperative pain relief technique and written informed consent for epidural catheter placement and participation was obtained. Patients who refused participation, had moderate to severe cardiac, renal, pulmonary or neurological diseases, significant scoliosis or kyphosis, morbidly obese or had coagulopathy were excluded from the study. Randomization was achieved by applying Microsoft excel random sequence and results were sealed in envelope.

The patients were assigned to three groups:
Group I: 6 mL of 0.25% bupivacaine.
Group II: 6 mL of 0.25% bupivacaine + 1 μg/kg of neostigmine.
Group III: 6 mL of 0.25% bupivacaine + 1 μg/kg of neostigmine + 0.5 μg/kg of dexmedetomidine.

Neostigmine is commercially available in 0.5 mg/mL concentration whereas dexmedetomidine is available as 0.1 mg/mL. Insulin syringe (40 units = 1 mL) was used for loading the required dose of study drugs, and this was added to 10 mL syringe containing 6 mL of bupivacaine. The markings on the syringe were concealed by a white plaster tape to ensure blinding. All patients were premedicated with Alprazolam 0.25 mg and Ranitidine 150 mg a night before and morning of surgery. Venous access was secured and Ringer lactate was started as coloading infusion. ASA prescribed monitoring was started and continued throughout the surgery.

Combined spinal-epidural anesthesia was performed (Portex® CSEcureä, SIMS Portex Inc) in L2-L3 or L3-L4 interspace with needle through needle technique in all patients in sitting a position. 3 ml of 0.5% hyperbaric Bupivacaine with 25 mcg of fentanyl was deposited in the subarachnoid space. A catheter length of 3-4 cm was left in the epidural space and the catheter fixation was secured with Lockit epidural fixator device. One hour into surgery, epidural was activated with 3 ml of 2% lignocaine in all patients. At the end of surgery, patients were given epidural medication according to the group assigned and shifted to the postoperative ward after 15 min. The primary investigator was blinded to the contents of epidural drug syringe.

Duration of sensory analgesia, hemodynamics, Bromage scores,[6] Visual analog scale (VAS) (zero for no pain to 10 for unbearable pain), sedation scores, nausea and vomiting were recorded after epidural injection and then hourly up to 10 h. Good pain relief was defined as VAS score ≤4. Once this score was reached, rescue analgesic (Injection Tramadol 50 mg intravenous [IV]) was administered and an epidural patient-controlled analgesia pump (elastomeric infusion pump, Royal Fornia Medical Equipment Co., Ltd.) containing 0.125% bupivacaine with 2 ug/ml fentanyl was started at 5 ml/h (fixed dose, continuous infusion with no top up doses). The total dose of tramadol allowed in our study was 4 mg/kg/24 h. Bradycardia was defined as heart rate (HR) <50 bpm and blood pressures (BP) <20% of baseline (at the time of administration of epidural study drug) was hypotension requiring colloid boluses. The colloid chosen was voluven (6% hetastarch, fresenious kabi) as 100 ml bolus for managing hypotension.

Statistical analysis

Sample size was determined based on estimates of the primary efficacy end point of "time to first patient request" for rescue analgesia, assuming a population mean difference of 2 h and a standard deviation (SD) of 2 h for all groups. Sixteen patients per group was considered necessary to detect statistical significance ($\alpha = 0.05$) with power ($1-\beta$) = 80%.

Statistical analyses were performed using the statistical package SPSS version 17.0 (Chicago, IL, USA). Statistical comparisons among the three groups were performed by using a two-way analysis of variance with subsequent comparisons of pairwise differences, where appropriate. VAS pain scores were analyzed by using repeated-measures analysis of variance with *post hoc* analysis using Tukey's *post-hoc* test. The proportion of patients that requested rescue medication was analyzed using the Cochran-Mantel-Haenszel test. Unless otherwise specified, data are mean ± SD, and a $P < 0.05$ was defined as significance.*symbol donates statistical significance between the parameters.

Results

All 60 neuraxial blocks were successfully placed in the first attempt. The patient's demographics as depicted in Table 1

was comparable. Figure 1 shows the different orthopedic procedures performed in our study.

The assessment of pain relief in the postoperative period was done by evaluating VAS scores at rest. Table 2 shows VAS scores at different times. Group I (16/20) and II (15/20) patients reached a VAS of 4 in 120 ± 18 and 168 ± 14 min respectively. 18/20 patients in Group III had same scores in 240 ± 15 min. Administration of tramadol improved pain scores in Group I and II and therefore, these patients showed a lower pain scores at 4th, 5th and 6th h measurements ($P < 0.05$).

The subjective sedation score was calculated as follows; 0 - restless patient with inadequate analgesia, 1 - calm and cooperative, 2 - patient asleep, arousable on verbal command, 3 - asleep, arousable on tactile stimulation, 4 - asleep, arousable with vigorous shaking and 5 - deep sleep, airway may need support. Addition of dexmedetomidine in Group III resulted in median sedation score of 3. Patients in Group I showed lower sedation scores, presumed to be a consequence of poor pain relief. Sedation scores were influenced by administration of rescue analgesic [Table 3].

The duration of analgesia was defined as the mean time to reach a VAS score >4 from the time of epidural injection of test drug. Patients in Group I had analgesia up to 144 min (123.86 ± 164.14), 176.25 min (139.87 ± 212.63) in Group II and 273.5 min (240.11 ± 306.89) in Group III, $P < 0.001$ [Figure 2].

Heart rates and BP showed a decreasing trend after administration of study drug in Group III. At no point of time, however, the mean HR were below 60 bpm. However, there was an appreciable fall in BP in Group III and 20% of patients had to be resuscitated with colloids in early postoperative phase [Figures 3-5].

SIgnificantly more patients in Group I and II required rescue analgesic than in Group III (70% vs. 50% vs. 20%, $P = 0.02$).

The addition of epidural adjuvants have not affected the duration of postoperative motor blockade in our study [Table 4].

Retching and vomiting was seen in 31/60 patients with Tramadol administration in all groups ($P = 0.67$). None of

Table 1: Comparison of demographics and surgical duration between the groups

Parameters	Mean (SD)		
	Group I	Group II	Group III
Age	44 (5)	40 (6)	45 (7)
Gender (male/female)	14/6	12/8	12/8
Weight	65 (4)	63 (4)	68 (6)
Duration of surgeries (min)	104 (3)	96 (5)	106 (4)

SD = Standard deviation

Table 2: VAS scores

Time	Mean ± SD			*P*
	Group I	Group II	Group III	
1st h	1.70±1.41	1.45±1.46	0.10±0.44	0.00
2nd h	4.15±2.25	3.30±2.47	0.60±1.27	0.00
3rd h	3.15±2.30	2.75±2.04	2.10±1.88	0.28
4th h	1.75±1.29	1.40±1.81	2.85±2.13	0.03
5th h	1.20±0.69	1.75±1.58	2.10±1.91	0.00
6th h	1.60±1.78	1.18±0.52	1.90±1.99	0.00
7th h	2.40±0.44	1.80±0.67	1.75±1.63	0.10
8th h	2.60±0.80	2.25±1.34	1.86±1.48	0.18
9th h	2.74±0.60	2.78±0.50	2.05±0.82	0.00
10th h	3.44±0.80	2.90±1.20	2.17±0.10	0.00

SD = Standard deviation, VAS = Visual analogue scores

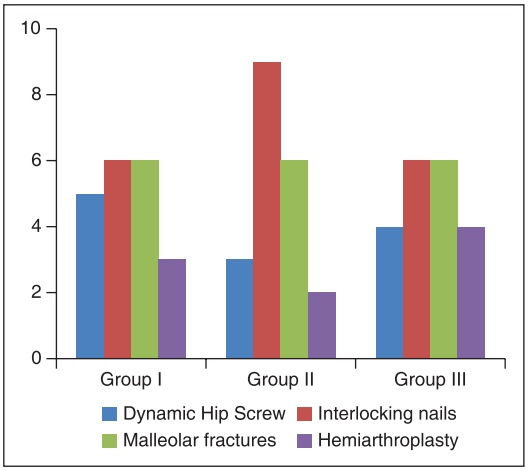

Figure 1: Histogram of operative procedures conducted

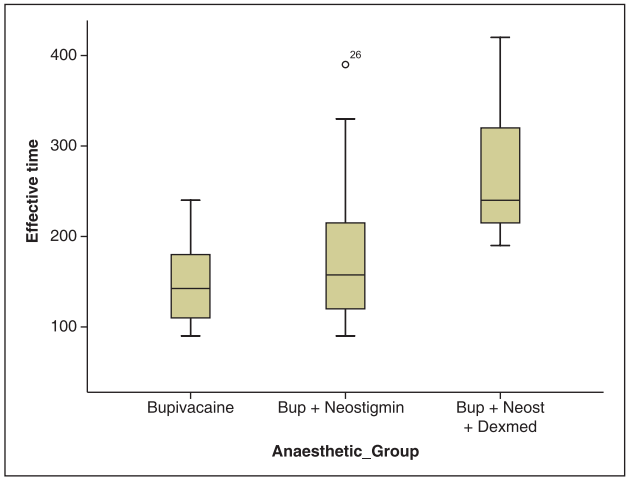

Figure 2: Box plot of effective duration of analgesia

Table 3: Sedation scores

Time	Mean ± SD			*P*
	Group I	Group II	Group III	
0 min	2.05±0.22	2.05±0.22	2.00±0.00	0.59
1 h	2.45±0.75	2.35±0.81	2.45±0.60	0.88
2nd h	2.05±0.75	2.05±0.82	2.55±0.75	0.00
3rd h	2.00±0.64	2.25±0.63	2.45±0.75	0.11
4th h	2.80±0.52	3.15±0.48	2.30±0.65	0.00
5th h	2.00±0.32	3.05±0.51	3.05±0.63	0.00
6th h	2.05±0.22	2.00±0.32	3.20±0.61	0.00
7th h	2.00±0.00	1.95±0.22	2.40±0.55	0.00
8th h	2.00±0.00	1.95±0.05	2.00±0.07	0.00
9th h	1.05±0.30	2.00±0.00	2.00±0.07	0.00
10th h	1.00±0.07	2.00±0.00	2.05±0.05	0.00

SD = Standard deviation

Table 4: Regression of motor block (min)

Anesthetic group	Mean	SD	*P*
I	114.5	57.62	0.236
II	117.0	56.67	
III	141.0	46.22	

SD = Standard deviation

our patients suffered with postdural puncture headache and neurological deficit in the postoperative period.

Discussion

The combination of dexmedetomidine and neostigmine in low doses to epidural bupivacaine provided better and longer duration of postoperative analgesia in orthopedic patients. The motor blockade was not significantly prolonged by the drugs.

Our choice of 0.5 μg/kg as a dose for dexmedetomidine has been previously used by Memis *et al.* as an additive to lignocaine in IV regional anesthesia for upper limb surgeries.[7] However, in epidural mixture this dose has not been previously reported in any clinical trial.

Visual analog scale scores-We achieved results similar to Maruan *et al.* with neostigmine. The authors had combined 1 ug/kg neostigmine to 0.6 mg morphine for similar surgical profile and reported the combination to be a clinically effective analgesic mixture.[8] A study by Jain *et al.* in Indian patients have cited a significant improvement in postoperative pain relief with the addition of dexmedetomidine.[5]

Sedation scores-In our trial, Sedation scores in Group III correlated with the results of Bajwa *et al.*, where dexmedetomidine (1 ug/kg) was used as an adjuvant to ropivacaine.[9] The onset of sedation was early and persisted for 4-5 h without any incidence of respiratory embarrassment. Epidural neostigmine has also been evaluated for sedation in

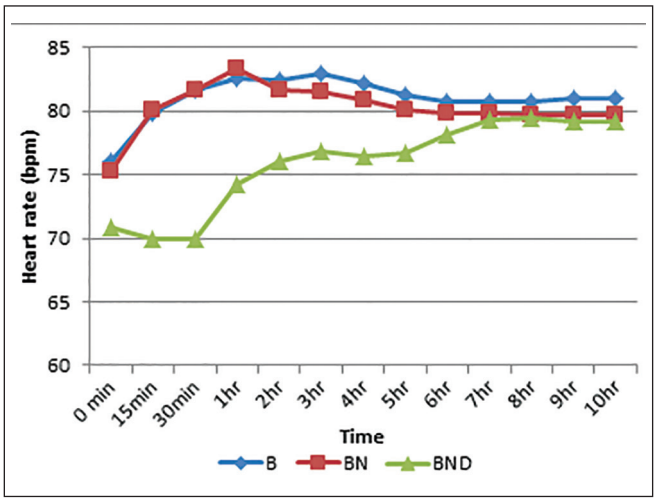

Figure 3: Comparison of heart rate between the groups

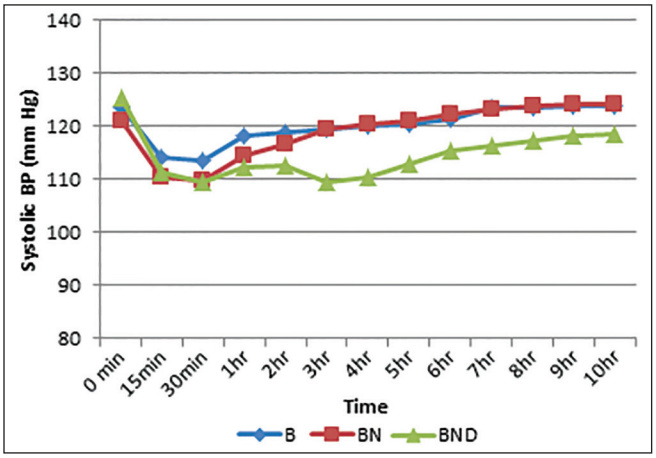

Figure 4: Comparison of systolic blood pressure between the groups

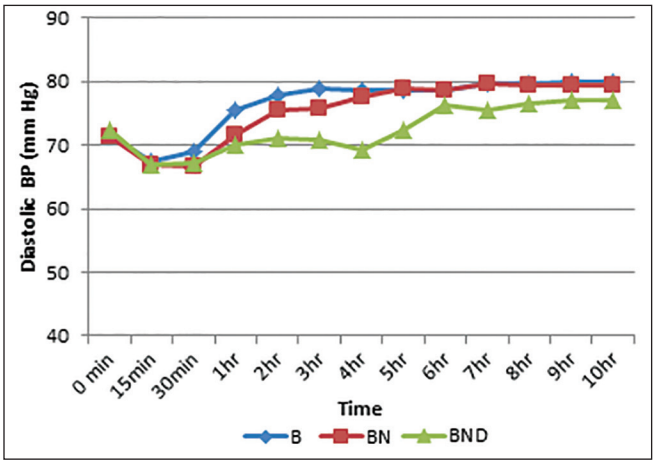

Figure 5: Diastolic blood pressure (mm Hg)

75 ug, 150 ug and 300 ug doses in obstetric analgesia by Kaya *et al.*[10] They have reported clinically significant analgesia for some hours in 300 ug group. Our patients in Group II have received lower dose and hence, sedation was not proven to be statistically significant.

Hemodynamic profile-patients in Group I and II exhibited stable HR and BP than Group III patients. Neuraxial neostigmine increases sympathetic outflow, thus counteracts the hypotension caused by bupivacaine and bradycardia caused by alpha 2 agonists.[11] Dexmedetomidine epidurally causes sympatholysis, thereby decreasing HR and BP in a dose-dependent manner, documented in a systematic review and metaanalysis by Wu *et al*.[12]

Adverse effects profile-cholinergic gastrointestinal (GI) side effects are the major problems with neostigmine. The incidence of nausea, vomiting and diarrhea are higher with intrathecal administration.[13] Maruan *et al*. have commented that doses as high as10 ug/kg of epidural neostigmine do not cause significant GI effects.[8]

Limitations of the study-Sensory level of block achieved ranged between T7 and T11. The sample size was clinically small. VAS is a subjective score and has a low specificity.[14] The chemical interactions between the study drugs have not been studied *in vitro*.

Konaki *et al*.[15] have expressed concerns of neurotoxicity (moderate to severe demyelination of white matter demonstrated in animal studies) following epidural administration of dexmedetomidine. So far, no anecdotal case report in humans is published to our knowledge.

Conclusions

The addition of only neostigmine to bupivacaine could not produce statistically significant differences in duration and quality of analgesia, when compared to bupivacaine alone. Epidural dexmedetomidine with neostigmine exhibited excellent synergism of analgesia with no increase in adverse effects of individual drugs.

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