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INTRATHECAL CLONIDINE WITH LEVOBUPIVACAINE FOR TRANSURETHRAL RESECTION OF PROSTATE: A RANDOMISED CONTROLLED TRIAL

Anesthesiology

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ABSTRACT

We studied the effects of intrathecal clonidine added to isobaric levobupivacaine for anesthesia & analgesia in transuretheral resection of prostate (TURP) surgery and observed there side effects. In this randomized, prospective, controlled trial, two groups of 50 patients were studied as (i) Patients in Group A received 15 mg (3ml) of 0.5% isobaric levobupivacaine and 0.30ml of 0.9% normal saline and (ii) Patients in Group B received 15 mg (3ml) of 0.5% isobaric levobupivacaine and 0.30ml (50µg) of clonidine. The duration of analgesia, variation in motor block, hemodynamic variations, any associated side effects due to intrathecal clonidine were recorded. It was observed that addition of small dose of clonidine to isobaric levobupivacaine given intrathecal resulted in faster onset, longer duration of analgesia & prolongation of motor blockade & there side effects (hypotension) were treatable. The finding suggests that clonidine added to isobaric levobupivacaine is an attractive option for improving the quality and duration of analgesia for treating pain and discomfort to the patient in transuretheral resection of prostate surgery.

KEYWORDS

Analgesia, Isobaric levobupivacaine, Intrathecal Clonidine, TURP.

INTRODUCTION:

While spinal anaesthesia has many advantages, the limited duration of action appears to be one of its downsides. Intrathecal α_2 agonists prolong the duration of action of local anaesthetics and reduce the required dose. The intrathecal use of clonidine, a partial α_2 adrenoceptor agonist, has been shown as an effective and safe procedure [1, 2]. Levobupivacaine is a long-acting local anaesthetic with a pharmacological structure similar to that of bupivacaine. Levobupivacaine has been shown to have a larger safety margin and less neurotoxic and cardiotoxic side-effects than bupivacaine [3].

In this study, we aimed to investigate the influences of clonidine added to levobupivacaine on the time of onset of spinal block and durations of sensory and motor blocks in patients undergoing transurethral endoscopic surgery by spinal anaesthesia.

AIM

To compare the analgesic effect of intrathecal levobupivacaine in combination with a small dose of clonidine versus intrathecal levobupivacaine alone in transurethral resection of prostate surgery and study the duration of analgesia, variation in motor block, hemodynamic variations in both the groups. Any associated side effects due to intrathecal clonidine like bradycardia, seddation and dryness of mouth were also studied.

MATERIALS AND METHODS

With approval from the Institutional Ethics Research committee and written informed consent, this prospective, randomized, placebo-controlled study was performed on 100 adult male patients, 45-75 years belonging to American Society of Anesthesiologists (ASA) physical status I, II, and III diagnosed as carcinoma prostate and posted for transurethral resection of prostate surgery. According to simple random sampling technique, all patients included in the study were assigned to one of the two groups. Every first patient was assigned to group A and every second patient was assigned to group B as per their admission in hospital.

Patient's who refused for regional anesthesia, with history of allergic reaction to the drug under study, low total leucocyte count, infection of local site, history of myocardial infarction, hypotension, respiratory disease, history of bleeding diathesis or coagulation disorders were excluded from the study.

Patients in Group A received 15 mg (3ml) of 0.5% levobupivacaine and 0.30ml of 0.9% normal saline and patients in Group B received 15 mg (3ml) of 0.5% levobupivacaine and 0.30ml (50µg) of clonidine. Volume of drugs in both the groups was equal (3.3 ml). All patients were preloaded with Ringer Lactate solution 500ml IV. With a 27G spinal needle, 3.3ml of drug as described above was injected in the subarachanoid space via interspace between L3-L4 or L2-L3 vertebra in sitting position & patient`s were then made supine without any delay.

Level of sensory blockade to pain was assessed by pin prick method and time for sensory blockade to reach maximum level was recorded. During the procedure all patients were administered 100% oxygen by face mask. Monitoring included heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), oxygen saturation (SpO_2), and 5 lead electrocardiograph at baseline ,every 1 min. till the block was achieved and then every 5 min till the procedure ended. Hypotension was treated with Inj. ephedrine 3-6 mg IV bolus and bradycardia with Inj. Atropine 0.6mg IV bolus. Any adverse episode in the form of nausea, vomiting, respiratory depression, itching and pruritis during and after the procedure was recorded. Any treatment given for side effects was recorded. Post operatively the severity of pain was assesed by using visual analogue score (VAS) (0 to10, 0-no pain and 10-worst imaginable pain). Motor Blockage of the lower extremities was determined by using Bromage scale. Sedation was assessed with a four-point verbal rating scale; 1 (no sedation) to 4 (unarousable with loss of verbal contact).

Post procedure pain was treated by Inj. Tramadol 100mg i.m. when needed by the patient for severe pain (VAS >5). Time was recorded for the need of rescue analgesia if needed.

The various data obtained, included the haemodynamic parameters (systolic, diastolic and mean blood pressure and pulse rate), duration of analgesia, time of rescue analgesia, level of pain by VAS score and movement of lower limb by Bromage scale were compared with baseline values within each group as well as with corresponding time duration among the groups.

STATISTICAL ANALYSIS:

Unless stated otherwise, data are expressed as mean ± SD. The mean value for each parameter was calculated using the formula, mean = $\sum Xi/n$ and standard deviation was calculated using the formula $\sqrt{1/n \sum (Xi - X)^2}$. The unpaired Student's T-test for equality of means was employed for inter group comparison after obtaining the mean values and the standard deviation and the 2-tailed significance (p-value) was calculated. The paired T-test was utilized for intra group comparison .SPSS statistical software(version 12.0) was utilized for this purpose. A p-value <0.05 was considered to be statistically significant whereas a value of <0.01 was taken as statistically moderately significant. P-values < 0.001 were considered to be highly significant statistically.

RESULTS

Demographic data

Both the groups were comparable with respect to their demographic profile [Table 1 and Figure 1].

Table 1 Demographic profile study of two groups

Demographic Variables Mean ± S.D.	Group A (n-50)	Group B (n-50)	'p' value
Age (years)	51.58 ± 7.38	52.40 ± 8.64	0.611
Weight (kg)	72.48 ± 7.93	74.74 ± 8.39	0.170
Height (cms)	176.62 ± 3.38	174.02 ± 3.04	0.536
BMI [wt./ht^2 (m)]	23.39 ± 2.96	24.68 ± 3.02	0.244

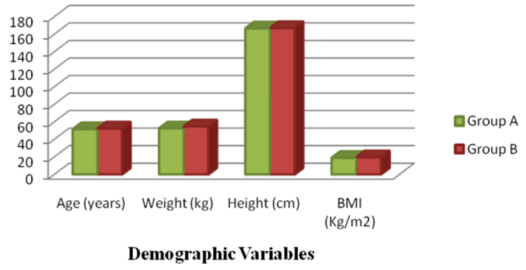


Figure 1: Demographic data

Characteristics of Spinal Block

Time of onset of sensory block was 2.7 ± 0.3 min in group A and in group B was 1.5 ± 0.2 min. Time of onset of motor block was 3.5 ± 0.5 min in group A and in group B was1.9 ± 0.5 min. The duration of motor blockade (return of Bromage score to I) was 96.30 ± 17.167 min in group A and in group B 143.60 ± 17.672 min. Duration of motor blockade was significantly higher in group B (p=0.001). Time of regression of spinal anaesthesia below level L1 was 136.10 ± 11.12 min in group B which was statistically longer than 95.20 ± 10.44 min in group A (p=0.001). (Table 2)

Table 2. Characteristics of Spinal Block

	Group A (min)	Group B (min)
Time of onset of sensory block (min)	2.7 ± 0.3	1.5 ± 0.2
Time of onset of motor block (min)	3.5 ± 0.5	1.9 ± 0.5
Duration of Motor Blockade (Return of Bromage score to I)	96.30 ± 17.167	143.60 ± 17.672
Regression of Sensory analgesia below L1	95.20 ± 10.44	136.10 ± 11.12
p= 0.001		

Comparison of VAS

VAS of the two groups was consistently lower at all times in the clonidine group. There was no significant difference at 15 and 30 min after the block. The difference was significant at 45 min (p< 0.05) and highly significant from 60 to 285 mins (p=0.001). There was no significant difference again at 300 min after the block. (Table 3, Figure 2)

Table 3. Visual Analogue Score

Time	Group A (Mean ± S.D.)	Group B (Mean ± S.D.)	'p' value
15 min	0.00 ± 0.000	0.00 ± 0.000	1.000
30 min	0.00 ± 0.000	0.00 ± 0.000	1.000
45 min	0.28 ± 0.970	0.00 ± 0.000	0.042
60 min	1.52 ± 2.288	0.00 ± 0.000	0.001
75 min	3.38 ± 2.294	0.00 ± 0.000	0.001
90 min	3.54 ± 1.787	0.18 ± 0.755	0.001
105 min	3.14 ±1.414	0.32 ± 0.891	0.001
120 min	3.34 ± 1.255	0.32 ± 0.879	0.001
135 min	3.30 ± 1.147	0.26 ± 0.664	0.001
150 min	3.06 ± 1.202	0.58 ± 1.279	0.001
165 min	2.94 ± 1.168	0.74 ± 1.440	0.001
180 min	2.90 ± 1.233	0.78 ± 1.375	0.001
195 min	2.70 ± 1.182	0.70 ± 1.199	0.001
210 min	2.48 ± 1.216	0.54 ± 1.034	0.001
225 min	2.18 ± 1.190	0.42 ± 0.758	0.001
240 min	1.94 ± 1.219	0.24 ± 0.591	0.001
255 min	1.60 ± 1.161	0.14 ± 0.452	0.001
270 min	1.26 ± 1.121	0.04 ± 0.198	0.001
285 min	0.66 ± 0.982	0.00 ± 0.000	0.001
300 min	0.04 ± 0.283	0.04 ± 0.283	1.000

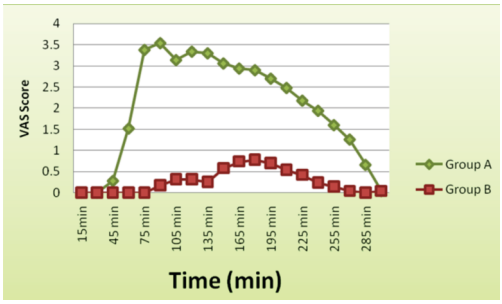


Figure 2. Visual Analogue Score (VAS)

Duration of Analgesia-

Duration of analgesia i.e. the time interval between spinal anaesthesia and first request of rescue analgesia was significantly higher in group B (192 ± 12.550 min) as compared to group A (107 ± 7.588 min), p= 0.001. Number of patients required rescue analgesia in group A was 22 (44%) and in group B was 5 (10%). Number of patients not required rescue analgesia was 28 (56%) in group A and in group B was 45 (90%). The difference was highly significant in both the groups (p=0.001) (Table 4, Figure 3).

Table 4. Rescue Analgesia

	Group A (n=50)	Group B (n=50)	'p' value
Duration of analgesia (min). {Time interval between spinal anaesthesia and 1st request of rescue analgesia}	107 ± 7.588	192 ± 12.550	0.001
Number (%) of patients required rescue analgesia	22 (44%)	5 (10%)	0.001
Number (%) of patients not required rescue analgesia	28 (56%)	45 (90%)	
Number (%) of patients required 2nd top up of rescue analgesia	5 (10%)	0 (0%)	0.022
Number (%) of patients not required 2nd top up of rescue analgesia	45 (90%)	50 (100%)	

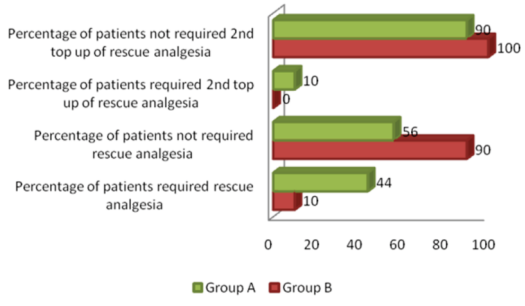


Figure 3. Rescue Analgesia

Comparison of hemodynamic parameters

The baseline blood pressure and heart rate was comparable in both groups. There was significant fall in systolic blood pressure in both the groups but the fall in the systolic blood pressure was more in group B as compared to group A. Maximum percentage of fall in group A was at 0-30 min (9.9673 ±9.20) and in group B was at 0-20 min (17.0339 ± 11.13).A small but statistically insignificant fall in diastolic blood pressure was observed in both the groups (p>0.05). Maximum percentage of fall in DBP in group A was seen at 0-25 min (8.6036 ±10.41) and in group B was at 0-20 min (12.1236 ± 8.83). Maximum percentage of fall of mean blood pressure in group A was seen at 0-30 min (8.4088 ± 9.23) and in group B was seen at 0-20 min (15.0661 ± 8.74).

The mean pulse rate amongst the group A and B at baseline was 88.18 ± 13.248 per min and 87.08 ± 12.003 per min respectively. The baseline difference in between the groups was comparable (p=0.664). Fall in pulse rate during the operative procedure was not significant in both the groups except at time interval of 0-5 min. Maximum percentage of

fall in PR in group A was seen at 0-25 min (7.9240 ± 10.14) and in group B was seen at 0-30 min (8.5903 ± 14.18). (Tables 5,6,7,8 and Figures 4,5,6,7)

Table 5. Comparison of Systolic Blood Pressure

Time	Group A (mmHg)	Group B (mmHg)	'p' value
0 min	132.52 ± 19.120	130.32 ± 19.172	**0.567**
5 min	125.98 ± 17.794	122.86 ± 18.758	**0.396**
10 min	123.06 ± 16.020	115.24 ± 17.691	**0.023**
15 min	120.30 ± 16.165	112.02 ± 16.806	**0.014**
20 min	119.96 ± 14.608	107.52 ± 18.053	**0.001**
25 min	120.14 ± 15.258	108.68 ± 15.853	**0.001**
30 min	118.28 ± 13.489	109.94 ± 12.553	**0.002**

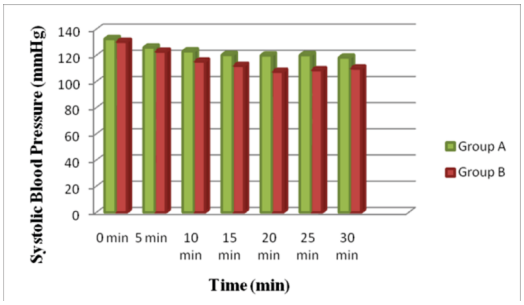


Figure 4. Comparison of Systolic Blood Pressure

Table 6. Comparison of Diastolic Blood Pressure

N=100

Time	Group A (mmHg)	Group B (mmHg)	'p' value
0 min	78.56 ± 10.059	79.00 ± 9.902	**0.826**
5 min	74.90 ± 9.956	74.42 ± 10.100	**0.811**
10 min	73.06 ± 8.888	70.90 ± 11.267	**0.290**
15 min	72.44 ± 9.442	70.08 ± 10.287	**0.235**
20 min	72.40 ± 8.889	68.50 ± 10.342	**0.046**
25 min	71.42 ± 9.727	69.58 ± 9.291	**0.336**
30 min	72.32 ± 9.595	70.04 ± 8.990	**0.223**

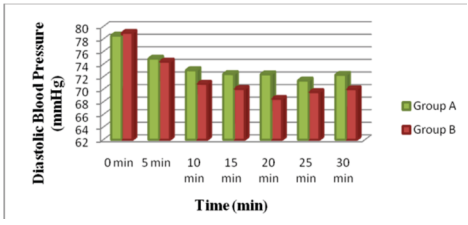


Figure 5. Comparison of diastolic blood pressure

Table 7 .Comparison of mean blood pressure

N=100

Time	Group A(mmHg)	Group B(mmHg)	'p' value
0 min	96.46 ± 12.163	96.26 ± 12.378	0.935
5 min	92.38 ± 11.505	90.88 ± 12.118	0.527
10 min	90.12 ± 9.629	85.76 ± 12.617	0.055
15 min	88.79 ± 10.576	84.30 ± 12.225	0.054
20 min	88.48 ± 9.455	81.48 ± 11.701	0.001
25 min	87.38 ± 10.170	82.72 ± 11.103	0.032
30 min	87.80 ± 10.357	83.64 ± 9.749	0.041

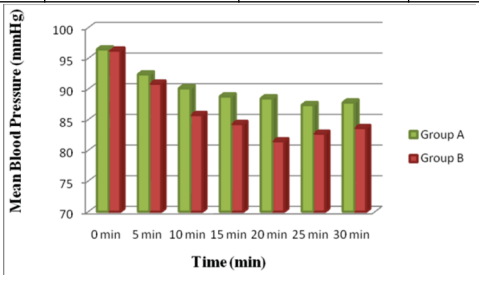


Figure 6. Comparison of mean blood pressure

Table 8 .Comparison of Pulse Rate

N=100

Time	Group A (per min)	Group B (per min)	'p' value
0 min	88.18 ± 13.248	87.08 ± 12.003	0.664
5 min	85.76 ± 13.142	86.18 ± 11.842	0.867
10 min	84.68 ± 12.658	82.92 ± 11.764	0.473
15 min	82.28 ± 11.858	82.28 ± 11.983	1.000
20 min	81.58 ± 12.076	80.44 ± 11.084	0.624
25 min	80.54 ± 10.545	78.86 ± 11.269	0.443
30 min	80.66 ± 9.768	78.68 ± 11.177	0.348

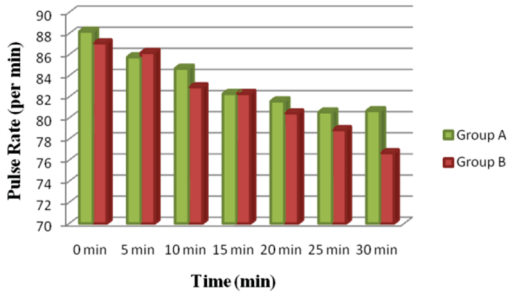


Figure 7.Comparison of pulse rate

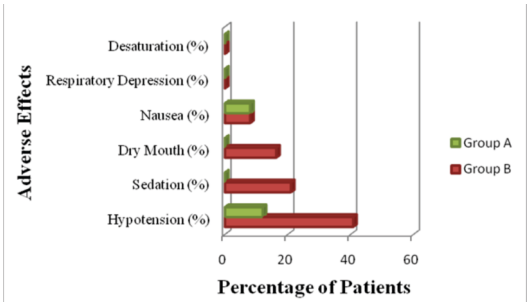
Side effects of clonidine

There was no significant change in respiratory rate and SpO2 from the baseline in both the groups (p> 0.05) and supplemental oxygen or any other form of airway management was not needed. Incidence of sedation was assessed by 4 point sedation score, which was higher and statistically significant in group B (21%), no patient was sedated in group A (p=0.001). Sedated patients had drowsiness with sedation score 2. None of the patients had sedation score of 3 and 4 in group B. Dryness of mouth in group B was higher (16.3%), which was statistically significant (p=0.003). Four (8%) patients in each group B had nausea, the difference in between the two groups was not significant (p=1.000). There was a statistically significant difference in number of patients who had hypotension intraoperatively. Twenty (40.8%) patients in group B and 6 (12%) patients in group A (p=0.001) had hypotensive episodes which was treated with small dose of 6mg ephedrine IV. (Table 9, Figure 8)

Table 9. Adverse Effects

Side Effects	Group A (n=50)	Group B (n=50)	'p' value
Hypotension	6 (12%)	20 (40.8%)	0.001
Sedation	0	13 (21%)	0.001
Dry mouth	0	8 (16.3%)	0.003
Nausea	4 (8%)	4 (8%)	1.000
Respiratory depression	0	0	
Desaturation	0	0	

Figure 8. Adverse Effects



DISCUSSION

Clonidine is a partial alpha 2 adrenergic agonist that has a variety of different actions including antihypertensive effects as well as the ability to potentiate the effects of local anesthetics. They act by binding to presynaptic C-fibers and postsynaptic dorsal horn neurons. Their analgesic action is a result of depression of the release of C-fiber transmitters and hyperpolarisation of postsynaptic dorsal horn neurons.[4] Local anesthetic agents act by blocking sodium channels. The prolongation of effect may result from synergism between local anesthetic and α_2-adrenoceptor agonist, while the prolongation of the motor block of spinal anesthetics may result from the binding of α_2-adrenoceptor agonists to motor neurons in the dorsal horn.[5]

Intrathecal α_2-receptor agonists have been found to have antinociceptive action for both somatic and visceral pain.[6]

Addition of clonidine has shown to result in the prolongation of the sensory blockade and a reduction in the amount or concentration of local anesthetic required to produce perioperative analgesia. Different routes for the administration of regional anesthesia, including intravenous, intrathecal and epidural ones, as well as the addition of clonidine for peripheral neural blockade, have been described. Most authors agree that the use of clonidine for regional neural blockade in combination with a local anesthetic results in increased duration of sensory blockade with no difference in onset time. The addition of clonidine to the local anesthetic opioid mixtures seems to produce analgesia of longer duration, more rapid onset and higher quality. The higher doses of clonidine were associated with a more cephalad spread of the spinal blockade and increased sedation and hypertension. [7]

Levobupivacaine has increasingly been used in the clinical anesthesia practice since last few years because of its safer pharmacological profile. Literary evidence has established the safety of levobupivacaine over bupivacaine when used in regional anesthesia as the incidence of various adverse outcomes is higher with the latter as compared to levobupivacaine. The incidence of adverse cardiac and neurological events was significantly higher with bupivacaine as compared to levobupivacaine when used in regional anesthesia. Similarly, the potential for CNS toxicity is lower with levobupivacaine as compared to bupivacaine.[8,9,10]

Milligan KR et al in 2000 studied the addition of the alpha(2)-adrenergic agonist clonidine to epidural infusions of levobupivacaine significantly improved postoperative analgesia in patients undergoing total hip replacement.[11]

Bazin Met al in 2011 studied the potentiation of analgesia for labour by the addition of clonidine to epidural low-concentration levobupivacaine with sufentanil in a randomised, double-blinded study. The study solutions, made of 100 ml levobupivacaine 0.0625% plus sufentanil 0.45 μg.ml(-1) and either 150 μg clonidine or no clonidine, were used for induction of analgesia, and for its maintenance with self-administered boluses and a continuous background infusion. He found that clonidine (1.36 μg.ml(-1)) added to the epidural solution of low-concentration levobupivacaine improves the quality of analgesia.[12]

Aliye Esmaoğlu in 2013 aimed to investigate the effect of adding dexmedetomidine to intrathecal levobupivacaine. Spinal anaesthesia was performed with 3 ml of levobupivacaine 0.5% isobaric with 0.3 mL of normal saline in Group L, or 3 mL of levobupivacaine 0.5% with 0.3 mL (3 μg) of dexmedetomidine in Group LD. Dexmedetomidine was diluted with normal saline to 10 μg/mL in patients undergoing transurethral endoscopic surgery. They concluded that addition of intrathecal dexmedetomidine to levobupivacaine for spinal anaesthesia shortens sensory and motor block onset time and prolongs block duration without any significant adverse effects.[13]

In the study of Strebel et al. [1] on orthopaedic cases, using clonidine at a dose below 150 μg in combination with isobaric bupivacaine in a dose-dependent fashion was shown to provide significantly prolonged duration of spinal anaesthesia and analgesia without disrupting the haemodynamic stability and inducing sedation.

Santiveri et al. [14] used 75 μg clonidine to prilocaine in patients undergoing transurethral resection of bladder tumours under spinal anaesthesia and reported prolonged sensory and motor blocks along with reduced postoperative analgesic requirement.

Thus we conclude, addition of 50 μg clonidine intrathecal to 0.5% isobaric levobupivacaine in spinal anaesthesia prolongs sensory and motor block durations without causing any significant side effects.

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