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A comparison of effects of intrathecal clonidine and intravenous clonidine on duration of spinal anaesthesia

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Abstract

Introduction: There are studies which infer that spinal anaesthesia can be prolonged after adding adjuvants to local anaesthetics or by oral premedication before the block is performed.

Aim of our study: To prolong the duration of spinal anaesthesia after the block has been performed.

The study was done to compare the effects of intrathecal and intravenous clonidine on duration of spinal anaesthesia and to evaluate any advantages or disadvantages of intravenous over intrathecal clonidine in terms of analgesia, sedation, post–operative shivering and hemodynamic stability.

Methodology: A prospective randomized double blind controlled comparative clinical study, was conducted on 60 patients, aged 20-60 years belonging to ASA I and II scheduled for elective infraumbilical procedures. Patient were divided into three groups of 20 each randomly, Group A- intrathecal bupivacaine (0.5% heavy) 3ml (15mg) + 75mcg of intrathecal clonidine, Group B- intrathecal bupivacaine (0.5% heavy) 3ml (15mg) + 3 mcg/Kg of intravenous clonidine over 10min, Group C – (control group) - intrathecal bupivacaine (0.5% heavy) 3ml (15mg) + 0.5ml of normal saline, intrathecally in L3-L4 interspace with a 25G Quinke's needle. Intraoperatively the parameters noted were; **Sensory characteristics-** Time of onset of analgesia (T10), Maximum level of analgesia achieved, Time taken for maximum level of analgesia, Time for sensory block to regress to T10, Total duration of analgesia(rescue analgesic on patient demand). Motor characteristics- Time of onset of motor blockade (grade 1 bromage), Maximum grade of motor blockage achieved, Total duration of motor blockade (regression to Bromage-I), Hemodynamic monitoring, Sedation levels (OAA/Sscale) and Shivering episodes.

Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables.

Results: Intravenous clonidine after bupivacaine spinal anaesthesia has characterstics similar to and comparable with intrathecal clonidine with bupivacaine with an added advantage of significant. Intraoperative and post-operative sedation, Protection against postoperative shivering and Beneficial in prolonged surgeries.

Keywords: Clonidine, Spinal anaesthesia, Bupivacaine, Motor blockade, Analgesia

Introduction

Analgesic actions of α2 adrenergic agonists have been exploited for more than 100 years.[(1)] (Cocaine, Epinephrine). α2 agonists are the drugs that were initially developed for their central anti-hypertensive effects. These drugs have also been found to have analgesic, sedative, anaesthetic sparing properties by virtue of which they are being increasingly used for pre-medication and adjuvants to intravenous and inhalational anaesthetic agents. They are also gaining popularity as adjuvants to local anaesthetic agents, in various blocks including centrineuraxial blockade and for post-operative analgesia as well. There is an extensive clinical experience with clonidine as an adjuvant with spinal, epidural or peripheral block and is well known to prolong and potentiate anaesthesia for surgery. The intrinsic analgesic effect of clonidine has been demonstrated with a large dose of clonidine alone given intrathecally or epiduraly to control both intraoperative and post-operative pain, by an opiod independent mechanism,[(2)] but the analgesia was not sufficient to use it as a stand alone drug to provide adequate surgical anesthesia.[(3)] For this reason it has been used as an adjunt to local anaesthetic rather than alone. Clonidine has been tested for neuro toxicity in animal studies and has been suggested that intrathecal clonidine is safe. US FDA has approved preservative free clonidine formulation meant for epidural use in 1996. Previous studies[(4,5)] have demonstrated that by adding a small dose of vasoconstrictors to anaesthetic agent can prolong the block, but there are no reports of prolonging the duration of spinal anaesthesia after the block has been performed.

A study by K. RHEE et al[(6)] have concluded that intravenous clonidine administration within 1 Hour after subarachnoid block prolonged bupivacaine spinal anaesthesia for approximately one hour without any adverse effects.

Our study was undertaken to compare the effects of intrathecal and intravenous clonidine on duration of spinal anaesthesia and to evaluate any advantages or disadvantages of intravenous over intrathecal clonidine in terms of analgesia, sedation, post – operative shivering and hemodynamic stability. Though not revolutionary, clonidine and other α2 agonists by any route are likely to expand the scope and improve the reliability and efficacy of regional anaesthesia.

Methods

Approval from hospital ethics committee was obtained. Patients posted for spinal anaesthesia in the age group of 20 to 60 years of ASA I & II were randomly selected. All patients had undergone preanaesthetic check up one day prior to the procedure including optimization, explanation about the procedure, written consent regarding the procedure, overnight fasting and premedication with Tablet ranitidine 150 mg and Tablet alprazolam 0.5mg on the night before surgery and morning on the day of surgery. The study population was divided randomly into 3 groups of 20 patients. Group A – 20 patients receive intrathecal bupivacaine heavy 0.5 percent 3.0 ml + 75 mcg of intrathecal clonidine + 10 ml of normal saline intravenous over 10 minutes immediately after block. Group B – 20 patients received intrathecal bupivacaine heavy 0.5 percent 3.0 ml + 0.5 ml normal saline intrathecaly + 10 ml intravenous clonidine at 3 mcg /kg diluted to 10 ml with normal saline over 10 min immediately after block. Group – C: (Control Group) 20 patients received intrathecal bupivacaine heavy 0.5% 3ml + 0.5 ml normal saline intrathecal + 10 ml normal saline intravenously over 10 min immediately after block. On arriving to OT each patient was preloaded with 10 ml /kg of ringer lactate and standard intra operative monitoring of pulse, NIBP, SPO2 and ECG were used. Under Aseptic precaution spinal block was given in L3 – L4 / L2 – L3 inter space in sitting position at a rate of 1 ml per 3 seconds using 25 G spinal needle. **Parameters Noted:** Time of onset of analgesia by cold swab; defined as time taken from injection of drug to onset of analgesia at T10 level; Maximum level of analgesia achieved, Time taken for maximum level of analgesia; Time taken for onset of motor blockade defined as time of injection of drug to the onset of motor blockage of grade1 bromagescale; Quality of motor blockade assessed by bromagescale; Total duration of procedure; Intra-operative hemodynamic monitoring of pulse rate, NIBP, SPO2, ECG at 0, 2, 5, 10 min after block and every 10 min till the end of procedure; Total duration of analgesia defined as the time taken from the onset up to the point where patient complaints of pain at operated site requiring rescue analgesic; Time taken for sensory block to regress to T10 level; Total duration of motor blockade defined by time taken from onset of motor blockade to complete recovery(bromage 0); Level of sedation recorded using the 5 level observers assessment of alertness / sedation scale (OAA/S scale); Any episode of shivering in the patient.

Grading of motor paralysis was done by modified bromage scale -Grade 0: No paralysis; Grade 1: Inability to raise extend leg, but flexion of knees, feet present; Grade 2: Inability to raise extend or flex knees but flexion of ankle and feet present; Grade 3: Full paralysis.

Sedation was assessed by 4 point Sedation Scale of Filos with Grade 1- Awake and alert; Grade 2. Awake and drowsy; Grade 3. Drowsy, but arousable responding to physical stimulus; Grade 4. Unarousable, not responding physical stimulus.

Results

All the groups studied were comparable with respect to age, gender, weight and ASA distribution and there were no significant difference in demographic data. All blocks were tested before starting the procedure till deemed adequate for surgery. No patients in any group required conversion to general anaesthesia or required additional analgesics during surgery. There was no significant difference regarding the type and duration of surgical procedures in all group. The median range of cephalad level of maximum sensory level was (T8 – T4). The quality of motor block was comparable between all groups.

Sensory Characteristics:-

i. Mean time of onset or sensory block
   a) Group A – 215.35 +/- 68.17 sec
   b) Group B – 250.50 +/- 83.33 sec
   c) Group C – 215.25 +/- 47.53 sec

No statistical or clinical significance was seen between 3 Groups (Group A, Group B, Group C)

ii. Mean time of onset maximum sensory level
   a) Group A – 424.60 +/- 159.62 sec
   b) Group B – 443.25 +/- 107.77sec
   c) Group C – 435.05 +/- 145.63sec

No statistical or clinical significance between the 3 Groups

iii. Total duration of sensory block(min)
   a) Group A- 286 +/- 74.51(min)
   b) Group B- 231 +/- 43.13(min)
   c) Group C- 194 +/- 21.87(min)

Mean total duration of sensory block was highest in Group A with pair wise statistical difference of

Grp A vs Grp B	0.004 [Strongly / Highly significant]
Grp A vs Grp C	0.001 [Strongly Significant]
Grp B vs Grp C	0.064 [Suggestive Significance only]

❖ Mean total duration of Analgesia
   a) Group A - 329.25+/-93.78 min
   b) Group B - 301.75+/- 34.23 min
   c) Group C - 207.75+/- 31.49 min

The mean total duration of analgesia was highest in Group A(329.25+/_93.78 min) and least in Group C (207.75 +/- 31.49 min) with a pair wise statistical significance of

Gp A vs Gp B – 0.310 [Not significant]
Gp A vs Gp C - 0.001 [Strongly significant]
Gp B vs Gp C – 0.001 [Strongly significant]
Note: No statistical significance between Group A and Group B

❖ Motor Characteristic

1. Onset of motor block (Grade III Bromage Scale)

Gp A – 151.10 +/- 100.28 sec
Gp B – 170.15 +/- 57.25 sec

Gp C – 169.25 +/- 86.41 sec
Note: No statistical significance between the 3 groups

2. Time for maximum motor blockade(min)

Gp A – 314.75 +/- 148.49 sec
Gp B – 283.10 +/- 90.45 sec
Gp C – 357.00 +/- 99.53 sec
Note: No statistical significance between the 3 groups

3. Quality of motor blockade – Grade III in all the 3 groups
4. Duration of motor blockade – was highest in Gp A (269.50 +/- 64.17 min) and least in Gp C (190.50 +/- 27.24 sec)

Grp A vs Grp B	0.083 [No significance]
Grp A vs Grp C	0.001 [Strongly Significant]
Grp B vs Grp C	0.020 [Moderately Significant]

❖ Sedation

Intraoperative sedation score is significantly more with Gp B

Postoperative sedation score is significantly more with Gp B

❖ Shivering

Gp A -4 patients
Gp B – 0 Patients
Gp C- 7 patients
Group B had nil episodes of shivering.

Table 1: Comparison of age distribution of patients studied

Age in years	Group A		Group B		Group C	
	No	%	No	%	No	%
18-20	0	0.0	2	10.0	3	15.0
21-40	8	40.0	3	15.0	6	30.0
41-60	12	60.0	13	65.0	11	55.0
>60	0	0.0	2	10.0	0	0.0
Total	20	100.0	20	100.0	20	100.0
Mean ±SD	44.95±11.71		45.40±15.46		41.40±14.51	

Samples are age matched with P=0.608

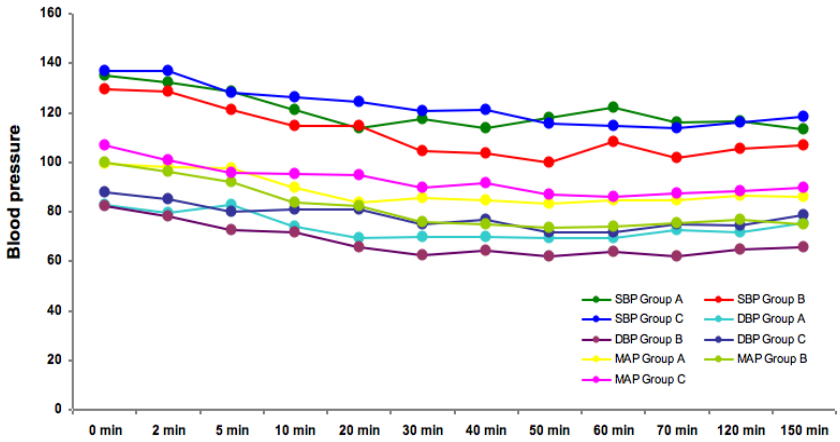

Table 2: Comparison of outcome variables between three groups

Outcome variables	Group A	Group B	Group C	Pair-wise significance		
				Group A vs Group B	Group A vs Group C	Group B vs Group C
Sensory onset T10 (sec)	215.35±68.17	250.50±83.33	215.25±47.53	0.239	1.000	0.237
Time for max sensory level(sec)	424.60±159.62	443.25±107.77	435.05±145.67	0.906	0.970	0.981
Motor onset grade1 (sec)	151.10±100.28	170.15±57.25	169.25±86.41	0.751	0.771	0.999
Time of max motor block	314.75±148.49	283.10±90.45	357.00±99.53	0.664	0.485	0.117
Total duration of motor lock(min)	269.50±64.17	234.75±52.45	190.50±27.24	0.083+	<0.001**	0.020*
Total duration of sensory block (min)	286.00±74.51	231.25±43.13	194.00±21.87	0.004**	<0.001**	0.064+

Rescue analgesic (min)	329.25±93.78	301.75±34.23	207.75±31.49	0.310	<0.001**	<0.001**

Table 3: Comparison of outcome variables between three groups(continued)

Outcome variables	Group A	Group B	Group C	P value
Max sensory level				
• T11, T10	1(5.0%)	0	4(20.0%)	0.120
• T9, T8, T7	9(45.0%)	9(45.0%)	4(20.0%)	
• T6, T5.T4	10(50.0%)	11(55.0%)	12(60.0%)	
Quality of motor block				
• I	0	0	0	NS
• II	0	0	0	
• III	20(100.0%)	20(100.0%)	20(100.0%)	

Discussion

Different agents with vasoconstrictive properties, like epinephrine, phenylephrine, and clonidine, have been used as adjuncts for prolonging the duration of spinal anaesthesia. Clonidine is also known to have prolonging effects on sensory and motor block when used as an oral premedication within two hours before bupivacaine spinal anaesthesia. The concentration of clonidine in the CSF after oral administration is 1/1000 of that after intrathecal administration.[33] So the spinal cord does not seem to be the main site of action when clonidine is administered orally. Analgesic action sites are supraspinal, spinal and peripheral sites and clonidine is known to be effective to all of them. In this study the analgesic effect of intravenous clonidine can be thought via a supraspinal pathway with a minor degree of peripherally mediated analgesic action. Intrathecal clonidine has been used in varying doses from 15mcg to 300mcg by various authors. Addition of lesser than 75mcg produces high quality of anaesthesia but did not prolong sensory or motor blockade.[6] Doses higher than 75mcg especially >150mcg did not produce significant hemodynamic changes but produce very deep sedation. 1mcg/kg of clonidine increased the duration of blocks by two folds and this dose was not associated with hemodynamic or respiratory clinically significant alterations, whereas 2mcg/kg was associated with more side effects. It is also found that maximum dose of intrathecal clonidine is 1mcg/kg and higher doses have been reported to cause important decreases in arterial pressures and marked sedation.[1,16,40] Hence in our study 75 mcg of clonidine was selected.

The effective dose of oral clonidine during bupivacaine spinal anaesthesia is 4.5mcg/kg and bio availability averages 75% therefore the effective dose of intravenous clonidine during bupivacaine spinal anaesthesia is approximately 3mcg/kg. The maximum dose of intravenous clonidine is limited by its action at peripheral alpha to adrenergic receptors. Previous human studies evaluating hemodynamic interaction of intravenous clonidine during general anasethesia, 4mcg/kg of clonidine was used.[41,42] To avoid cardio vascular depression, the dose of intravenous clonidine during spinal anaesthesia should be less than that during general anaesthesia and as such spinal anaesthesia decreases sympathetic activities to a greater extent than general anaesthesia. So a dose of 3mcg/kg intravenously was selected in this study.

Clonidine attenuates cardiovascular reactions and provides circulatory stability by its action at central alpha-2 adrenergic receptors. But intravenous clonidine especially when infused rapidly at high plasma concentrations, may result in vasoconstriction and increased arterial blood pressue by peripheral alpha-2 adrenergic stimulation. Previous clinical studies have showed that 2.5mcg or 5 mcg /kg of clonidine mixed in 10ml of normal saline administered intravenously over 60 sec did not increase mean arterial blood pressure compared with baseline and decreased mean arterial pressure 15min after administration.[43] In our study 3mcg/ kg of clonidine mixed in 10ml of normal saline was administered intravenously for 10 min to avoid stimulation of peripheral alpha-2 adrenergic receptors.

Clonidine is rapidly distributed with half-life 10.8 +/- 40.7 min in a two compartment model. Also clonidine is rapidly absorbed after oral administration, reaching a peak plasma concentration within 60 – 90 min.[3] Oral clonidine 150 – 300 mcg when used 120 min after bupivacaine spinal anaesthesia, failed to increase duration of spinal anaesthesia. In our study the time of clonidine administration was determined by considering the time of peak plasma concentration which would reach more rapidly than oral clonidine therefore. Intravenous clonidine was administered in 10 min after the spinal block because half-life of clonidine is 10.8+/- 4.7 min.

Intravenous clonidine administered upto 60 minutes after spinal block prolonges Bupivacaine spinal anaesthesia without any adverse effects. It may take a significant period of time to fix long acting local anaesthetic, and the levels of spinal anaesthesia with hyperbaric bupivacaine can be altered upto 60min after injection. Thus intravenous clonidine is thought to be able to prolong spinal anaesthesia in this period depending upon the bupivacaine fixation time.

Conclusion

From the present study it can be concluded that intravenous clonidine after bupivacaine spinal anaesthesia has characterstics similar to and comparable with intrathecal clonidine with bupivacaine in terms of Sensory and motor onset; Maximum sensory and motor block achieved; duration of motor block; Duration of analgesia; Hemodynamic stability, with and added advantage of significant Intraoperative and post-operative sedation; Protection against postoperative shivering; Beneficial in oncosurgeries.

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