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INTRATHECAL CLONIDINE AS ADJUNCT TO HYPERBARIC BUPIVACAINE: A DOSE COMPARATIVE STUDY

Anesthesiology

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ABSTRACT

Background: Many studies in past have shown that addition of clonidine (15-30 µg) to intrathecal local anaesthetic improves intraoperative analgesia and increases the duration of sensory and motor block. We conducted a prospective randomised double blinded study to evaluate the lowest dose of intrathecal clonidine as adjunct to hyperbaric bupivacaine that will produce maximum benefit with minimum side effects.

Material and methods: Eighty patients of ASA grade I and II, scheduled for total abdominal hysterectomy (TAH) under spinal anaesthesia were divided randomly into four groups. Control group (Group I) received 13.5mg 0.5% hyperbaric bupivacaine. Study groups received 15µg (Group II), 30µg (Group III) and 45µg (Group IV) made to 3ml volume with 13.5mg 0.5% hyperbaric bupivacaine.

Result: The mean time of onset of block was lower while duration of analgesia and motor blockade was prolonged in all clonidine groups (Group IV > Group III > Group II). The change was less significant in Group III and IV. 40% patients in Group IV and 20% patients in Group III had significant fall in mean arterial blood pressure (MAP). 60% patients in Group IV and 20% in Group III developed bradycardia. 90% patients were sedated in Group IV.

Conclusion: We concluded that addition of clonidine to intrathecal bupivacaine significantly reduces the onset time of sensory and motor block, prolongs duration of spinal block with 30µg being optimum dose.

KEYWORDS

Intrathecal clonidine, bupivacaine, subarachnoid block.

INTRODUCTION

Clonidine is a partial α_2 adrenoreceptor agonist used intrathecally, with a well established record of efficacy and safety.[1] Its addition to local anaesthetic prolongs the duration of both motor and sensory spinal blockade.[2-4] However the commonly administered doses produce hypotension and bradycardia.[5,6]

Most of the studies have used clonidine in dose range of 75µg and above.[7-9] Recently few studies have used 15-150µg of intrathecal clonidine in surgical patients.[2,3,10] Therefore we studied the effects of low dose intrathecal clonidine (15-45µg) with 13.5mg 0.5% hyperbaric bupivacaine comparing with the effects of bupivacaine alone in patients undergoing TAH.

MATERIAL AND METHODS

This prospective randomised double blind study was conducted in our department from July 2017 to Feb 2018. An informed and written consent was taken from 80 patients (ASA I-II) scheduled for elective TAH. The patients on cardiovascular medications, history of hypersensitivity to clonidine or local anaesthetics and those with conditions that preclude spinal anaesthesia were excluded from this study.

Standard PAC and routine investigations were done and informed written consent from all participants was obtained. Every patient was familiarized with linear visual analog scale (VAS 0= no pain and 10= worst imaginable pain).[11] Patients were kept fasting for 6 h and premedicated with oral alprazolam 0.25mg on previous night. In operating room NIBP, ECG and SpO_2 were attached and intravenous (IV) access was secured. IV preloading was done with 10 ml kg^{-1} ringer lactate over 30 minutes. Heart rate, systolic/diastolic blood pressure recorded after preloading were taken to represent the basal haemodynamic parameters. Under all aseptic precautions, a midline spinal puncture at L_{3-4} space in sitting position with 25 gauge Quincke needle was performed. The patients were randomly allocated into one of the four groups (n=20) and received a coded intrathecal drug volume of 3.0ml at a rate of 1ml $5sec^{-1}$ with 13.5mg 0.5% hyperbaric bupivacaine , with saline ± clonidine. Group I received bupivacaine with saline (0.3ml) while Group II-IV received 15µg, 30µg and 45µg clonidine respectively added to bupivacaine in the same syringe. The drug combinations were prepared by a fellow anaesthesiologist who was not involved in the study.

The patient was then turned supine and time of onset of sensory block (by pin prick method using 25G short bevelled needle), grade of motor block (using Modified Bromage scale), level of sedation [using Modified Wilson sedation scale (0- oriented, 1- drowsy, 2- arousable to mild physical stimulation, 3- unarousable to mild physical stimulation)][12] and pain score (10cm VAS) were recorded every min for 5 min after subarachnoid block, every 5 min until surgery lasted, every 15min till 3hrs and later at hourly intervals until 6hrs after the injection. Degree of motor block was assessed by Modified Bromage scale as follows[13]:

I. Free movement of legs and feet
II. Just able to flex knees with free movement of feet
III. Unable to flex knees, but with free movement of feet
IV. Unable to move legs and feet

The maximum ascent of sensory blockade, time to achieve highest sensory block, two segment regression of block and duration of analgesia (time to first analgesic request of diclofenac sodium 75mg intramuscular provided at VAS≤4)) were also noted. IV fluids were administered according to blood loss and haemodynamic in instability. Haemodynamic instability was defined as 30% reduction in MAP from baseline and treated with 300ml of additional fluids and IV ephedrine 6mg bolus if required. The patients were observed in OT and recovery room for any other side effects and need of additional medications.

The mean and standard deviations for the observed data were calculated and compared with the control and within study groups using Student's t-test. A p-value of <0.05 was taken as significant and p < 0.01 was considered highly significant. The sample size of 20 patients per group was based on the assumption that an increase of 60min in the duration of spinal anaesthesia and increase of 30% in the time interval from spinal anaesthesia to the request to supplemental analgesia would be detected (β=0.05, β=0.8), both of which were considered clinically meaningful.

RESULTS

All the groups were similar in respect of age, weight, height, ASA grade and duration of surgery (Table 1). The youngest patient in our study was 35 years old and the oldest was 75 years old.

Table 1. Patient characteristics

Parameter	Group I	Group II	Group III	Group IV
Age (yrs)	40.91±5.11	41.14±6.15	42.19±5.81	44.20±6.05
Weight (kg)	57.72±6.82	59.26±7.51	54.14±6.75	57.75±5.71
Height (cm)	166.30±5.71	166.32±7.15	164.44±6.09	168.40±7.10

ASA Grade (I:II)	10:10	12:8	13:7	15:5
Duration of surgery (min)	62.40±6.65	59.95±5.40	65.44±6.81	64.34±7.10

Table 2. Characteristics of block

Parameter	Group I	Group II	Group III	Group IV
Onset of sensory block (min)	2.10±0.76	1.55±0.30	0.94±0.09	0.90±0.06
Onset of motor block (min)	8.51±0.61	3.58±0.40	2.80±0.90	2.65±0.60
Highest level of block	T7 (T4-8)	T7 (T4-8)	T6 (T4-8)	T6 (T4-8)
Time to achieve highest sensory block (min)	14.52±5.91	9.32±3.65	9.14±4.58	6.37±2.21
Time to first analgesic request (min)	150.80±46.71	210.15±31.77	242.40±39.45	275.55±40.46
Time to regression to L3 dermatome (min)	182.50±36.95	230.40±35.60	270.50±40.44	290.46±45.61
Highest Bromage scale III IV	 5 15	 2 18	 2 18	 0 20
Time to achieve highest Bromage scale (min)	14.52±5.91	10.32±3.65	7.14±4.58	6.37±2.21
Duration of motor block (min)	153.40±20.44	203.61±21.55	218.64±25.14	305.11±24.64
Side effects: Hypotension Bradycardia Desaturation Resp. depression Sedation	 2 0 0 0	 3 2 0 0 2	 4 4 0 0 9	 8 12 0 0 18

Table 3. Statistical significance (p-Value)

Parameter	I:II	I:III	I:IV	II:III	II:IV	III:IV
Onset of sensory block	<0.01	<0.01	<0.0001	<0.01	<0.0001	0.106
Onset of motor block	<0.0001	<0.0001	<0.0001	<0.01	<0.0001	0.538
Time to highest sensory block	<0.01	<0.01	<0.0001	0.891	<0.01	<0.05
Time to first analgesic request	<0.0001	<0.0001	<0.0001	<0.01	<0.0001	0.013
Time to regression to L3 dermatome	<0.0001	<0.0001	<0.0001	<0.01	<0.001	0.151
Time to achieve highest bromage scale	<0.05	<0.0001	<0.0001	<0.05	<0.01	0.502
Duration of motor block	<0.0001	<0.0001	<0.0001	<0.05	<0.001	<0.0001

The mean time of onset of sensory block was significantly lower in Group II-IV (1.55±0.30min, 0.94±0.09min and 0.90±0.06min resp.) as compared to Group I (2.10±0.76min) (p<0.01). The difference between Group II and III (p<0.01) as well as Group II and IV (p<0.0001) was also observed to be statistically very significant. However, there was no statistical difference between Group III and IV (p=0.106).

The mean time of onset of motor block was very significantly lower in Group II-IV (3.58±0.40min, 2.80±0.09min and 2.65±0.60min resp.) as compared to Group IV (p<0.0001). The difference was statistically very significant between Group II and III (p<0.01) as well as Group II and IV (p<0.0001) but insignificant between Group III and Group IV (p=0.538).

There was no statistical difference between the highest level of sensory block achieved in different groups but the highest level of sensory block was achieved significantly faster in Group II-IV (9.32±3.65min, 9.14±4.58min and 6.37±2.21min resp.) as compared to Group I (14.52±5.91min) (p<0.01). The difference was not statistically significant between Group II and III (p=0.891) but was statistically significant between Group II and IV (p<0.01) as well as Group III and IV (p<0.05).

The time to first analgesic request at VAS ≤4 was maximum in Group IV (275.55±40.46min) and minimum in Group I (150.80±46.71min). The difference between Group I and all clonidine groups; between Group II and III as well as between Group II and IV was statistically significant (p<0.0001, p<0.01 and p<0.0001 resp.). The difference was insignificant between Group III and Group IV (p=0.013).

The time to regression to L_3 dermatome was significantly lower in Group I (182.50±36.95min) as compared to Group II-IV (230.40±35.60min, 270.50±.40.44min and 290.46±45.61min resp.). The difference was also statistically significant between Group II and III (p<0.01) as well as Group II and IV (p<0.001) but insignificant between Group III and IV (p=0.151).

The highest Bromage scale was achieved statistically faster in all clonidine groups as compared to Group I (p-value for Group I:II, I:III and I:IV was <0.05, <0.0001 and <0.0001 resp.). While the difference in time was also statistically significant in Group II vs III (p<0.05) and Group II vs IV (p<0.01) but was statistically insignificant in Group III vs IV (p=0.502).

The total duration of motor block was significantly prolonged in all clonidine groups as compared to Group I (p<0.0001). The difference in duration was also significant in Group II vs III (p<0.05), Group II vs 1V (p<0.001) and Group III vs IV (p<0.0001).

40% patients in Group IV and 20% patients in Group III had significant fall in mean arterial blood pressure (MAP). 60% patients in Group IV and 20% in Group III developed bradycardia. No episodes of desaturation or respiratory depression were seen in any group. Eighteen patients in Group IV and 9 patients in Group III had grade 2 sedation.

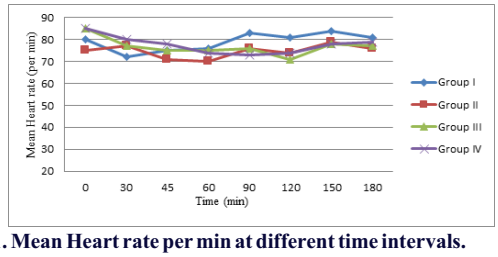

Fig 1. Mean Heart rate per min at different time intervals.

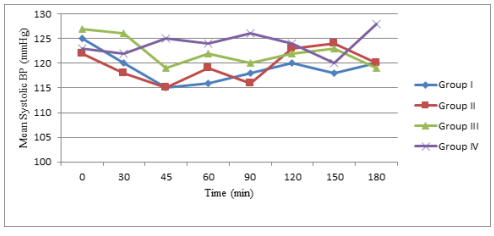

Fig 2. Mean Systolic Blood Pressure (mmHg) at different time intervals.

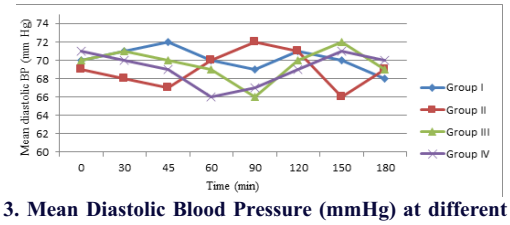

Fig 3. Mean Diastolic Blood Pressure (mmHg) at different time intervals.

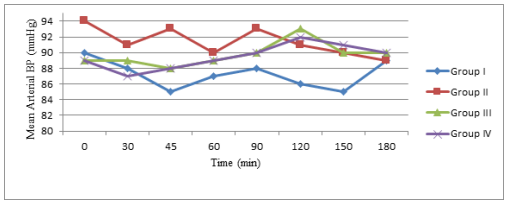

Fig 4. Mean Arterial Blood Pressure (mmHg) at different time intervals.

DISCUSSION

Clonidine is a selective partial agonist for α_2 adrenoreceptors. Its analgesic effect is mediated spinally through activation of post-synaptic α_2 receptors in substantial gelatinosa of the spinal cord. It is known to increase both sensory and motor block of local anaesthetics by 30-50%. This effect has been reported using doses as high as 1 or 2 $\mu g\ kg^{-1}$. At this dose improved analgesia is associated with systemic side effects such as sedation, bradycardia and hypotention.[14] Gautier and colleagues recommended 15-45µg of clonidine as optimal for supplementing spinal anaesthesia.[15] so, keeping within this range we compared different doses of intrathecal clonidine (15µg, 30µg and 45µg) to evaluate the lowest dose required to produce maximal benefit with minimal side effects.

We observed that addition of clonidine improved the onset time, speed of spread and duration of block in a dose dependent manner. The maximum benefit was seen with 45µg dose but hypotension (40%), bradycardia (30%) and sedation (90%) was observed at this dose. The benefits were similar with 30µg dose with lesser incidence of hypotension (20%), bradycardia (20%) and sedation (45%).

Our findings are consistent with those of Kanazi et al who compared the onset and duration of sensory and motor block as well as haemodynamic changes and level of sedation following intrathecal bupivacaine supplemented with either dexmedetomidine(3µg) or clonidine(30µg). They observed that addition of low dose intrathecal bupivacaine or clonidine produces a significantly shorter onset of motor block and a significantly longer sensory and motor block than bupivacaine alone. They also stated that addition of low dose dexmedetomidine or clonidine to bupivacaine did not cause a significant decrease in blood pressure intraoperatively or post-operatively.[16] Intarthecal local anaesthetics block the sympathetic outflow and reduce the blood pressure. The sympathetic block is usually near maximal with the doses used for spinal anaesthesia. The addition of low dose of α_2-agonist to a high dose of local anaesthetics does not further affect the near-maximal sympatholysis.[17] Dexmedetomidine 3µg and clonidine 30µg have an equipotent effect on characteristics of the block without any significant haemodynamic instability or sedation.[16]

Gecaj-Gashi et al in their study showed that addition of low dose intrathecal clonidine (25µg) to low dose of bupivacaine increased the onset of motor block, onset and duration of sensory block (thereby prolonging post operative analgesia), without delaying motor block in patients undergoing transurethral surgical procedures. They also noted that relative haemodynamic stability was preserved in both groups and hence suggested this adjuvant especially for ambulatory anaesthesia as it prolonged post-operative analgesia, but not motor block.[18]

Thakur et al compared two different doses of clonidine (15µg and 30µg) added to 11mg hyperbaric bupivacaine in patients undergoing inguinal herniorrhaphy under spinal anaesthesia and observed that addition of 15µg and 30µg of clonidine to bupivacaine intrathecal were found to be equally effective in respect of duration and quality of sensory block, motor block and time to first analgesic request. This finding is in contrast to our observation of statistically significant prolongation of sensory and motor block on increasing the dose of clonidine from 15 to 30µg and can be attributed to lower dose of bupivacaine(11mg) used in their study. Clonidine 30µg was associated with a higher incidence and duration of hypotension than 15µg clonidine and hence they concluded that the preferred dose of clonidine as adjuvant to local anesthetics, when prolongation of spinal anesthesia is desired, is 15µg.[19]

Kakunje et al studied the characteristics of sensory and motor blockade, duration of analgesia and side effects with addition of two different doses of clonidine (15µg and 30µg) to hyperbaric ropivacaine (0.5%) in patients undergoing lower limb and lower abdominal surgery. They concluded that addition of low-dose intrathecal clonidine causes a significant prolongation of sensory and motor blockade as well as post operative analgesia compared with saline placebo. They found that even though 30µg clonidine significantly prolonged the duration of sensory and motor blockade compared to 15µg clonidine group the duration of post operative analgesia was similar between these groups. Also, addition of clonidine significantly increased the incidence of intra-operative hypotension and bradycardia which could be easily managed with routine clinical measures.[20]

Saxena et al in their study compared three different doses of clonidine (15µg, 30µg and 37.5µg) as adjuvant to hyperbaric bupivacaine and cloncluded that addition of clonidine to bupivacaine significantly reduces onset time with increase in duration of spinal block with 30µg as optimum dose.[21]

CONCLUSION

Hence we conclude that addition of low dose intrathecal clonidine to bupivacaine significantly improves the onset and duration of sensory and motor block while maintaining haemodynamic stability. A dose of 30µg clonidine provides maximum benefit with minimum side effects.

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