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Effect of intrathecal and intravenous clonidine given as adjuvant to bupivacaine in spinal anaesthesia

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ABSTRACT

Introduction: Clonidine potentiates sensory and motor blockade of epidural and peripheral nerve block. Our aim in this study was to evaluate effect of intrathecal and intravenous clonidine, on spinal anaesthesia. **Materials and Methods:** Patients who met the selection criteria were randomly divided into three groups. **Group I:** Spinal anaesthesia with 0.5% heavy bupivacaine 3ml, **Group II:** Spinal anaesthesia with 0.5% heavy bupivacaine 3ml + inrathecal clonidine 75 µg, **Group III:** Spinal anaesthesia with 0.5% heavy bupivacaine 3ml + intravenous clonidine 3 µg/kg. **Statistical Analysis:** Computer software SPSS version 20 was used for the statistical analysis of the data. A p value of 0.05 or less was considered as statistically significant. **Observation and Results:** The mean time of onset of sensory block in Group I, II and III was 5.32, 4.32 and 4.25 minutes ($p < 0.001$). Time of onset of motor block was 10.10, 7.12 and 6.84 minutes in Group I, II and III ($p < 0.001$). The duration of sensory block was 169.75, 291.20 and 293.75 minutes in Group I, II and III ($p < 0.001$). The duration of motor block was 149.25, 208.80 and 215.63 minutes in Group I, II and III ($p < 0.001$). The time for demand of analgesia was 137.50, 364.80 and 371.31 minutes in Group I, II and III ($p < 0.001$). Hypotension was the most common side effect in the three groups. **Conclusion:** Clonidine is a good alternative choice as adjuvant to spinal anaesthesia in addition to opioids.

Key words: Analgesia, Bupivacaine, Clonidine, Motor Block, Spinal Anaesthesia, Sensory Block

INTRODUCTION

Spinal anaesthesia or Sub-Arachnoid Block (SAB), is a form of regional anaesthesia involving injection of local anaesthetic agents into the subarachnoid space through a fine needle. The first spinal analgesia was administered in 1885 by a neurologist named James Leonard Corning when he accidentally pierced the dura mater while experimenting with cocaine in a dog[1]. The first planned spinal anaesthesia for surgery in man was administered by August Bier in 1898[2]. Bupivacaine is the local anaesthetic most commonly used for spinal anaesthesia, although lignocaine, tetracaine, ropivacaine, procaine, levobupivacaine and prilocaine can also be used. The onset of action with bupivacaine is moderate and duration is intermediate. The duration of anaesthesia is longer with bupivacaine than with any other commonly used local anaesthetic. It has also been noticed that after spinal anaesthesia there is a period of analgesia that persists after the return of sensation, during which time the need for strong analgesics is reduced.

Clonidine, an imidazoline derivative centrally acting α-2 adrenergic agonist. It crosses the blood brain barrier and acts in the hypothalamus to induce a decrease in blood pressure. Clonidine stimulates all three α2-receptor subtypes with similar potency. Alpha 2A receptors also mediate essential components of the analgesic effect of nitrous oxide in the spinal cord. Clonidine is also a potent sedative and analgesic. Clonidine functions as a sympatholytic by stimulating presynaptic α2-receptors leading to decreased release of norepinephrine at both central and peripheral adrenergic terminals. In addition to its influence on the autonomic nervous system, it is well established that

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clonidine is an effective analgesic, and this is also attributable to its α2-agonist activity. A tremendous amount of modulation of incoming pain signals occurs in the dorsal horn of the spinal cord prior to being sent to higher centres in the CNS. Nociceptive stimuli promote release of excitatory transmitters from primary afferents in the dorsal horn. To compensate, there is simultaneous release of norepinephrine from descending inhibitory neurons, which binds to α2-receptors in the dorsal horn to diminish after pain transmission, thereby producing analgesia. Thus, it is obvious that drugs acting on α2-receptors should influence the transmission and perception of pain. Therefore, it is the mimicking of the actions of descending inhibitory fibres by which clonidine, and all α2-agonists, causes analgesia. As cholinergic activation in the dorsal horn has also been shown to impart analgesia and clonidine increases Ach levels in lumbar CSF. Thus, α2-agonists impart analgesia through both cholinergic and noradrenergic transmission.

Clonidine also potentiates sensory and motor blockade of epidural and peripheral nerve block. Three mechanisms for this have been given. First, clonidine has intrinsic ability to block conduction in C and A δ fibres and will intensify conduction block of local anaesthetics. Second, clonidine may cause local vasoconstriction and thus impair vascular removal of epidural local anaesthetics. Third, it has been shown that any analgesic, whether neuraxial or systemic, will augment peripheral or spinal blockade.

Our aim in this study is to evaluate whether clonidine when given by intrathecal and intravenous route, has any effect on spinal anaesthesia, by comparing the onset and duration of sensory and motor block and duration of post-operative analgesia.

MATERIALS AND METHODS

After clearance from the ethical committee of the institute, this prospective, randomised case control study was started in the anaesthesiology department. The study included ASA grade 1 and 2 patients of either sex, aged between 20 and 60 years, posted for elective lower abdominal surgery and giving informed consent for the procedure. The patients excluded from the study were those with history of hypertension/taking antihypertensive drugs, history of hypersensitivity to local anaesthetics or clonidine, body weight greater than 120 kg or less than 40 kg, height less than 140 cm, any neurological disorder, and any contraindication to spinal anaesthesia or pregnancy.

After calculating the number of patients to be selected for the study according to the normal distribution theory, we decided to take 30 patients in each group.

All the patients posted for surgery under spinal anaesthesia and who met the selection criteria were randomly divided into three groups of 30 patients.

Group I: Spinal anaesthesia with 0.5% heavy bupivacaine 3 ml (15 mg)

Group II: Spinal anaesthesia with 0.5% heavy bupivacaine 3 ml (15 mg) + inrathecal clonidine 75 µg

Group III: Spinal anaesthesia with 0.5% heavy bupivacaine 3 ml (15 mg) + intravenous clonidine 3 µg/kg

All the patients went through pre anaesthetic check-up a day before surgery which included a detailed history, physical examination and appropriate investigations as per requirement. On the day of surgery, after shifting the patient to the OT, an intravenous access was attained and patient was preloaded with 20 ml/kg of crystalloid solution (Ringer Lactate). Standard anaesthetic monitors like Pulse oximetry, ECG and Non-invasive blood pressure were attached. After all aseptic precautions, lumbar puncture was performed in sitting position at L2–3/3–4 intervertebral space with a 25 guage Quincke's spinal needle. After free flow of CSF, 3 ml of heavy bupivacaine 0.5% was given in all the ~~the~~ three groups. Along with it, in Group I 0.5 ml of intrathecal saline was given, in Group II 75 µg clonidine was given intrathecally and in Group III clonidine 3 µ/kg diluted to 5 ml was given intravenously slowly over 8–10 minutes after performing the subarachnoid block. After the block the patient was again made to lie supine and vitals (Heart rate, systolic and diastolic blood pressure and mean arterial pressure) were monitored at regular intervals – every 5 min for the first half an hour and then every 15 min till the end of surgery. Sensory block was assessed by response to pin prick. Onset of sensory anaesthesia was defined as the time from the block given to no pain to pin prick at T 10. Motor block was assessed by the Bromage scale. Motor block onset was defined as the time from the block to score of Bromage 2.

Sedation was assessed by Ramsay sedation scale and analgesia was assessed by VAS. Intraoperative vitals of the patient, any adverse effects and total duration of surgery were noted. In the postoperative period, the time for the demand of first analgesic was noted. Duration of analgesia was defined as the time from block to the time for first analgesic demand by the patient in the postoperative period. Duration of sensory block was taken as the time for regression of sensory block to L1 level and duration of motor block was taken as the time for regression of motor block to a score of Bromage 0.

STATISTICAL ANALYSIS

Computer software SPSS version 20 was used for the statistical analysis of the data. For analysis of demographic data Chi square test was used and comparison of the groups for block characteristics was done by one-way ANOVA with bonferroni. A p value of 0.05 or less was considered as statistically significant.

OBSERVATIONS AND RESULTS

The aim of our study was to compare the effect of clonidine given intrathecally or intravenously as adjuvant to bupivacaine, on the block characteristics of spinal anaesthesia.

Table 1 shows the demographic characteristics of the groups. The mean age of patients in Group I, Group II and Group III was 39.5, 38.68 and 41.88 years respectively. All the groups were comparable with respect to age. Out of 30 patients in Group I, 14 were male and 16 were female, in Group II there were 15 male and 15 female patients and in Group III there were 16 male and 14 female patients. The groups were comparable with respect to age. As shown in (Table 1), the mean weight of patients in Group I was 60.50 kg, in Group II was 61.08 kg and in Group III was 57.25 kg. There was no statistically significant difference in weight in the four groups. As is evident from the table, the four groups were comparable with respect to height and BMI also.

Table 2 shows the baseline parameters in the three groups. The baseline SpO2 in Group I was 99.65%, in Group II was 99.72% and in Group III was 99.47%. The mean heart rate in Group I was 82.95 beats per minute, in Group II was 85.12 beats per minute and in Group III was 79.31 beats per minute. The mean systolic blood pressure in Group I was 127.70 mm of Hg, in Group II was 126.64 mm of Hg and in Group III was 128.20 mm of Hg. The mean diastolic blood pressure in Group I, II and III was 74.20, 73.68 and 75.93 mm of Hg respectively. All the three groups were comparable with respect to baseline parameters.

Table 3 shows the block characteristics. As shown in table, the mean time of onset of sensory block in Group I, Group II and Group III was 5.32, 4.32 and 4.25 minutes. The sensory onset was significantly earlier than the control group ($p < 0.001$). The mean time of onset of motor block was 10.10 minutes in Group I, 7.12 minutes in Group II and 6.84 minutes in Group III. The motor block onset was significantly faster than the control group ($p < 0.001$). The mean duration of sensory block was 169.75 minutes in Group I, 291.20 minutes in Group II and 293.75 minutes in Group III ($p < 0.001$). The mean duration of motor block was 149.25 minutes in Group I, 208.80 minutes in Group II and 215.63 minutes in Group III ($p < 0.001$). The mean time for demand of analgesia was 137.50 minutes in Group I, 364.80 minutes in Group II was 364.80 minutes and in Group III was 371.31 minutes ($p < 0.001$).

Table 1: Demographic characteristics

	GROUP I (Control)	GROUP II (Intrathecal)	GROUP III (Intravenous)	P VALUE
AGE (YEARS)	39.95± 12.02	38.68± 12.13	41.88 ± 13.579	0.73
SEX (M:F)	14:16	15:15	16:14	0.57
WEIGHT (KG)	60.50 ± 10.314	61.08 ± 8.698	57.25 ±6.933	0.38
HEIGHT (CM)	159.70 ± 8.247	161.44± 7.53	160.13 ± 7.9	0.74
BMI	23.59 ±2.57	23.36 ± 2.35	22.29 ± 1.80	0.21

Table 2: Baseline parameters of patients

	GROUP I	GROUP II	GROUP III	P VALUE
SPO2	99.65 ± 0.484	99.72 ± 0.458	99.47 ± 0.743	0.37
HR (beats/min)	82.95 ± 9.698	85.12 ± 9.471	79.31 ± 15.713	0.29
SBP (mm Hg)	127.70 ± 12.80	126.64 ± 13.784	128.20 ± 15.20	0.93
DBP (mm Hg)	74.20 ± 7.592	73.68 ± 6.77	75.93 ± 8.51	0.64

Table 3: Block characteristics in the study groups				
	GROUP I	GROUP II	GROUP III	P AVLUE
SENSORY ONSET (MIN)	5.32 ± 0.67	4.32 ± 0.81	4.25 ± 0.72	< 0.001
MOTOR ONSET (MIN)	10.10 ± 2.99	7.12 ± 2.39	6.84 ± 2.16	< 0.001
SENSORY DURATION (MIN)	169.75 ± 26.16	291.20 ± 19.39	293.75 ± 19.45	< 0.001
MOTOR DURATION (MIN)	149.25 ± 26.42	208.80 ± 17.46	215.63 ± 26.26	< 0.001
DEMAND FOR ANALGESIA (MIN)	137.50 ± 30.63	364.80 ± 6.69	371.31 ± 8.86	< 0.001

Table 4: Incidence of side effects			
	GROUP I Number (%)	GROUP II Number (%)	GROUP III Number (%)
BRADYCARDIA	4 (13.33)	5 (16.66)	6 (20)
DRY MOUTH	0	1 (3.33)	2 (6.66)
HYPOTENSION	6 (20)	12 (40)	25 (50)
SEDATION	0	7 (23.33)	23 (76.66)
SHIVERING	9 (30)	2 (6.66)	2 (6.66)

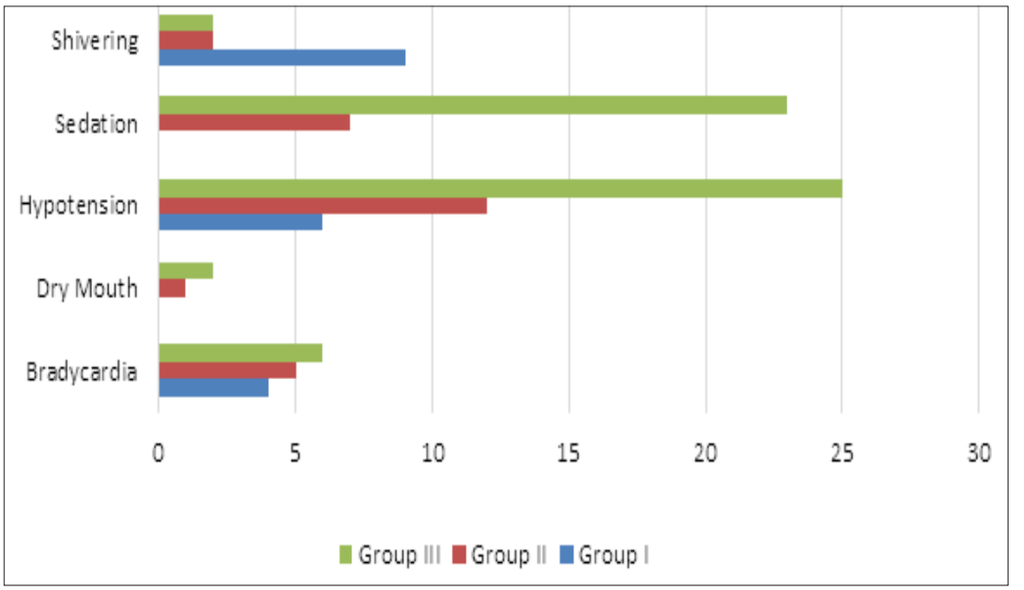

Figure 1. Incidence of side effects.

Table 4 and Figure 1, shows the incidence of side effects in the three groups. In Group I, bradycardia was seen in 4(13.33%) patients, hypotension in 6(20%) patients and 9(30%) patients had shivering. In Group II, 5(16.66) patients had bradycardia, 1(3.33%) patient complained of dry mouth, 12(40%) patients had hypotension, 7(23.33%) patients had sedation and 2(6.66%) patients experienced shivering. In Group III, 6(20%) patients had bradycardia, 25(50%) patients had hypotension, 23(76.66%) patients had sedation and 2(6.66%) patients experienced shivering as side effect.

DISCUSSION

Vasoconstrictors have been used since ages as adjuncts to local anaesthetics for prolongation of spinal anaesthesia. In addition to vasoconstrictor, intrathecal opioids, α2-agonists like dexmedetomidine and clonidine are also effective in prolonging the local anaesthetic induced sensory and motor blockade.

The present study was designed to study the effect of clonidine on spinal anaesthesia when given as adjuvant by intrathecal, and intravenous routes with intrathecal bupivacaine 0.5% with respect to onset and duration of sensory and motor block, duration of analgesia, time for demand of analgesic and side effects.

The present study was carried out on 90 patients of ASA grade 1 and 2 of either sex aged between 18 and 60 years scheduled for elective surgery under spinal anaesthesia.

EFFECT OF INTRATHECAL CLONIDINE

In the present study 75 µg clonidine when given with 15 mg of bupivacaine 0.5% intrathecally, resulted in faster onset of sensory and motor block as compared to the control and intravenous clonidine group. Intrathecal clonidine group had a significantly longer duration of sensory and motor block than the control and intravenous group. The patients in intrathecal group had a delayed demand for analgesia in the immediate postoperative period. These findings are in concurrence with the findings in earlier studies[3–9]. Racle et al.,[3] demonstrated that intrathecal clonidine 150 µg prolonged motor blockade by 38% and sensory blockade by 46% when used as an aduct to spinal anaesthesia with bupivacaine. Victor Whizat-Lugo et al.,[4] compared dexmedetomidine and clonidine as adjuvant in spinal anaesthesia and observed that both prolong the duration of spinal anaesthesia. The duration of sensory blockade was increased by one hour and motor blockade by 20 minutes in the clonidine group. Study by L. Niemi[5] using 3 µg/kg clonidine intrathecal with bupivacaine spinal anaesthesia showed lower blood pressure and heart rate in the clonidine group than in control group. He found that with intrathecal clonidine the duration of bupivacaine spinal anaesthesia was significantly prolonged.

The mechanism by which intrathecal α2-agonists prolong the motor and sensory block is under speculation. It may be an additive or synergistic effect secondary to the different mechanisms of action of the local anaesthetics and intrathecal α2-agonists. Local anaesthetics act by blocking sodium channels, α2-agonists act by binding to the presynaptic C-fibres and postsynaptic dorsal horn neurons. They produce analgesia by depressing release of C-fibre transmitters and by hyperpolarisation of post synaptic dorsal horn neurons.

EFFECT OF INTRAVENOUS CLONIDINE

In our study the patients receiving intravenous clonidine experienced a faster onset of sensory and motor block, a significantly longer duration of block and delayed requirement for analgesic in the postoperative period. Similar findings have been observed in the studies conducted in past. Study conducted by Prerana N Shah using 3 µg/kg intravenous clonidine with bupivacaine spinal anaesthesia showed that the sensory and motor blockade duration was significantly prolonged in the clonidine group as compared to the saline group[10]. Rhee K et al.,[11] in 2003 studied the effect of intravenous clonidine on duration of spinal anaesthesia. They observed that the duration of sensory and motor block was longer in clonidine group compared with the control group and the incidence of bradycardia and hypotension was not different in the two groups. They concluded that when given within 1 hour of spinal block, intravenous clonidine prolonged bupivacaine spinal anaesthesia. V.S. Reddy et al.,[12] compared and evaluated the efficacy of intravenous dexmedetomidine with clonidine and placebo on spinal blockade duration, postoperative analgesia and sedation in patients undergoing surgery in bupivacaine spinal block. They concluded that single dose intravenous clonidine resulted in early onset, rapid establishment of sensory and motor blockade, prolongation of analgesia into the postoperative period and stable cardiovascular parameters.

The analgesia produced by α2-agonists like clonidine is due to their action at spinal, supra-spinal, direct analgesic and/or vasoconstricting actions on blood vessels[13]. The locus coeruleus and the dorsal raphe nucleus are the important central neural structures where these drugs act to produce sedation and analgesia[14]. This supra-spinal action can explain the prolongation of spinal anaesthesia after administration of clonidine intravenously. The mechanism of motor block produced by α2-agonist is unclear but there is some evidence that clonidine results in direct inhibition of impulse conduction in the large, myelinated A-α fibers.

In our study, two segment regression time of sensory block and time of first request for analgesic in the intravenous clonidine group was prolonged significantly. This can be explained by the affinity of clonidine for α2-receptors. The mechanism for prolongation of motor block by clonidine is unclear but there is speculation that it may be due to direct inhibition of impulse conduction in the large, myelinated A-α fibers.

It is not clear whether the effect of clonidine is mediated locally at the level of the spinal cord or whether the effect is mediated systemically. IV clonidine achieves higher plasma concentrations and more rapidly than intrathecal injection. The mechanism of prolongation of sensory and motor block by clonidine is not known. It is speculated that the mechanism of analgesia is depression of transmitter release from C-fibres and postsynaptic dorsal horn neuron hyperpolarisation. Motor block prolongation is due to binding of clonidine to motor neurons in the dorsal horn.

INCIDENCE OF SIDE EFFECTS

In our study, hypotension was the most common side effect observed in all the groups, with highest incidence in the intravenous clonidine group followed by intrathecal clonidine group. Sedation was most common in the intravenous group followed by intrathecal group. Bradycardia was common in all the groups. Shivering was most common in the control group.

The hemodynamic changes that is hypotension and bradycardia are explained due to decrease in central sympathetic outflow as observed in study conducted by Filos KS et al.,[15].

CONCLUSION

We can conclude from this study that clonidine when given intrathecally and intravenously, along with spinal anaesthesia results in early onset, prolonged duration of sensory and motor block and prolonged analgesia in immediate postoperative period with no significant increase in the incidence of side effects. Thus, clonidine is a good alternative choice as adjuvant to spinal anaesthesia in addition to opioids.

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