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Intrathecal Clonidine as an adjuvant for Postoperative Analgesia

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ABSTRACT

Recent years have seen a great re-awakening of interest in sub arachanoid blockade. Various drugs have been used along with local anaesthetics for prolongation of spinal analgesia like opiates, benzodiazepines, neostigmine etc. Many of these drugs have serious adverse effects like respiratory depression, pruritus, vomiting etc. A properly chosen adjuvant to local anaesthetic agent produces the best way to achieve a good quality regional block. To compare the effect of intrathecal Clonidine 75 micrograms (µg) to 2.5 milliliter (ml) of 0.5% hyperbaric Bupivacaine, with regards to 1) Sensory characteristics, 2) Motor characteristics, 3) Side effects. we performed this study on a patients posted for lower abdominal surgery belonging to ASA I and age group between18-60 years after obtaining an written informed consent and ethical clearance. Sample size 50. Addition of preservative free Clonidine 75µg to intrathecal hyperbaric Bupivacaine (0.5%) significantly produces prolongation of analgesia (327±30mins) than compared to the control Bupivacaine group of only 167±25mins with no serious adverse effect noted perioperatively. With this study we conclude intrathecal Clonidine in the dose of 75µg along with 2.5 ml of 0.5% hyperbaric Bupivacaine provides an attractive alternative combination to anesthesiologist armamentarium for prolonging spinal analgesia.

Keywords: Intrathecal, Clonidine, Hyperbaric, Sensory block, Motor block, Bromage scale.

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INTRODUCTION

Bupivacaine is the most commonly employed local anaesthetic for sub arachanoid block. Post operative pain relief is an important issue with Bupivacaine. Many adjuvants are commonly used to overcome this demerit. So our concern is to choose an ideal adjuvant with Bupivacaine which provides a stable intraoperative condition, prolonging the post operative analgesia with minimal side effects. Clonidine is an selective alpha (α) 2 agonist, routinely used as an premedicant for general anaesthesia. Its use decreases the requirement of analgesics and anaesthetic drugs intraoperatively. Intrathecal administration of Clonidine produces analgesia by acting on alpha 2 adrenoreceptors which are located on primary afferent terminals both at peripheral and spinal nerve endings. Agonistic action of this receptor inhibits transmission of nociceptive stimuli in the dorsal horn of the spinal cord. This Effect mimics that of nor-adrenaline released by inhibitory descending pathways. Nor-adrenaline inhibits the activity of wide dynamic range(WDR) neurons thereby producing analgesia [1].

Clonidine has been used by oral, epidural, spinal, perineural and parenteral routes to obtain post-operative analgesia [2].

METHODS:

Over a period of 5 months duration, a prospective randomized double blinded study was taken up in our institute. The sample size of 50 study population, belonging to the inclusion criteria was divided randomly into two groups (TABLE 1):

Inclusion criteria: All patients aged between a) 18-60 years, b) ASA Grade I and II c) Patients posted for lower abdominal surgeries.

TABLE—1: DEMOGRAPHY

	GROUP B	GROUP BC	*P* value
MEAN AGE	38.2	37.6	>0.05
MEAN WEIGHT	54.2Kg	52.3Kg	>0.05
MALE:FEMALE RATIO	10:15	11:14	0.1

Exclusion criteria: a) Patients with local sepsis, b) Patients with bleeding diathesis, c) Patients with raised intracranial pressure(ICP), d) Patients with any co-morbid diseases like ischemic heart disease (IHD), hypertension, bronchial asthma, diabetes mellitus and morbidly obese patients.

Control Group B (n=25) received 2.5 ml of 0.5% hyperbaric Bupivacaine along with 0.5 ml of normal saline. And study Group BC (n=25) received 2.5 ml of 0.5% hyperbaric Bupivacaine + (75µg) 0.5 ml of Clonidine. The study was double blinded, spinal anesthesia was given by the anesthesiologist with the study drug, who was not involved in the patients monitoring. The

patients and the monitoring anesthesiologist were blinded to the study solutions. Ethical committee clearance and patients consent were obtained.

All the patients were premedicated on the night before surgery with tablet Ranitidine 150 mg and tablet Alprazolam 0.5mg. On the day of surgery, intravenous (i.v) line with 18G cannula was secured. Patients were connected to multichannel monitor displaying electrocardiogram (ECG), oxygen saturation (SPO2) and non-invasive blood pressure (NIBP). All the patients were preloaded with 10 ml/kg of ringer lactate. Under aseptic precautions, lumbar puncture was done using 23G spinal needle at L2- L3 or L3- L4 space. After confirming the free flow of cerebrospinal fluid (CSF), the study drugs were injected into the sub- arachanoid space at the rate of 1ml given in 3 seconds, with the operation table kept flat. Patients were turned supine immediately and were given supplemental oxygen.

The following parameters were noted after SAB:

1) Time of onset of analgesia: defined as time taken from the injection of the drug to onset of analgesia at T-10 level, 2) Maximum level of analgesia achieved. 3) Time taken for achieving maximum level of analgesia, 4) Time taken for onset of motor blockade, 5) Quality of motor blockade assessed by Bromage scale, 6) Total duration of surgery, 7) Intra operative hemodynamic monitoring in the form of heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure(DBP) measured immediately after SAB, 2^{nd} min, 5^{th} min,10^{th} min and every 15 min till the end of surgery, 8) Total duration of analgesia: defined as the time taken from the onset of analgesia to the point where the patient complained of pain in the operated site requiring rescue analgesics (VAS[visual analogue scale] >5).

- Hypotension was defined as reduction of SBP, more than 30% below the base line value or SBP< 90mmHg[3], and it was treated with increased rate of IV fluids and if needed with Vasopressors.
- Bradycardia was defined as HR < 60 beats per minute and was treated with i.v. atropine.
- Any other side effect associated with the administration of intrathecal Clonidine was noted.
- The results were statistically analyzed using 'P' value obtained from student 't' test.

RESULTS

The groups were comparable with respect to age, sex, weight (TABLE 1). There was no statistically significant difference in the type(*p* >0.05) and duration of surgery (TABLE 2). Sensory characteristics are tabulated (TABLE 3). Group BC shows early onset of sensory loss (2mins 40secs) with one segment higher block (T4) than the controlled group, similarly the mean time for achieving maximum level blockade (T4>T5) for Group BC(6mins 12secs) was early than Group B(8mins 40secs). Block regression was significantly slower with addition of intrathecal Clonidine and the mean total duration of analgesia was significantly prolonged to nearly 6 hours in Group BC than compared to nearly 3 hours in control Group B. There was no

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serious complications like respiratory depression, pruritus, itching, sedation observed in either groups.

TABLE—2: SURGICAL PROCEDURES PERFORMED

	GROUP B	GROUP BC
SURGICAL PROCEDURES (INGUINAL HERNIA, APPENDICECTOMY Etc)	15	18
GYNECOLOGICAL PROCEDURES (ABDOMINAL HYSTERECTOMY)	10	07

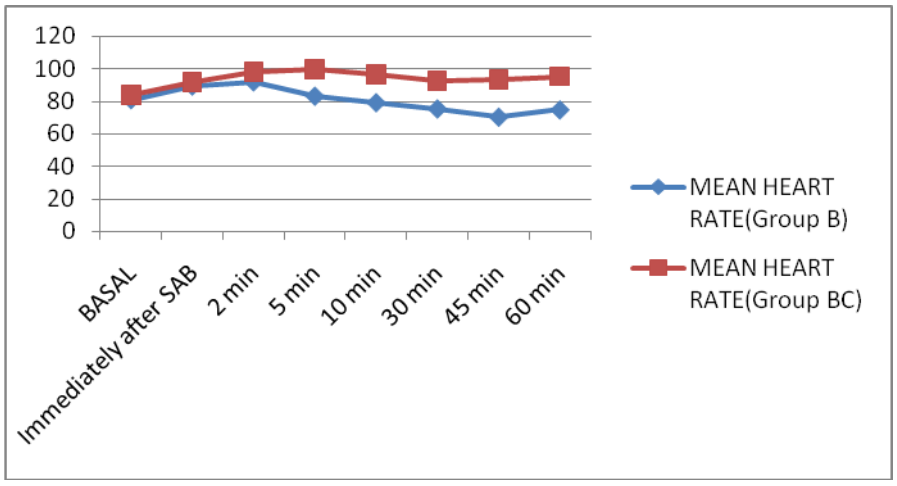
TABLE—3: SENSORY CHARATERISTICS

	GROUP B	GROUP BC	*P* value
MEAN ONSET TIME	3 mins 10 secs	2mins 40secs	<0.05
MEAN Max LEVEL OBTAINED	T5	T4	
MEAN TIME FOR ACHIEVING MEAN Max LEVEL	8 mins 40 secs	6mins 12secs	<0.05
MEAN TOTAL DURATION OF ANALGESIA	167 mins	327 mins	<0.005

TABLE—4: MOTOR CHARACTERISTICS

	GROUP B	GROUP BC	*P* value
MEAN TIME REQUIRED TO ATTAIN MAX MOTOR BLK	5 mins 04secs	3mins 40secs	<0.05
QUALITY O MOTOR BLOCKADE	Bromge grade III→ 85%, grade II → 15%	Bromage grade III→100%	
DURATION OF MOTOR BLOCKADE	135 mins	210 mins	<0.005

TABLE—5: HEMODYNAMIC CHANGES – GROUP B AND GROUP BC



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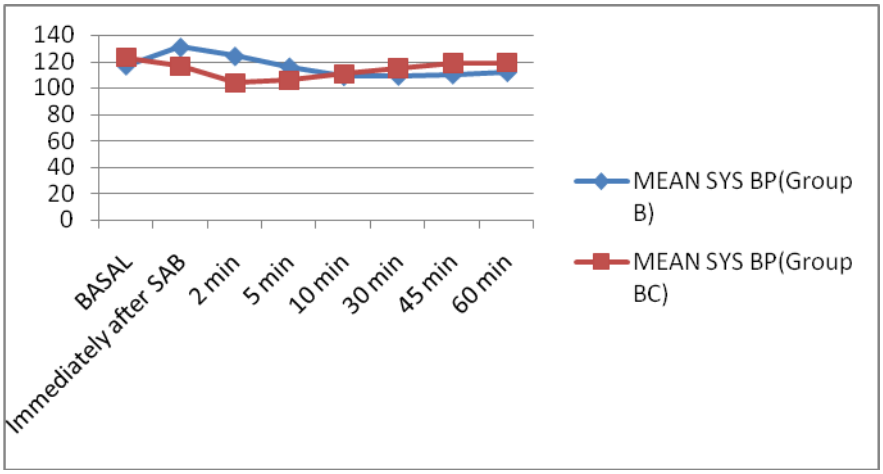
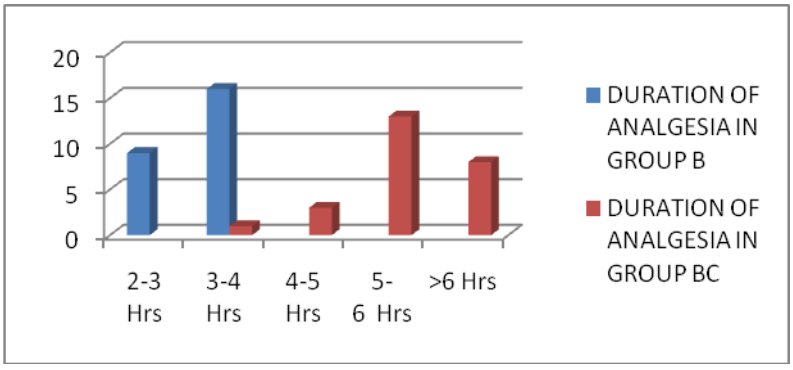


TABLE—6 DURATION OF SURGERY

TIME INTERVAL	GROUP B	GROUP BC
45-60 min	18	20
60-120 min	7	5

TABLE—7 DURATION OF POST OPERATIVE ANALGESIA

TIME INTERVAL	DURATION OF ANALGESIA IN GROUP B	DURATION OF ANALGESIA IN GROUP BC
2-3 Hours	9	
3-4 Hours	16	1
4-5 Hours		3
5-6 Hours		13
>6 Hours		8



In the present study (TABLE 4), we noticed that there was earlier onset of motor blockade and prolonged duration of motor blockade in Group-BC compared to Group-B.Intraoperative need of vasopressor was more with Group BC compared to Group B (TABLE 5,6). Three patients exhibited hypotension with SBP< 80 mmHg. It occurred 15- 30 min. after SAB. Two patients required three doses of Mephentermine to maintain SBP at 100 mm. Hg. In one patient, hypotension was associated with Bradycardia. It responded to i.v. Atropine. Subsequently in all these three patients there were no further changes in SBP or HR. No patient

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had sedation, post dural puncture headache or transient neurological symptoms at the post operative follow up.

DISCUSSION

Many innovative techniques have been used for prolonging spinal analgesia. Combined Spinal Epidural is one such technique. But it is time consuming and technically difficult. Spinal opiate definitely prolongs the spinal analgesia. But its use is associated with the risk of respiratory depression and urinary retention. Vasopressors are also used for prolonging the spinal analgesia. But its use is associated with the risk of anterior spinal artery syndrome. Clonidine, α-2 adrenergic agonist, can prolong the spinal analgesia without any above mentioned side effects.

Clonidine, a partial α-2 adrenergic agonist, has antinociceptive properties (Gligore.M. 1987, Kersten. J. 1995, Armands, et al 1998). Clonidine has been used orally, epidurally and intrachecally to prolong the analgesia provided by local anaesthetics when given intrathecally or epidurally[2].

Dosage selected: Clonidine has been used in varying doses from 15µg to 300µg intrathecally by various authors. Recently it has been established that with Local Anaesthetics, the maximum dose of intrathecal Clonidine to be 1-2µg/kg. Higher doses of sole Clonidine is said to produce marked sedation as well as hemodynamic disturbances. Plateau effect of analgesic effect of Clonidine is seen around a dose of 150µg[4,5]. In view of this, in the present study we selected a dose of 75µg of Clonidine.

Clonidine produces spinal cholinergic activation: Cholinergic interaction in spinal α-2 adrenergic receptors which are located on descending nor-adrenergic pathways produces nor-adrenaline release that causes analgesia directly and also it releases acetyl choline (Ach) to produce analgesia. Clonidine also blocks Aδ and C- fibers at lamina V, thereby producing analgesia[1,6,7].

In the present study (TABLE 3), we noticed that in Group- BC onset time for sensory blockade was earlier compared to Group- B, showing that Clonidine enhances action of spinally administered local anaestheics. However, there was no clinically significant difference in the maximum level of blockade achieved in both the groups.

In Group-BC, we found analgesia lasting up to 327 minutes compared to 167 minutes in Group-B. This clearly shows that, intrathecally administered Clonidine, significantly prolongs the duration of analgesia when administered with Local Anaesthetic agents which concurs with kalso et al[11].

Clonidine is said to prolong the motor blockade produced by local Anaesthetic agents[1]. Clonidine produces local vasoconstriction by acting on vascular smooth muscle (α-

receptors), which decreases absorption of local anaesthetics from sub arachanoid space thereby prolonging the duration of action[8,9,10].Hence, in the present study also (TABLE 4), we noticed earlier onset of motor blockade and prolonged duration of motor blockade in Group-BC compared to Group- B. The quality of motor blockade also improved with the addition of intrathecal Clonidine. This particular property may be advantageous in situations where unexpected prolongation of the surgical procedures, wherein we can still provide adequate relaxation for the surgical procedure.

Clonidine after neuraxial administration affects arterial blood pressure in a complex manner because of opposing actions at different sites. The α-2 adrenergic agonism produces sympathicolysis and reduces the blood pressure through effects on brainstem nuclei and on sympathetic pre-ganglionic neurons. However, these effects are counteracted by direct vasoconstriction resulting from the effect of α-1 and α-2 adrenergic agonistic actions on the peripheral vasculature[1,11].

Hemodynamic disturbances following intrathecal Clonidine depends upon: a) Segmental site of injection, b) Patient position, c) Rate of injection, d) Temperature of the injected solution, e) Preloading, f) The baricity of local anaesthetics employed.

Conflicting views are given with regard to BP changes following various doses of intrathecal Clonidine. The BP changes is said to follow a U shaped pattern (TABLE 5). Smaller doses is said to produce fall of BP by the effect on central brain stem nucleus and pre-ganglionic sympathetic inhibition. Larger doses is said to maintain BP through its effects on peripheral vasculature[2].

In the present study (TABLE 5), we did not notice severe hemodynamic disturbances. In the present study the decreased incidence of hypotension may be attributed to preloading done and keeping the OT table flat and use of hyperbaric Bupivacaine. From the present study it is seen that intrathecal Clonidine in the dose of 75µg does not produce significant hemodynamic disturbances. However, occasional episodes of hypotension can occur with this drug. However, it responds to routine measures.

In the present study (TABLE 7), in Group-BC the total duration of analgesia was significantly higher compared to Group-B. This ability of intrathecal Clonidine to prolong analgesia without any side effects has many fold advantages. It provides adequate post-operative analgesia. In unexpected prolongation of superficial surgical procedures, maintenance of analgesia provides additional time for the surgeon to complete the surgery without resorting to General Anaesthesia[1,2,11].

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CONCLUSION

The use of intrathecal Clonidine significantly produces prolongation of analgesia and motor relaxation without any side effects, giving us a safe edge in situations where there is unexpected prolongation of surgical procedure occurs.

Hence, intrathecal Clonidine in the dose of 75µg along with 2.5 ml of 0.5% hyperbaric Bupivacaine provides an attractive alternative combination to anesthesiologist armamentarium for prolonging spinal analgesia.

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