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A clinical study of peri operative effectiveness of adjuvant Neostigmine with intrathecal Bupivacaine for lower abdominal surgeries.

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Abstract: *Spinal anaesthesia results in sympathetic blockade, sensory analgesia and motor blockade. It requires a small volume of drug to produce profound and reproducible sensory analgesia and motor blockade; in contrast, epidural anesthesia necessitates the use of a large mass of local anesthetic that produces pharmacologically active systemic blood levels, which may be associated with side effects and complications unknown with spinal anaesthesia. Many lower abdominal surgical procedures require muscle relaxation, and spinal Bupivacaine alone provides only modest motor block. Various drugs have been used along with local anaesthetics for prolongation of spinal analgesia and motor block like opiates, benzodiazepines, clonidine etc. The present study was intended to know whether intrathecal Neostigmine can meet the above mentioned requirements.* ***Methodology:*** *we performed this prospective study on patients posted for lower abdominal surgery belonging to ASA I and age group between 18-60 years after obtaining a written informed consent and ethical clearance.* ***Result:*** *Addition of neostigmine 50µg to intrathecal hyperbaric Bupivacaine significantly produces prolongation of analgesia than compared to the control group with no serious adverse effects perioperatively.* ***Conclusion:*** *Intrathecal Neostigmine in the dose of 50µg with 0.5% hyperbaric Bupivacaine provides an attractive alternative combination to anaesthesiologist armamentarium for managing lower abdominal surgeries.*

Keywords: Analgesia*, Bupivacaine, Hyperbaric, lower abdominal surgery, Neostigmine.*

I. Introduction

Bupivacaine is the most commonly employed local anaesthetic for sub arachanoid block. Peri operative hemodynamic status and post operative pain relief are important issues with Bupivacaine. Many adjuvants are commonly used to overcome these demerits. So our concern is to choose an adjuvant with Bupivacaine which provides a stable intraoperative condition, prolonging the post operative analgesia with minimal side effects.
Neostigmine is a white crystalline powder which is odorless and readily soluble in water. It is a synthetic quaternary ammonium compound. Neostigmine is an anticholinesterase agent, which inhibits the hydrolysis of acetyl choline by competing with acetylcholine for the attachment to acetyl cholinesterase, as a result acetylcholine accumulates at cholinergic synapses and its effects are prolonged and exaggerated. Spinal Neostigmine apparently activates descending pain inhibitory systems that rely on a spinal cholinergic interneuron, probably exacerbating a cholinergic tonus that is already activated during the post operative period [1] and seems to be extremely efficient for alleviating somatic pain.

II. Aim Of Study

To compare the effect of intrathecal Neostigmine in the dose of 50µg with 2.5 ml of 0.5% hyperbaric Bupivacaine & 2.5 ml (12.5mg) of Intrathecal 0.5% hyperbaric Bupivacaine. With regard to: 1) Sensory characteristics, 2) Motor characteristics, 3) Side effects.

III. Materials And Methods

A prospective randomized controlled study was taken up in our institute over a period of 6 months. ***Inclusion criteria:*** All patients aged between a) 18-60 years, b) ASA Grade I & II c) Patients posted for Lower Abdominal Surgeries. ***Exclusion criteria:*** a) Patients with local sepsis; b) Patients with bleeding diathesis, c) Patients with raised ICP d) Patients with any co-morbid diseases like IHD, Hypertension, Bronchial asthma, Diabetes Mellitus & morbidly obese patients.

The study population belonging to the inclusion criteria was divided randomly into two groups (TABLE 1): Group B (n=25) served as control, received 2.5 ml of 0.5% Hyperbaric Bupivacaine along with 0.5 ml of normal saline. And Group BN (n=25) received 2.5 ml of 0.5% hyperbaric Bupivacaine + 50µg of Neostigmine. 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 & the monitoring Anesthesiologist were blinded to the study solutions. Ethical committee clearance & patients consent were obtained. All the patients

were premedicated on the night before surgery with tab Ranitidine 150 mg and tab. Alprazolam 0.5mg. On the day of surgery, after securing i.v line with 18G cannula. Patients were connected to multichannel monitor displaying ECG, SPO2 & NIBP. All the patients were preloaded with 10 ml/kg of RL. Under aseptic precautions, lumbar puncture was done using 23G spinal needle at L2- L3 or L3- L4 space. After confirming the free flow of 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 & 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 HR. SBP& 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 >5).

- Hypotension was defined as reduction of SBP, more than 30% below the base line value [2] or SBP recording <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 & was treated with i.v. atropine.
- Any other side effect associated with the administration of intrathecal Neostigmine was noted.

At the end of the study, the data was complied systematically and was subjected to statistical analysis using student't' test and SPSS version 10.0 for windows. Value of $p<0.05$ was considered significant.

IV. Discussion

The aim of good post operative analgesia is to produce a long lasting, continuous effective analgesia with minimum side effects. Commonly used local anaesthetics for intrathecal anaesthesia are Lignocaine and Bupivacaine in India. Bupivacaine 0.5% heavy has more prolonged action compared to Lignocaine but the post operative analgesic duration is limited. Other method of prolonging analgesia is using a continuous epidural analgesia, which is technically more difficult and more costly, which the patients coming to the government hospital may not afford. Hence, an intrathecal additive to these local anaesthetics forms a reliable and reproducible method of prolonged post operative analgesia. This technique being simple and less cumbersome has gained a wide acceptability. Commonly used intrathecal additives to local anaesthetics include Opioids, Clonidine, and Neostigmine.

The groups were comparable with respect to age, sex, weight and ASA physical status. There was no statistically significant difference in the type, duration of surgery (p >0.05) (TABLE 1) and type of surgery (TABLE 2).

Spinal administration of Neostigmine, an acetyl cholinesterase inhibitor, inhibits breakdown of the endogenous neurotransmitter acetylcholine, thereby inducing analgesia [4,5], hence it is an another alternative non opioid additive to local anaesthetics which lacks pruritis, respiratory depression, urinary retention, decreased motility of gut as their side effects. In the present study, we noticed (TABLE 3) that in Group- BN onset time for sensory blockade was earlier compared to Group- B, showing that neostigmine enhances action of spinally administered local anaesthetics. However, there was no clinically significant difference in the maximum level of blockade achieved in both the groups. In Group-BN, we found (Fig. 1) analgesia lasting upto 300 minutes compared to 200 minutes in Group-B. This clearly shows that, intrathecally administered neostigmine, significantly prolongs the duration of analgesia when administered with local anaesthetic agents.

Hemodynamic disturbances following intrathecal local anaesthetics 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.

Intrathecal administration of Neostigmine causes an amplification of action acetylcholine released at preganglionic sympathetic neurons resulting in increase in heart rate and blood pressure [6, 7]. In our study (Fig. 2) intra operative blood pressure was well maintained in the Neostigmine group with minimal magnitude of change occurring as late as 40^{th} min of only 4 mmHg fall of systolic blood pressure compared to 19 mmHg fall at 5^{th} min in Group B concurs with Krukowski et al[6] study. However, there was increase in pulse rate of 18 beats/min at 5^{th} min in Neostigmine group, than compared with 10 beats/min increase in Group B at 2^{nd} min this was also observed by JG Klamt [8] with administration of 100 micrograms of Neostigmine intrathecally. This is due to excitatory action of Neostigmine on preganglionic sympathetic neurons are more pronounced after injection directly into intermediolateral cell column than after intrathecal injection [9].

In addition to the potential direct inhibition of motor activity by administration of Neostigmine, it was speculated [10] that increased spinal levels of acetylcholine may augment motor block as a result of axonal

conduction block from spinal Bupivacaine. Neostigmine enhanced motor block from spinal Bupivacaine may be useful in the clinical setting. Many lower-extremity surgical procedures require muscle relaxation, and spinal Bupivacaine alone provides only modest motor block [11]. In our study (TABLE 4) the mean time for motor onset was significantly faster in Neostigmine group (Group BN=1.96 mins) when compared to Group B=2.44 mins, similarly the mean time taken for maximum motor blockade was clinically and significantly faster in Neostigmine group (Group BN=3.32 mins) than compared to Group B=4.64 mins and mean time taken for regaining complete motor power was prolonged significantly in Neostigmine group (Group BN=193 mins) than Bupivacaine group (Group B= 150 mins). This concurs with the study result (mean duration of 220 mins) conducted by JG Klamt et al [8].

Nausea, vomiting and urinary incontinence were the most distressing side effects observed in the Neostigmine group using more than100 micrograms [12]. Cholinergic sites in the brainstem and thoracic and cervical spinal cord may involve in mediation of nausea/vomiting side effect [8]. Roastral spread of Neostigmine to this brainstem site is proposed to be the cause for nausea and vomiting [7, 13]. Hence, by keeping the patients in sitting posture or by diluting the drug with hyperbaric solution prevents the drug to act on supra spinal site to produce this side effect [12]. In the present study (TABLE 5; Fig. 3) perioperatively nausea vomiting were noticed in the both the groups which were statistically insignificant $p>0.05$.

TABLE –1: DEMOGRAPHY

	GROUP B	GROUP BN
MEAN AGE	30.8	28.72
MEAN WEIGHT	60.36Kg	56.36Kg
MALE:FEMALE RATIO	18:07	18:07

TABLE—2: SURGICAL PROCEDURE

	GROUP B	GROUP BN
SURGICAL PROCEDURES (INGUINAL HERNIA: APPENDICECTOMY)	16:9	15:10

TABLE –3: SENSORY CHARATERISTICS

	GROUP B	GROUP BN
MEAN ONSET TIME	2mins 42secs	1mins 38secs
MEAN Max LEVEL OBTAINED	T5	T4
MEAN TIME FOR ACHIEVING MEAN Max LEVEL	7 mins 24 secs	6mins 28secs
MEAN TOTAL DURATION OF ANALGESIA	207.6±45mins	300.0±54 mins

FIGURE–1: DURATION OF POST OPERATIVE ANALGESIA

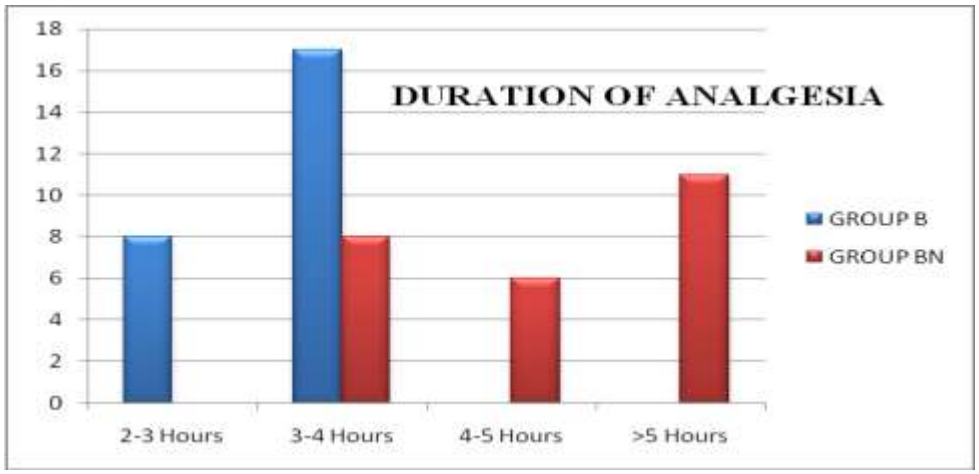
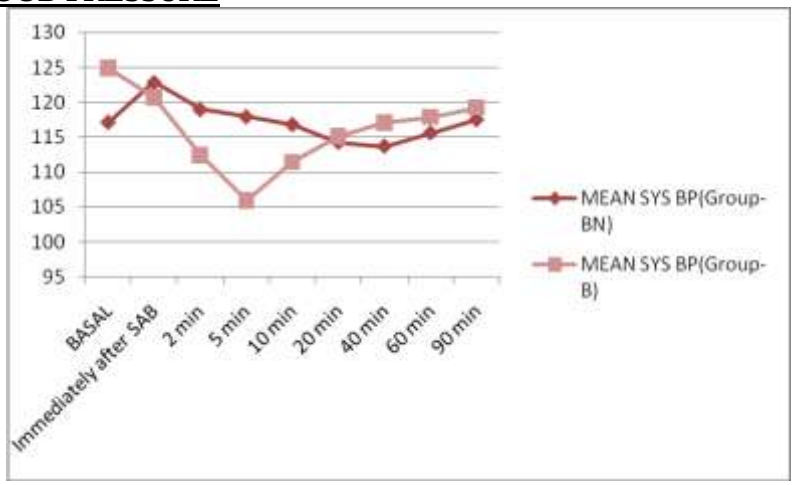


FIGURE -2: HEMODYNAMIC CHANGES – GROUP B & GROUP BN

SYSTOLIC BLOOD PRESSURE



HEART RATE

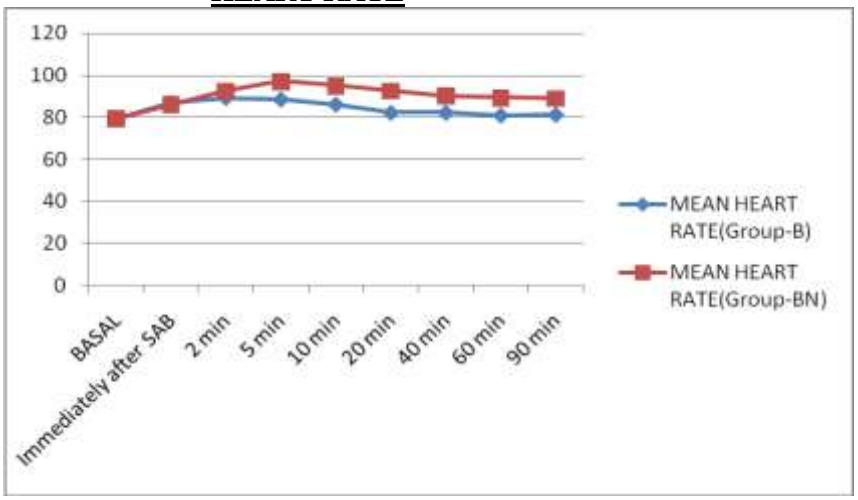


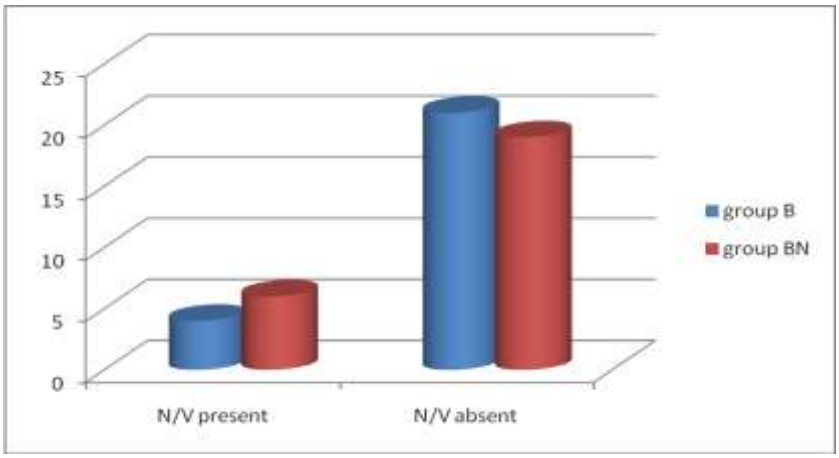
TABLE –4: MOTOR CHARACTERISTICS

	GROUP B	GROUP BN
MEAN ONSET TIME	2mins 44secs	1mins 56secs
QUALITY O MOTOR BLOCKADE	Bromge grade III→ 85%, grade II → 15%	Bromage grade III→100%
MEAN TIME REQUIRED TO ATTAIN MAX MOTOR BLK	4mins 64secs	3mins 32secs
DURATION OF MOTOR BLOCKADE	150±38 mins	193±40mins

TABLE –5: PERI OPERATIVE NAUSEA & VOMITING

GROUP	PRESENT	ABSENT
GROUP B	04	21
GROUP BN	06	19

FIGURE-3: INCIDENCE OG NAUSEA/VOMITING



V. Conclusion

From the present study, it can be concluded that: A) Intrathecal Neostigmine in the dose of 50µg significantly decreases the onset time of sensory analgesia and motor blockade. B) It significantly prolongs the duration of motor blockade and provides an adequate surgical relaxation intraoperatively C) It provides long lasting analgesia upto 6 hours. D) In the dose of 50µg Neostigmine use intrathecally is not associated with any significant hemodynamic disturbance or respiratory depression.

Significant prolongation of analgesia & adequate motor relaxation without any side effects gives a safe edge in situations where there is unexpected prolongation of surgical procedure.

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