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Comparison of Intrathecal Clonidine and Neostigmine with Intrathecal Bupivacaine for Lower Abdominal Surgeries

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Abstract: ***Background and Aims: Use of adjuvant drugs in SAB prolongs the duration of the action. This study was conducted to compare the effects of intrathecal clonidine with neostigmine added to hyperbaric bupivacaine intrathecally, with regards to sensory characteristics, motor characteristics, haemodynamic parameters. Methods: This was a prospective randomized double blind study in 50 patients of ASA grade I and II status & aged between18 to 60 years. First group received intrathecal Clonidine 75 µg and 3 ml (15 mg) of intrathecal 0.5% hyperbaric bupivacaine (group C) and second group received neostigmine 50 µg with 3 ml (15mg) of intrathecal 0.5% hyperbaric bupivacaine (group N). Results: Addition of 50 µg neostigmine hastened the onset of sensory block (N - 96 ±12 secs, C-150 ±14 secs, P value as <0.05) and motor block (N-150± 18secs, C-240 ±30secs, P value as <0.05) compared to clonidine. Haemodynamics were maintained in both the groups. Group C had prolonged analgesia (380 ±45mins) compared to N group (300 ±28mins) (P < 0.05) with nausea and vomiting in Group N. Conclusion: Clonidine as adjuvant produces prolonged postoperative analgesia and Neostigmne as adjuvant produces good sensory and motor for the surgical procedure with fewer side effects.***

Keywords: Analgesia, clonidine, hyperbaric, lower abdominal surgery, neostigmine

1. Introduction

Patientsexperience varying degrees of intraoperativepain and discomfort during the end of the surgery, if the expected operative time is prolonged thanmaximum duration of action of the drug. It is commonly observed inpatients undergoing prolonged lower abdominal surgeries under spinal anaesthesia with Bupivacaine alone[1]. Alleviation of this discomfort and pain is a must and it requires either supplementation with analgesics liked opioid drugs/ Ketamine or induction of general anaesthesia during the surgery which is cumbersome.

There are different approaches to prevent pain and discomfort

1) By Increasing in the dermatomal level of sensory blockade: increase in the dosage of the Bupivacaine increases dermatomal level of blockade and there by increasing the duration of blockade. However there are some potential side effects like significant hypotension and bradycardia.
2) By adding adjuvants to Bupivacaine.

Most commonly used adjuvants are opioids and they have undesirable side effects like pruritis, nausea, vomiting, acute urinary retention.There are also other adjuvant drugs which are nonopioid drugs are in use. These non opioid drugs have the advantage over opioids as adjuvants as they have lesser side effects.

This study was conducted to compare the intrathecal effects of two non opioid drugs - neostigmine and clonidine. The aims of this study were to observe the adjuvant drug effects on sensory, motor block characteristics and haemodynamic parameters.

Clonidine

It is an imidazoline derivative. It is a Selective partial α_2 agonist agent, routinely used as a premedication drug during general anaesthesia. It reduces the requirement of analgesics & anaesthetic drugs intraoperatively. Intrathecal clonidine produces analgesia by its indirect action i.e., by inhibiting the activity of wide dynamic range (WDR) neurons.[2] It acts on substantia gelatinosa and within the brainstem nuclei involved in analgesia. Clonidine has been in use by oral, epidural, spinal, perineural & parenteral routes to obtain post-operative analgesia.[3]

Neostigmine

It is a Quaternary ammonium ion and it is an Anticholinesterase agent. It increases the acetylcholine concentrations at cholinergic synapses. Intrathecal Neostigmine prevents of breakdown of synaptically released Acetyl choline & thus by causing analgesia. It activates descending pain inhibitory systems that depends on a spinal cholinergic interneuron, probably accentuating a cholinergic tonus that is activated already, during the postoperative period and seems to be extremely efficient for reducing somatic pain.[4]

Aim

The aim of our study is to compare the pharmacological effects of Neostigmine and Clonidine on sensory block, motor block characteristics and haemodynamic parameters.

2. Materials and Methods

After obtaining approval from Institutional ethical Committee and informed consent from 50 patients of age between 18 and 60 years belonging to ASA grade I and II have been randomly allotted into two different groups of 25

each. Group Cand Group N using computer generated numbers.

Patients of either of age 18 - 60 years, belonging to ASA grade I and II, who were posted for lower abdominal surgeries were included in the current study, where as patients who refused to give approval, patients with known sensitivity to study drugs and local anaesthetics, patients who are on adrenergic receptor antagonizing drugs, and patients with Co-morbid diseases like ischaemic heart disease (IHD), Hypertension (HTN), bronchial asthma, Diabetes Mellitus (DM) were excluded from the study.

every patient who was included in the study received 3.5ml of drug intrathecally. Group C (n=25): patients received 3ml of 0.5% hyperbaric Bupivacaine with 0.5ml (75mcg) of Clonidine. Group N (n=25): patients received 3ml of 0.5% hyperbaric Bupivacaine with 0.5ml (50mcg) of Neostigmine. 1ml of Neostigmine ampoule contains 0.5mg.

0.1 ml(50mcg) is taken and diluted to 0.5 ml with 0.9%Nacl. Blinding was thoroughly maintained as both the patients and the monitoring anaesthesiologist were blinded to the study solutions. All the drug solutions were prepared by anesthesiologist who was not involved in the administration of anesthesia or in observation of patients.

All the patients who were allotted into study groups were premedicated on the night before surgery with tab. Ranitidine 150 mg and tab.Alprazolam 0.5 mg. On the day of surgery, intravenous (IV) access was established with an 18G cannula. Patients were connected to multichannel paramonitor displaying electrocardiogram (ECG), oxygen saturation (SPO2) and non-invasive blood pressure (NIBP) and basal vital readings were recorded. All the patients were preloaded with 10 ml/kg of ringer lactate through the iv access. Under strict aseptic precautions, lumbar puncture was performed using a 25G spinal needle at L3/L4 space in left lateral decubitus position. Clear free flow of cerebrospinal fluid (CSF) is confirmed. the study drugs were injected into the sub arachnoid space @ 0.2ml/second with the operation table kept flat. Patients were turned supine immediately.

The following parameters were noted: Time of onset of analgesia (time taken from the injection of the drug to loss of pin prick at T10 level), dermatomal spread of analgesia achieved in the cephalad direction, Time taken for onset of motor block (time taken for complete inability to flex the lower limbs at hip joint), Quality of motor blockade is assessed by Bromage scale,[5]Intraoperative haemodynamic monitoring includes heart rate (HR), systolic blood pressure (SBP) measured immediately after sub arachnoid block (SAB), at 2nd min, 5th min, 10th min and every 5 min till the end of surgery). Total duration of analgesia (time from the onset of analgesia to the point where the patient complained of pain at the surgical site requiring rescue analgesics.total duration of motor block (complete recovery of motor power).

Hypotension was defined as reduction of systolic blood pressure (SBP) by greater than 30% below the baseline value or systolic blood pressure (SBP) to < 90 mm Hg and was treated with increased rate of infusion of IV fluids and vasopressor (Inj. Mephentermine 6 mg). Bradycardia was defined as heart rate (HR) < 60 bpm. and was treated with inj.Atropine IV. Any other side effect associated with the administration of intrathecal Neostigmine and Clonidine was noted.

The data were presented as mean ± S.D. All categorical data analyzed using Chi-square test as required and continuous and nominal variables by using student *'t'* test. Value of $P<$ 0.05 was considered significant. Statistical Package for Social Sciences (SPSS) version 10.0 for windows was used for statistical analysis.

3. Results

The demographics and duration of surgery were comparable among both the groups.

Table 1: Demographic Trends

Parameter	Group N	Group C
Mean age (years)	29 ±8.76	36.05± 8.09
Mean weight (kg)	55.48± 8.63	53.5 ± 9.07
Male: Female ratio	17:08	10:15
Duration of surgery(min)	120.18± 11.14	135.66±18.53

Group N showed early onset of sensory block (96 ± 12secs) compared to group C (150 ± 14 sec), (P < 0.05). The spread of sensory block in the cephalad direction was similar in both the groups. The mean total duration of analgesia was prolonged in group C (380 ± 45 min) compared to group N (300 ± 28 min) (P < 0.05) Table 2. Onset of motor block was 150 ± 18 secs in group N compared to 240 ± 30 secs in group C (P < 0.05). Recovery from motor block took 170 ± 30 mins in group N compared to 230 ± 50 mins in group C. Table 3.

Table 2: Sensory Characteristics

Parameter	Group N	Group C	P value
Mean onset of time (sec)	96 ±12	150 ±14	<0.05
Median cephalad spread	T 6	T6	
Mean total duration of analgesia (min)	300 ±28	380 ±45	<0.05

Table 3: Motor Characteristics

Parameter	Group N	Group C	P value
Mean time required to attain maximum block (sec)	150± 18	240 ±30	<0.05
Quality of motor blockade	Bromage grade 3	Bromage grade 3	
Duration of motor blockade (min)	170 ±30	230 ±50	<0.05

Increase in heart rate was noted in both groups following sub arachnoid block (SAB) with mean maximum increase of 10 beats/min noted at 5th min in group N, compared increase of 12 beats/min noted at 2nd min in group C. blood pressure was well maintained in the intra operative period in the neostigmine group with mean magnitude of change of only 4 mmHg, compared to mean maximum fall of 20 mmHg at 30th min in group C .In group C ten patients exhibited systolic blood pressure (SBP) between 100 - 105 mm of Hg, which occurred 15-30 min after SAB and considered insignificant. None of the patients required injection Mephentermine as the fall in SBP is insignificant. There were no significant changes in the mean heart rate in either

of the groups and no one in any of the groups required Atropine to be given.

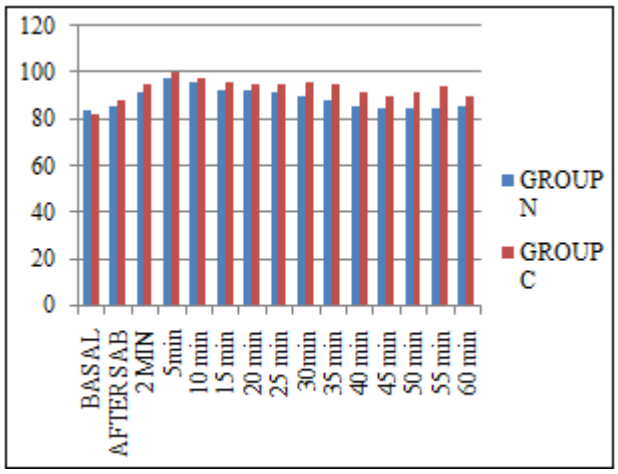

Figure 1: Heart Rate Comparison

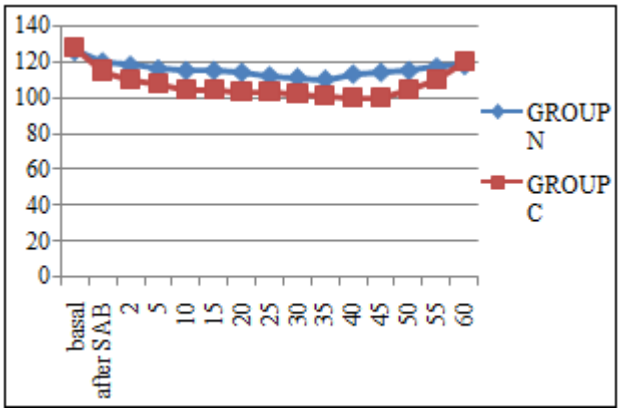

Figure 2: SBP Comparison

45 patients of Clonidine group of patients had mild to moderate sedation but no one had respiratory depression during the surgery which is beneficial to the patient. Sedation among the patients is assessed with four point sedation scale. 40 Neostigmine group of patients complained of severe nausea and vomiting post operatively and required anti emetics like Ondansetron on the day of surgery. No patients of either groups had pruritus, post dural puncture headache or transient neurological symptoms at intraoperative period or during post-operative follow up.

4. Discussion

Clonidine is an imidazolidinine derivative and a selective partial agonist for α_2 adrenoreceptors. It produces spinal cholinergic activation. Cholinergic interaction in spinal α_2 adrenergic receptors which are located on descending nor-adrenergic pathways produces nor-adrenaline release which inturn causes analgesia directly and also it releases acetyl choline (Ach) to produce analgesia.[6,7] Clonidine also blocks C and Aδ-fibers at lamina V, thereby producing analgesia.It acts on vascular smooth muscle (α-receptors) and produces local vaso constriction, which results in the decreased absorption of local anaesthetics from sub-arachnoid space thereby prolonging the duration of action. It has been used in varying doses from 15 µg to 300 µg intrathecally by various authors to prolong the duration of sensory and motor block and for analgesia.the maximum dose of intrathecal clonidine along with local anesthetics is to be 1-2 µg/kg. Higher doses of Clonidine alone is said to produce marked sedation as well as significant changes in the haemodynamic parameters. Plateau effect of analgesic effect of clonidine is seen around a dose of 150µg.[8,9]hence, in the present study a dose of 75 µg of intrathecal clonidine was used.Patients were observed to have mild to moderate sedation without any respiratory depression during the surgery when Clonidine was given intrathecally and were assessed with four point sedation scale.

Four-point sedation scale

- 0-Fully awake
- 1-mildly sedated (drowsy and responds to call)
- 2-moderately sedated (drowsy and responds to tactile stimulation)
- 3-severely sedated (deep sedation, unresponsive).

The incidence of sedation was significant in clonidine group compared to other group. Similar observation was made by previous studies with different doses of intrathecal clonidine which is beneficial to the patient during the surgery. In the present study conducted in our institute , we observed that onset for sensory blockade was faster when neostigmine is used as an adjuvant to intrathecal Bupivacaine, showing that neostigmine enhances the action of sub arachnoid administration of local anaesthetic drugs. sub arachnoid administration of neostigmine, an acetyl cholinesterase inhibitor, inhibits breakdown of the endogenous neurotransmitter acetylcholine, thereby inducing analgesia,[10] hence it is considered as an another alternative non opioid additive to local anaesthetics devoid of opioid associated side effects. Intrathecal administration of Clonidine with local anaesthetic agents significantly prolongs the duration of analgesia. We also noted that duration of analgesia was prolonged with intrathecal clonidine compared to intrathecal neostigmine providing pain relief to the patient for a longer duration.

Clonidine is believed to prolong the motor blockade produced by local anaesthetic agents. However it did not have any side effects and patients were compliant in Group C. Coniine acts on vascular smooth muscle (α-receptors) and produces local vase constriction, which decreases absorption of local anaesthetics from sub-arachnoid space thereby prolonging the duration of action. In addition to the potential direct inhibition of motor activity by administration of neostigmine, it was speculated that increased spinal levels of acetylcholine may augment motor block as a result of axonal conduction block from spinal bupivacaine. In present study, the mean time for motor block onset and the mean time taken for maximum motor blockade was significantly faster in neostigmine group than compared to group C. Similar results were obtained in the study conducted by Klamt *et al*. Contrary to intravascular administration, intrathecal administration of neostigmine causes an increase in heart rate and blood pressure because, acetylcholine stimulates of preganglionic sympathetic neurons. In our study, there was an increase in heart rate in patients receiving intrathecal neostigmine, but intraoperative blood pressure was well maintained and this is in agreement with observations of Klamt.The excitatory action of neostigmine on preganglionic sympathetic neurons are more pronounced

after injection directly into intermediolateral cell column than after intrathecal administration further explaining the heart rate response noticed in this study.

Conflicting views are given with regard to blood pressure changes following various doses of intrathecal clonidine. Smaller doses are said to produce fall in blood pressure which follows a U shaped curve, by the effect on central brain stem nucleus and pre-ganglionic sympathetic inhibition. Larger doses are said to maintain BP through its effects on peripheral vasculature. There was no significant hypotension following intrathecal administration of 75 µg of clonidine in the present study when compared with the studies conducted by yoga narasimhaet.al., where there was significant hypotension in Clonidine group of patients in whom they required doses of Neostigmine to maintain blood pressure within normal limits.

Intrathecal administration of neostigmine produces well-known side effects of nausea and vomiting perioperatively due to rostral spread of neostigmine to the brainstem site. Dilution of drug with local anaesthetic usually reduces the incidence of nausea and vomiting Keeping the patients in sitting posture while administering the drug or by diluting the drug with hyperbaric solution prevents the rostral spread. In our study the incidence of nausea and vomiting was much higher even after taking all the measures to prevent nausea and vomiting. Literature search did not provide a proper insight into the equipotent doses of clonidine and neostigmine for intrathecal use, hence this may be a limitation in the present study. More studies with adequate sample size may be required to establish the equipotent doses of these drugs.

5. Conclusion

Clonidine at 75µg intrathecally with 15mg of Bupivacaine has prolonged duration of analgesia than Neostigmine. Patients with Neostigmine needed rescue analgesia whereas Clonidine did not. In addition Clonidine has intraoperative sedative action which was beneficiary to the patient during surgery. There were no significant side effects with Clonidine where as Neostigmine group of patients had severe nausea and vomiting perioperatively. Hence, Clonidine is better than Neostigmine as an adjuvant to intrathecal Bupivacaine

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