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Original Article

A Comparison of Intrathecal Neostigmine and Clonidine for Post-operative Analgesia in Total Abdominal Hysterectomies

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Abstract

Background: Intrathecal neostigmine 5 μg and clonidine 30 μg with bupivacaine produce substantial antinociception and potentiate analgesia of bupivacaine.

Aims: The aim was to investigate the effect of intrathecal neostigmine and clonidine on post-operative analgesia and hemodynamic when added to 0.5% hyperbaric bupivacaine.

Subjects and Methods: In this prospective, randomized, and double-blind study, we took 90 patients of ASA Grade I and II adult female patients posted for total abdominal hysterectomies.patients were assigned into three groups of 30 patients each. Patients of Group 1 received neostigmine 5 μg, Group 2 received clonidine 30 μg, and Group 3 received normal saline as an adjuvant to 3 ml of hyperbaric bupivacaine. Onset, duration of analgesia, heart rate, mean arterial pressure, and adverse effects were recorded. Recorded data were statistically analyzed. $P < 0.05$ was statistically significant.

Results: The mean duration of analgesia was significantly longer in Group 2 followed by Group 1 and lowest in Group 3. Additional analgesic requirement was significantly less in Group 2 followed by Group 1 and Group 3. The pain score was significantly less in Group 2. The incidence of hypotension and bradycardia was the lowest in Group 1.

Conclusion: Neostigmine and clonidine both provide longer post-operative analgesia and neostigmine also provides better hemodynamic stability with fewer side effects.

Key words: Neostigmine, Clonidine, Postoperative analgesia

INTRODUCTION

Anesthesiologists succeed to a greater extent by rendering the patient absolutely pain free during surgery, but despite advances, many patients continue to experience considerable discomfort in the post-operative period. Inadequate post-operative analgesia may result in significant morbidity which may delay recovery and increase hospital stay.[1]

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Spinal anesthesia is routinely performed for lower abdominal surgeries and lower limb procedures. Local anesthetic (LA) alone provides the short duration of its effects. To increase the quality and duration of spinal analgesia, a number of adjuvant is added to LAs, i.e. opioids (morphine, fentanyl, sufentanil, etc.), neostigmine, clonidine, dexmedetomidine, and midazolam, etc., are add intrathecally. These adjutants not only reduce the dose of LAs but also provide prolonged post-operative analgesia with reduced incidence of side effects such as central nervous system depression, motor effects, or hypotension.

Neostigmine is anticholinesterase agent which increases the acetylcholine (Ach) concentration at the cholinergic synapse by blocking the activity of true and pseudocholinesterase.[2] In post-operative period descending noradrenergic or cholinergic antinociceptive spinal system

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is activated by ongoing pain causing an increase in the release of Ach, which in the presence of neostigmine results in augmented analgesia. It has no untoward side effects such as respiratory depression, pruritis, and drowsiness as experienced with intrathecal narcotics.[3]

Clonidine is an alpha-2 receptor agonist which has gained popularity in recent times as an adjuvant in spinal anesthesia. Analgesic effect of clonidine mediated by α2-adrenoceptors situated in the dorsal horn of spinal cord. The antinociceptive properties of clonidine indicate that it might be useful as an alternative to intrathecal opioids for postoperative analgesia,[4] thus also avoiding the adverse effect of opioids.

Aims and Objectives

1. To study and compare the effect of intrathecal neostigmine and intrathecal clonidine on post-operative analgesia.
2. To study and compare the hemodynamic parameters and side effects.

MATERIAL AND METHODS

The present study was randomized prospective study, conducted in the Department of Anesthesiology S.S. Medical College, Rewa, Madhya Pradesh, India. After getting approval from Institutional Ethics Committee, 90 female patients of ASA Grade I and II, aged between 30 and 50 years scheduled for total abdominal hysterectomy were included in this study. Informed consent was taken from all the patients.

Patients fulfilling the selection criteria were randomly divided into 3 groups of 30 patients each:

Group 1: Injection bupivacaine hydrochloride heavy 0.5% 15 mg (3 ml) intrathecal
Injection neostigmine 5 μg (1 ml) intrathecal

Group 2: Injection bupivacaine hydrochloride heavy 0.5% 15 mg (3 ml) intrathecal
Injection clonidine 30 μg (1 ml) intrathecal

Group 3: Injection bupivacaine hydrochloride heavy 0.5% 15 mg (3 ml) intrathecal
Injection normal saline 1 ml intrathecal.

Patient taking any medication (ace inhibitors, calcium channel blockers, adrenergic agonist, or any contraindication to subarachnoid block were excluded from the study.

Pre-anesthetic examination was done a day before surgery. All the patients were kept nil by mouth for at least 6 h. The patient was shifted to the operating room; an IV line was secured. All patients were premedicated with injection ondensetron 4 mg 30 min before surgery. All the monitoring equipments (non-invasive blood pressure, pulse oximetry, and electrocardiography) were attached, and baseline values of heart rate, blood pressure, SPO_2, and respiratory rate were recorded. All patients were preloaded with 15 ml/kg ringer lactate's solution.

The patients were placed in sitting position. Under all aseptic precautions, lumbar puncture was performed through midline approach in between L3 and L4 intervertebral spaces using 25 G Quincke's spinal needle. After the free flow of cerebrospinal fluid (CSF) study drugs which were prepared by another resident and provided in coded syringes were injected into the subarachnoid space.

Level of sensory blockade was assessed using a 23 G hypodermic needle (pinprick analgesia extending cranially at least to the T8 dermatome). Duration of effective analgesia was measured as the time from intrathecal drug administration to the patient's first complain of pain.

The level of motor blockade was assessed by modified Bromage scale [Table 1]. Duration of motor blockade was recorded as the time from onset of motor block to the time when the patient was able to raise his limb.

Hemodynamic parameters, i.e. heart rate, systolic blood pressure, diastolic blood pressure, and SPO_2 were recorded at different time intervals. Side effects, i.e. bradycardia, hypotension, nausea, vomiting, sedation, desaturation or hypoxemia (SPO_2 < 90%), and any other were also recorded.

Bradycardia (heart rate <60/min) treated with injection atropine 0.6 mg IV, hypotension (fall of systolic blood pressure >20% OR systolic blood pressure <90 mm hg) was treated with IV fluids and/or injection mephentermine 6 mg IV.

Pain was assessed by visual analog scale score at 2 h, 4 h, 6 h, and 24 h after surgery.

All recorded data were decoded, tabulated and statistically analyzed by Student's *t*-test, Chi-square test. $P < 0.05$ was taken as statistically significant.

RESULTS

All patients were demographically similar in regards to age, weight, height, and duration of surgery and it can be

Table 1: Modified Bromage scale

1	No paralysis
2	Inability to lift outstretched leg
3	Inability to flex the knee
4	Total paralysis of lower limb

Table 2: Patient's characteristics

Patient's characteristics	Group 1	Group 2	Group 3	*P* value
Age in years (mean±SD)	31.7±4.8	29.6±3.7	30.5±2.8	>0.05
Weight in kg (mean±SD)	55.67±4.21	55.17±6.22	56.04±1.77	>0.05
Height in cm (mean±SD)	153.93±4.03	153.77±3.40	153.67±3.57	>0.05
Duration of surgery in minutes	106.33±12.994	107.87±10.954	106.55±11.757	>0.05

SD: Standard deviation

Table 3: Comparison of sensory and motor block

Criteria	Group 1	Group 2	Group 3	*P* value
Onset of sensory block (in seconds)	90.57±15.5	107.60±14.79	110.00±11.54	<0.05
Onset of motor block (in seconds)	107.10±14.7	192±34.00	193.83±34.33	<0.05
Duration of analgesia (in minutes)	314.67±15.11	387.07±83.17	244.90±35.05	<0.05

Table 4: Side effects

Complication	Group 1	Group 2	Group 3
Hypotension	0	3	2
Bradycardia	0	2	3
Nausea	2	0	1
Vomiting	0	0	0
Sedation	0	0	0
Cardiac arrest	0	0	0
Resp. depression	0	0	0

presumed that the groups were comparable for the purpose of the study [Table 2].

All the patients in each group have achieved complete sensory block up to T8 and complete motor block (Bromage scale grade 3).

Onset of sensory block was earlier (90.57 ± 15.5 s) in Group 1 than Group 2 (107.60 ± 14.79 s) and Group 3 (110.00 ± 11.54 s). The difference was statistically significant between Group 1 and Group 2 ($P < 0.05$).

Onset of motor block was 107.10 ± 14.7 in Group 1 compared to 192 ± 34.00 in Group 2 and 193.83 ± 34 in Group 3. Early onset of motor block in Group 1 is also clinically significant ($P < 0.05$).

Duration of analgesia was longer in Group 2 (387.07 ± 83.19) than Group 1, (314.67 ± 15.11), and Group 3 (244.90 ± 35.05) minutes Group 2. This difference was statistically significant between all three groups ($P < 0.05$) [Table 3].

The differences in mean pulse rate mean systolic and diastolic blood pressure at different time intervals were almost similar in all the groups.

Most common side effects found in our study were hypotension, bradycardia, nausea, and sedation. Mild hypotension was found in three patients of Group 2 and two patients of Group 3 it was easily corrected with crystalloid infusion and 6 mg IV mephentermine. Bradycardia observed in two patients in Group 2 and three patients in Group 3 and corrected with IV atropine 0.6 mg. Complained of nausea was in two patients of Group 1 and one patient of Group 3. Other side effect was minimal, i.e., sedation, Shivering etc [Table 4].

DISCUSSION

Recent research has focused on non-opioid spinal receptors that inhibit transmission of pain signals. A number of adjuvant has been added to the intrathecal LAs for supplementation of intraoperative anesthesia and post-operative analgesia.

Neostigmine and clonidine both are widely available at a very affordable price. Absence of neurotoxicity, respiratory depression, etc., has been established in several studies when administered intrathecally.[5,6] It has encouraged us to compare the effectiveness and adverse effects of these two drugs when used as an adjuvant with intrathecal bupivacaine.

Spinal administration of neostigmine block the activity of true and pseudocholinesterase thus inhibits the breakdown of endogenous neurotransmitter Ach that has intrinsic analgesic properties.[7-9] High density of muscarinic cholinergic receptor binding sites has been demonstrated in substantia gelatinosa and Lamina III and V of dorsal grey matter of spinal cord.[10,11] The concentration of Ach in CSF increases with painful stimulus and remains at a plateau for 4–6 h.[12] The concentration of neostigmine in CSF even after the lowest dose was adequate to significantly inhibit cholinesterase in CSF.[13,14] Pain itself activates a pain inhibitory system at the level of spinal cord. This effect is due to spinal-supraspinal spinal loop and descending inhibitory system.[11]

Clonidine is an imidazoline derivative with selective partial α2-adrenergic receptor agonistic activity which has analgesic effect at spinal level mediated by postsynaptically situated α2-adrenoceptors in the dorsal horn of spinal cord in substantia gelatinosa. Cholinergic interaction in spinal α2-adrenergic receptors which are located on descending noradrenergic pathways produces noradrenaline release that causes analgesia directly, and also it releases Ach to produce analgesia clonidine also blocks A and C-fibers at Lamina V, thereby producing analgesia.[15-17]

Clonidine was used in different doses from 15 μg to 450 μg, and many previous studies concluded that minimum 30 μg dose of clonidine provide a significant increase in the duration of sensory block, motor block, and spinal analgesia without increasing the incidence of side effects.[15,18] On the other hand, neostigmine was used in different dose ranges from 5 μg to 750 mg by intrathecally but a low dose of 5 μg sufficient to cause early onset of sensory and motor block.[19] With higher doses (>150 μg)[6,20] it has more pronounced side effect such as nausea and vomiting due to rostral spread, but in our study, we used only 5 μg to alleviate these side effects.

In our study, we noticed that neostigmine cause early onset for sensory and motor blockade then clonidine, also mean time taken for maximum motor blockade was significantly faster in neostigmine group than clonidine. Similar results were obtained in a study by Klamt *et al*.[15] Due to the potential direct inhibition of motor activity by administration of neostigmine; it was speculated that increased spinal levels of Ach may augment motor block as a result of axonal conduction block from spinal bupivacaine.

We also noted that duration of analgesia was prolonged with the addition of clonidine compared to neostigmine because it produces local vasoconstriction by acting on vascular smooth muscle (receptors), which decreases absorption of LAs from subarachnoid space.[21-23]

Sedation and hypotension are the central effects of α2-adrenergic receptors may occur after clonidine administered by any route. Higher doses of (50-450 mcg) clonidine have been associated with hypotension, bradycardia, and higher degree of sedation.[18,24,25] In our study, as we use clonidine 30 mcg is usually not associated with such effects.

The incidence of hypotension and bradycardia was less with neostigmine as compared to clonidine suggested the more hemodynamic stable property of neostigmine as reported by Carp *et al*. and Pan.[26,27]

CONCLUSION

From our study, it was concluded that both intrathecal neostigmine and clonidine can provide longer post-operative analgesia, but neostigmine causes better hemodynamic stability with less side effects.

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