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Original Article

"Comparative Evaluation of Intrathecal Neostigmine with Intrathecal Fentanyl for Post-operative Pain Relief"

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Abstract

Background: Anticholinesterases increase the concentration of acetylcholine at the postsynaptic sites which cause prolonged analgesia.

Aims Objectives: To evaluate and compare the effects of intrathecal neostigmine and intrathecal fentanyl on post-operative pain relief.

Materials and Methods: After informed consent, 60 female patients of age between 40 and 60 years, belonging to ASA Grades 1 and 2, posted for TAH under spinal anesthesia were included in the study and randomly divided into 2 groups of 30 each. Patients of Group 1 received intrathecal injection of bupivacaine 0.5% 15 mg (3 ml) with 5 µg neostigmine, and Group 2 received intrathecal injection of bupivacaine 0.5% 15 mg (3 ml) with 25 µg fentanyl.

Results: The mean duration of analgesia in Groups 1 and 2 was 594.67±95.18 min and 309.67±44.91 min, respectively. It was observed that duration of analgesia in Group 1 was longer and statistical significant in comparison to Group 2.

Conclusion: Intrathecal neostigmine provides prolonged post-operative analgesia than intrathecal fantanyl with less side effect and better hemodynamic stability.

Key words: Bupivacaine, Fentanyl, Neostigmine, Total abdominal hysterectomy

INTRODUCTION

A lot of survey over a long time show that many patients still suffer from moderate to severe post-operative pain.[1] There are various methods used for post-operative pain relief, i.e., infiltration of wound with local anesthetics, central neural blockade with adjuvants, and intravenous opioids.[2]

Today regional analgesic technique play an important role in post-operative control of pain, either intrathecally or epidurally, local anesthetic with opioids (morphine, fentanyl, sufentanil, etc.), neostigmine, clonidine, dexmedetomidine, and midazolam, etc. However, use of these adjuvants is not free from their side effects such as respiratory depression, pruritus, urinary retention, sedation, nausea, and vomiting.

Intrathecally neostigmine inhibits the activity of both true and pseudocholinesterases and thereby enhancing acetylcholine at various cholinergic sites which have been shown to cause analgesia.[3] This synaptically released acetylcholine act on muscarinic and nicotinic site on dorsal horn of spinal cord. In post-operative period, descending noradrenergic or cholinergic antinociceptive spinal system is activated by ongoing pain causing an increase in release of acetylcholine, which in the presence of neostigmine results in augmented analgesia.

Opioids analgesics are the cornerstone for the treatment of post-operative pain; these agents generally exert their

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analgesic effects through micro receptors in the central nervous system (CNS).[2] Receptor activation leads to G protein-mediated potassium channel opening (μ and Δ) and calcium channel closure (kappa), with an overall reduction in intracellular calcium. This reduces the release of excitatory transmitter (glutamate and substance P) from presynaptic C fibers but not from A fiber terminals with consequent reduction in nociceptive transmission.[4]

Aim and Objective

1. To study and compare the effect of intrathecal neostigmine and intrathecal fentanyl on post-operative analgesia
2. To study and compare the side effect.

MATERIALS AND METHODS

This is a randomized, prospective study was carried out in the Department of Anaesthesia Shyam Shah Medical College, Rewa, Madhya Pradesh. After informed consent from each of the patient, 60 female patients of ASA Grades I and II, between age groups 40-60 years, weight 45-60 kg and posted for total abdominal hysterectomy under spinal anesthesia were included in the study and randomly divided into 2 groups of 30 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 fentanyl 25 μg (1 ml) intrathecal.

Patients having systemic cardiovascular, respiratory, hepatic, renal or CNS disorders, hemorrhagic disorders, deformities of the spinal cord or vertebral column, and any other contraindication for spinal anesthesia have been excluded from this study.

Preanesthetic examination was done a day before surgery. All the patients were kept nil by mouth for at least 6 h. All patients were preloaded with 15 ml/kg ringer lactate's solution. Baselines HR, systolic blood pressure, diastolic blood pressure, and SPO_2 were recorded.

Under all aseptic precautions, lumber puncture was performed through midline approach in sitting position between L2-L4 intervertebral spaces using 25 G Quincke's spinal needle. After the free flow of cerebrospinal fluid, injection bupivacaine with neostigmine injected in Group 1 and bupivacaine with fentanyl in Group 2.

Level of sensory blockade was assessed using a 23 G hypodermic needle. Duration of effective analgesia was measured as time from intrathecal drug administration to the patient's first complain of pain.

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

Following that subarachnoid block heart rate, systolic blood pressure, diastolic blood pressure, and SPO_2 were recorded at different time intervals. Side effects, i.e., hypotension, nausea, vomiting, desaturation or hypoxemia (SPO_2 <90%), and any others were also recorded. Bradycardia (heart rate <60/min) treated with injection atropine 0.6 mg intravenous (IV); hypotension (fall of systolic blood pressure >20% OR systolic blood pressure <90 mm hg) was treated with IV fluids and/or injection mephentermine 3 mg IV; respiratory depression (respiratory rate <10 or SPO_2 <90%) was recorded and treated by oxygen by face mask.

Pain was assessed by visual analog scale score from "0" as no pain to "100" as worst possible pain at 2, 4, and 24 h after operation.

The data were tabulated and analyzed by student's *t*-test and Chi-square test. $P < 0.05$ was taken as statistically significant. All were analyzed using SPSS software 11.5.

RESULTS

All groups were demographically similar ($P > 0.05$) in regards to age, weight, heights, and duration of surgery, and it can be presumed that the group was comparable for the purpose of the study (Table 2).

All patients in each group have achieved sensory block up to T6 dermatome and complete motor block (Bromage scale Grade 3) (Table 3).

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

Criteria	Group 1	Group 2
Age in years (mean±SD)	45.20±7.71	43.03±7.87
Weight in kg (mean±SD)	55.67±4.21	55.17±6.22
Height in cm (mean±SD)	153.93±4.03	153.77±3.40
Duration of surgery in minutes	106.33±12.994	107.87±10.954

SD: Standard deviation

The mean onset of sensory block in Groups 1 and 2 was 246.57±95.56 s and 263.97±50.92 s, respectively. This onset of sensory block was comparable in Groups 1 and 2 (Table 3).

The mean onset of motor block in Groups 1 and 2 was 533.90±112.10 s and 553.83±47.12 s, respectively. It was comparable in both the groups (Table 3).

The mean duration of analgesia in Groups 1 and 2 was 594.67±95.18 min and 309.67±44.91 min, respectively. It was observed that duration of analgesia in Group 1 was longer and statistical significant in comparison to Group 2 (Table 3).

The mean of heart rate and systolic and diastolic blood pressure was comparable in both groups and was found to be insignificant.

The most common side effects found in our study were hypotension, bradycardia, nausea, vomiting, shivering, pruritus, and respiratory depression. Mild hypotension was found in 2 patients of Group 1 and 7 patients of Group 2 it was easily corrected with crystalloid infusion and 6 mg IV mephentermine. Bradycardia observed in 1 patient in Group 1 and 4 patients in Group 2 and corrected with IV atropine 0.6 mg. Complained of nausea was in 3 patients of Group 1 and 1 patient of Group 2. Vomiting was in 2 patient of Group 1 and not in any patients of Group 2. Other side effects were minimal, i.e., pruritus and shivering (Table 4).

DISCUSSION

Total abdominal hysterectomies associated with moderate to severe pain, thus it may delay recovery and return to daily living.[5] It can cause unstatisfaction of patients with their anesthesia and surgical experiences.[6]

Table 3: Comparison of sensory and motor block

Parameter	Group 1	Group 2
Onset of sensory block in seconds	246.57±95.560	263.97±50.902
Onset of motor block in seconds	533.90±112.106	553.83±47.121
Duration of analgesia in minutes	594.67±95.185	309.67±44.912
Time of rescue analgesia in hrs	9.33±2.477	5.87±1.408

Table 4: Side effects

Complication	Group 1	Group 2
Hypotension	2	7
Bradycardia	1	4
Nausea	3	1
Vomiting	2	0
Shivering	0	2
Pruritus	0	2
Respiratory depression	0	0

Intrathecal neostigmine provides post-operative analgesia; it was first described by Naguib and Yaksh.[7] Neostigmine has several advantages such as easily available, cost-effective, reliable, and durable post-operative analgesia and also no untoward side effects such as respiratory depression, pruritus, and drowsiness as expressed with intrathecal opioids.[8,9] Although it was used in different dose ranges from 5 μg to 750 mg by intrathecally. With higher doses (>150 μg),[10,11] it has more pronounced side effects such as nausea and vomiting, but in our study, we used only 5 μg to alleviate these side effects.

In our study, intrathecal neostigmine cause prolonged duration of analgesia up to 12 h then intrathecal fentanyl, this support the finding of Lauretti *et al.* and Garg *et al.*[12,13]

In our study, intrathecal neostigmine increases the time of firstr esque analgesia, reported by Lauretti *et al.*[14] and Pan and Mok in their study.[15] It decreases the requirement of other analgesics and provides longer post-operative analgesia as compared to intrathecal fentanyl (Sergio D Belzarna), and this correlates with the finding of Lauretti *et al.*, Seldasen *et al.*, Fareed Ahmed *et al.*, and Mohammed Algohary.

The rostral spread of neostigmine to the brainstem has contributed to the severity of the side effects such as nausea and vomiting as shown by Hood *et al.*[10] It was the common side effect of neostigmine, which limits its use but with lower dose and premedication with antiemetics, it can be easily controlled.

Incidence of hypotension and bradycardia was less with neostigmine then fentanyl suggested the more hemodynamic stable property of neostigmine as reported by Carp *et al.* and Pan and Mok.[5,16]

Shivering, pruritus, and respiratory depression mostly occurred with intrathecal fentanyl were not reported with neostigmine also possessing it more superiority than fentanyl.

It has been proved that intrathecal neostigmine with very low dose can be used to provide post-operative analgesia without distressing adverse effects such as severe nausea, vomiting, and evacuation of bowel and bladder.[10]

CONCLUSION

From this study, it was concluded that intrathecal neostigmine provides longer post-operative analgesia

than intrathecal fentanyl, with less side effect and better hemodynamic stability.

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