

EFFECT OF TRANSDERMAL NITROGLYCERINE WITH BUPIVACAINE PLUS NEOSTIGMINE SPINAL ON THE DURATION OF ANALGESIA- A CASE CONTROL STUDY

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ABSTRACT

BACKGROUND

Neostigmine with bupivacaine is widely used for improving postoperative analgesia. However, to reduce the adverse effects and to prolong post-operative intrathecal analgesia other adjuvants have been used along with neostigmine.

MATERIALS AND METHODS

Patients aged between 30 to 50 years scheduled for surgery below the umbilicus, were systematically randomized into 2 groups. Both the groups received bupivacaine with neostigmine, only group 2 received transdermal nitroglycerine patch. Both the group were assessed for vitals & duration of analgesia.

RESULTS

The mean age was 34.5 ± 9.51 years in group I and 36.1 ± 10.4 years in group II. There was no statistically significant difference in the vitals. Duration of analgesia was longest in group II and the difference between two groups was statistically significant.

CONCLUSION

Addition of transdermal nitroglycerine patch to bupivacaine + neostigmine spinal anaesthesia produced significant increase in duration of analgesia.

KEYWORDS

Nitroglycerine, Transdermal Analgesia.

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BACKGROUND

Surgical pain or "post-operative pain" is a universal phenomenon experienced by millions of patients, who undergoes surgical operation due to the severe tissue damage following the surgery.¹ A pain free postoperative period aids in early mobilization and thereby reduces mortality and morbidity of any surgical operation.²

The importance of peripheral and central modulation in nociception has fostered the concept of "preemptive analgesia" in patients undergoing surgery. This type of management pharmacologically induces an effective analgesic state prior to the surgical trauma. This may involve infiltration of the wound with local anaesthetic, central neural blockade, or the administration of effective doses of opioids, NSAIDS or ketamine. Experimental evidence suggests that preemptive analgesia can effectively attenuate peripheral and central sensitization to pain. Although some studies have failed to demonstrate preemptive analgesia in humans, other studies have reported significant reduction in postoperative analgesic requirements in patients receiving

preemptive analgesia. Multimodal therapy is defined as two or more analgesic agents or techniques used in combination. The American Society of Anesthesiologists (ASA) "Practice Guidelines for Acute Pain Management in the Perioperative setting" contains the following statement: During the administration of anaesthetics for surgery, the needs of many patients may be best met by taking advantage of the combined effects of several agents. Similarly, there is growing conviction that a multimodality approach to providing perioperative analgesia has advantages over the use of a single modality. The literature supports the efficacy of two or more analgesic techniques (including non-pharmacologic methods) used in combination for the control of perioperative pain, especially when different sites and/or mechanisms of action are involved and/or when synergy of effect is achieved. The literature also indicates that multimodality approaches are associated with side effects, no greater than those resulting from single analgesic techniques for perioperative pain management.

Various drugs have been tried in the subarachnoid space along with local anesthetics with the aim of improving the duration of post-operative analgesia. The cholinesterase inhibitor, neostigmine is one such adjuvant which is widely used. However, it was associated with many unwanted side effects, hence to reduce the adverse effects and to prolong post-operative analgesia, other adjuvants have been used along with neostigmine.

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The aim of this study was to systematically review current evidence of analgesic enhancement of intrathecal neostigmine by the addition of transdermal nitroglycerine patch on bupivacaine spinal anaesthesia.

MATERIALS AND METHODS

After approval from Ethical Committee, the study was conducted at Medical College Kottayam over a period of one year. This prospective study was conducted on 60 adult patients of ASA physical status I and II, aged 30 to 50 years scheduled for surgery below the umbilicus.

Exclusion Criteria

- Patient refusal.
- Patients having cardio-pulmonary illness.
- Patients having metabolic disorders.
- Patients with nervous system disorders.
- History of hypersensitivity reaction to any of the study medications.
- Patients having gastrointestinal disorders.
- Patients with sinus bradycardia.
- Bleeding disorder.
- Infection at the site of lumbar puncture.
- Patients on opioids or chronic analgesic abuse.

Patients were systematically randomized into 2 groups, consisting 30 patients in each group. Group I patients received intrathecal injection of 15 mg bupivacaine with 5 mcg of neostigmine and transdermal placebo patch (control group). Group II patients received intrathecal injection of 15 mg bupivacaine with 5mcg of neostigmine and transdermal nitroglycerine patch (5 mg/24 hours), applied on a non-anaesthetized area after 20 minutes (case group). Pre-anaesthetic checkup was done, all patients were familiarized with 0-10 cm visual analogue scale, for pain (VAS P) and nausea (VAS N). All patients received tab alprazolam 0.25 mg and tab ranitidine 150 mg orally on the previous night of surgery. Patients were pre-medicated with midazolam 0.05 mg/kg intravenously and hydration with ringer's lactate solution 10 ml/kg preoperatively in the holding room. Lumbar puncture was performed at L3-L4 level, with 26 gauge spinal needle and the drug solution was injected intrathecally over 30 seconds as per the group allocation. Heart rate and SpO2 were monitored continuously. Any fall in the heart rate below 60 beats per minute was treated with incremental doses of intravascular (IV) atropine 0.3 mg injection. Intraoperative nausea was treated by IV ondansetron 4 mg injection. Vitals were monitored throughout the surgery.

Data thus obtained were analyzed using Microsoft Excel 2003, Chi square test (Fisher Exact Probability Test) and student t test for comparison between groups. A 'p' value of <0.05 was considered significant.

RESULTS

In the present study, we included two groups with 30 study subjects in each group. The mean age was 34.5 ± 9.51 years in group I and 36.1 ± 10.4 years in group II.

N=30	Group I (Mean ± SD)	Group II (Mean ± SD)	p-value
Age (in years)	34.5 ± 9.51	36.1 ± 10.4	0.665
Height (cms)	165.4 ± 7.829	167.2 ± 7.496	0.775
Weight (Kg)	65.13 ± 9.153	68.0 ± 7.414	0.390

Table 1. Distribution of Age, Height and Weight Among the Two Groups

There is no statistically significant difference in distribution of age, height and weight in two groups.

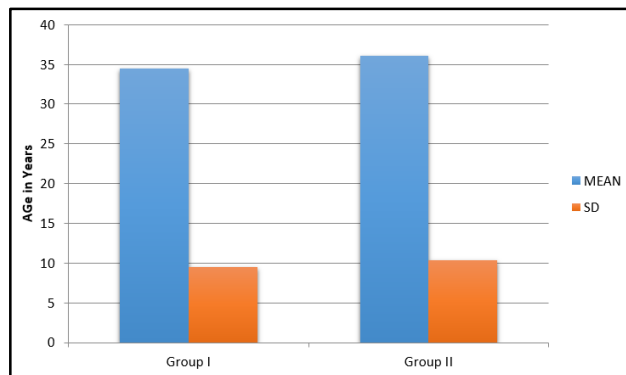


Figure 1. Distribution of Age Among Both the Groups

Heart Rate	Group I	Group II	P-value
Pre-operative	76 ± 8.26	76.43 ± 8.68	0.837
Intra-operative	70.93 ± 7.75	72.46 ± 7.51	0.577
Post-operative	75.03 ± 8.59	75.3 ± 7.68	0.994

Table 2. Comparison of Heart Rate among the Two Groups

There was no statistically significant difference in heart rate among the two groups.

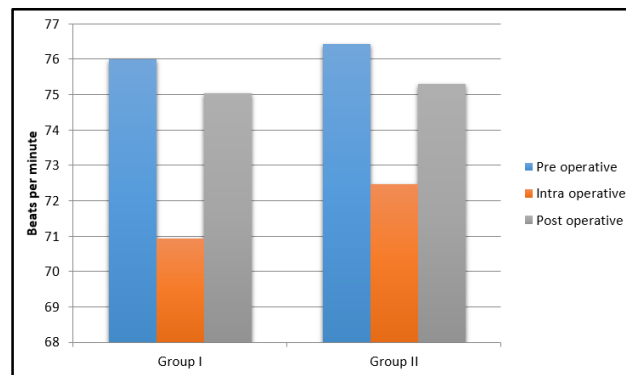


Figure 2. Comparison of Pulse Rate

Mean Arterial Pressure	Group I	Group II	P-value
Pre-operative	86.76 ± 6.53	87.5 ± 5.9	0.975
Intra-operative	81.53 ± 4.81	83.73 ± 4.55	0.072
Post-operative	84.06 ± 4.41	85.93 ± 4.58	0.136

Table 3. Comparison of Mean Arterial Pressure

There was no statistically significant difference in mean arterial pressure in two groups.

	Group I	Group II	p-value
Mean \pm SD	2.36 \pm 0.41	7.14 \pm 1.81	0.0726

Table 4. Comparison of Duration of Analgesia (Hours)

Duration of analgesia was longest in group II and this difference was statistically significant.

DISCUSSION

Surgical operation involves tissue damage followed by post-operative pain, which delays the recovery and thereby increases the morbidity and mortality. An acceptable anaesthetic technique must have characteristics such as rapid onset and reversal of effects. It must maintain stable hemodynamic during operation without need to increase blood transfusion. Lastly, an excellent anaesthetic must decrease recovery room stay, while reducing postoperative pain, nausea, vomiting, and requirement for additional analgesics.

The aim of this study was to systematically review current evidence of analgesic enhancement of intrathecal neostigmine by the addition of transdermal nitroglycerine patch on bupivacaine spinal anaesthesia.

It has been proved that intrathecal neostigmine alone can be used to provide analgesia, but at higher doses which produces distressing adverse effects like severe nausea, vomiting and evacuation of bowel and bladder. This has precluded the use of neostigmine as a sole analgesic agent. When used in very low doses along with local anaesthetics like lignocaine or bupivacaine, it did not prolong postoperative analgesia.

In our study the duration of analgesia was analysed as period between complete onset of sensory blockade to the time at which patient started complaining of pain or first rescue analgesic was given using VAS score. On statistical analysis, patient belonging to group I complained of pain earlier than group II. There was statistically significant delay in the onset of pain in group II. Our study showed a mean duration of 7.142 (SD \pm 1.81) hours in patients belonging to group II. We came to conclusion that addition of a transdermal nitroglycerine patch (5 mg/24 hr) provides a good duration of postoperative analgesia and this correlates with the findings of Lauretti et al³ and Gurvinder Kaur et al⁴

Lauretti et al. in 2000 conducted a study to determine whether association of transdermal nitroglycerine, would enhance analgesia from a low dose of intrathecal neostigmine in patients undergoing gynaecologic surgery during spinal anaesthesia. They concluded that neither intrathecal 5 μ g neostigmine alone nor transdermal nitroglycerine alone (5 mg/day) delayed the time to administration of first rescue analgesics, the combination of both provided an average of 14 hour of effective postoperative analgesia after vaginoplasty, suggesting that transdermal nitroglycerin and the central cholinergic agent neostigmine may enhance each other's antinociceptive effects at the dose studied.³

Gurvinder Kaur et al in 2007 conducted a study to assess the effect of transdermal nitroglycerin patch (5 mg/24 hours) on the analgesia of intrathecal neostigmine (5 μ g)

and incidence of untoward effects. They found a statistically significant longer duration of analgesia in patients who received both intrathecal neostigmine and transdermal nitroglycerine than in patients who received neostigmine alone.⁴

The present study did not show any significant changes on cardiovascular parameters. The mean heart rate and mean arterial pressures were comparable in both the groups in the intra and post-operative periods and was found to be statistically insignificant.

However, in a study conducted by Hood et al it was noted that intrathecal neostigmine of 50 μ g did not affect any measured cardiovascular variable. Intrathecal neostigmine in doses of 750 μ g was associated with increased blood pressure and heart rate probably due to excitatory action on preganglionic sympathetic neurons.⁵ Krukowski et al (1997) found that intrathecal neostigmine did not have any significant effect on mean arterial pressures.⁶

Lauretti et al (1998) in a multicenter study of intrathecal neostigmine for analgesia on 92 patients undergoing vaginal hysterectomy under spinal anaesthesia with doses of 25 μ g, 50 μ g and 75 μ g found that heart rate and BP did not differ in groups who received bupivacaine alone and along with neostigmine.⁷

Lauretti et al. in 2000 conducted a study to determine whether association of transdermal nitroglycerine would enhance analgesia from a low dose of intrathecal neostigmine in patients undergoing gynaecologic surgery during spinal anaesthesia. Their study shown that there were no significant changes on cardiovascular parameters, while using nitroglycerine transdermal patch along with intrathecal neostigmine.³

CONCLUSION

Duration of analgesia was longest in bupivacaine + neostigmine + transdermal nitroglycerine group. Addition of transdermal nitroglycerine patch to bupivacaine + neostigmine spinal anaesthesia produced significant increase in duration of analgesia.

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