Original Research Article

A study to evaluate the efficacy of transdermal nitroglycerine patch in enhancing analgesia of intrathecal neostigmine following inguinal hernioplasty under bupivacaine subarachnoid block

Arpit Agrawal[1*], Ankit Agarwal[2], Anuruddha Singh[3]

[1]Senior Resident, M.G.M. Medical College and M.Y. Hospital, Indore, Madhya Pradesh, India
[2]Senior Resident, M.G.M. Medical College and M.Y. Hospital, Indore, Madhya Pradesh, India
[3]Assistant Professor, Sri Aurobindo Medical College, Indore, Madhya Pradesh, India

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Abstract

Objectives: We aimed to evaluate and compare the safety and efficacy of combining intrathecal neostigmine with transdermal nitroglycerine patch for pain relief in patients undergoing inguinal hernioplasty under bupivacaine subarachnoid block. And to evaluate the adverse effects of intrathecal neostigmine with transdermal nitroglycerine patch. **Methodology**: After taking informed consent, 60 patients of ASA Grade I and II were systematically randomized into two groups of 30 each. Patients were infused with Ringer's lactate solution 10ml/kg preoperatively. Group N patients received Intrathecal injection of 15 mg of 0.5% hyperbaric bupivacaine with 10 mcg of neostigmine and transdermal nitroglycerine patch (5 mg/24 hours). Group P patients received Intrathecal injection of 15 mg 0.5% hyperbaric bupivacaine with 10 mcg of neostigmine and transdermal placebo patch. Subarachnoid Block was performed at L3-L4 level, with 25 gauge spinal needle and 3.5 ml of the drug solution was injected intrathecally per the group allocation. Sensory block was assessed by using pin prick method and motor block was checked by using modified Bromage scale. Pulse rate, blood pressure and SpO2 were monitored. Intra-operative complications were noted. Sample size was calculated to be 60 with a total of two groups with a power of 90 % and a alpha of 0.05. Test for analysis among two groups was done by Unpaired t test. A p value less than 0.05 was taken statistically significant. **Results:** The characteristics of study were comparable among two groups. The mean duration of analgesia in Group N was significantly longer ($p < 0.001$) than in Group P (367.4 ± 16.7 vs. 218.7 ± 16.8 min respectively). Group P had higher VAS scores and the number of rescue analgesic requirement was significantly more in Group P as compared to Group N. Hemodynamic changes remained insignificant in both groups. Incidences of side effects were not significant in both the groups. **Conclusion:** We conclude that the nitroglycerin transdermal patch used as an adjuvant to intrathecal neostigmine and bupivacaine prolongs postoperative analgesia.

Keywords: Inguinal hernioplasty, neostigmine, nitroglycerine, nitric oxide, postoperative analgesia

Introduction

"poena" is a Latin word which means pain**,** penalty or punishment. The paramount goal of medical science is relief of pain. There is severe tissue damage in surgery and post-operative pain is a universal phenomenon experienced by millions of patients throughout the world. subarachnoid block is one of the most adaptable regional anesthesia techniques available today as it is very economical and easy to administer with the advantage of providing surgical anesthesia[1]. Hyperbaric bupivacaine 0.5% is the most commonly used drug for spinal anesthesia[2]. Prolongation of pain relief by various adjuvants, for example opioids (morphine, fentanyl), ketamine, clonidine, and neostigmine, have been investigated by various investigators. Intrathecal administration of neostigmine, an acetyl cholinesterase inhibitor, inhibits breakdown of the endogenous neurotransmitter acetylcholine, thereby inducing analgesia, hence it is an alternative non-opioid additive to local anaesthetics[3]. Several researches stated that nitroglycerin (NTG) patch application in addition to neuroaxial S (+)-ketamine, neostigmine, or sufentanil, enhances postoperative analgesia and reduces the need for other analgesic medication[4,5,6]. This study was undertaken to evaluate efficacy of transdermal nitroglycerin patch with regard to its analgesic enhancing effects, when used as an adjuvant to intrathecal neostigmine and bupivacaine.

*Correspondence
Dr. Arpit Agrawal
Senior Resident, M.G.M. Medical College and M.Y. Hospital, Indore, Madhya Pradesh, India
E-mail: arpitagrawal878@gmail.com

Methodology

The study was conducted at MGM Medical College, Indore. After taking ethical committee approval and written inform consent 60 adult patients between 18–60 years of age belonging to American Society of Anesthesiologists (ASA) physical status I or II, of either sex, who were admitted for elective Inguinal Hernioplasty surgeries, were recruited for the study. Patients with previous subarachnoid surgeries, spine deformities, hemorrhagic disorders and cardio respiratory co-morbidities were excluded from our study. All the patients received tablet etizolam 0.5 mg orally on the night before surgery. All patients were familiarized with 0–10 verbal analogue scale (VAS) for pain and instructed to inform whenever they felt pain at the operated site in the postoperative ward. The patients were randomly allocated into two groups of 30 each via computer generated random tables. Group N received intrathecal injection of 15 mg (3 ml) of 0.5% hyperbaric bupivacaine, 10 µg of neostigmine diluted to 0.5 ml with distilled water to make a total volume of 3.5 ml + transdermal nitroglycerin (tNTG) patch (5 mg/24 h).. Group P received intrathecal injection of 15 mg (3 ml) of 0.5% hyperbaric bupivacaine, 10 µg of neostigmine diluted to 0.5 ml with distilled water and Transdermal placebo patch. Each group received a total intrathecal drug volume of 3.5 ml. In the preanesthesia room, patients were premedicated with IV midazolam 0.05 mg/kg and preloaded with ringer lactate 10 ml/kg. In the operation theatre, In sitting position lumbar puncture was performed

at L3-L4 level, with 25 gauge spinal needle and 3.5 ml of the drug solution was injected intrathecally over 30-35 sec as per the group allocation. Sensory block was checked using pin prick method and motor block was assessed by modified Bromage scale, 0: No motor block, 1: Inability to raise extended leg but able to move knees and feet, 2: Inability to raise extended leg and move knee but able to move feet, 3: Complete block of motor limb. Oxygen was administered by Hudson face mask at the rate of 4-6 L/min. The transdermal patch (placebo or nitroglycerin) was applied on the thorax (ventral, T2-T4), in a nonanesthetized area, 20 min after spinal puncture. Total nitroglycerin content of transdermal nitroglycerin patch was 25 mg; total drug releasing area was 10 cm2. It delivered nitroglycerin at the rate of 20-25 µg/ cm2/h or 5 mg/24 h. Pulse rate, blood pressure and SpO2 were monitored till the end of surgery. Intra-operative complications like hypotension, bradycardia, nausea, vomiting, shivering were noted and treated as required. Hypotension greater than 15% below the baseline value was treated by the incremental dose of mephenteramine 6 mg IV. Any fall in the heart rate < 60 beats per minute was treated with incremental doses of IV atropine 0.3 mg. Intraoperative nausea was treated with ondansetron 4 mg IV, Shivering was treated with 100% oxygen, warm fluids and adequate covering. No other sedation / analgesic drug was given to the patients. Time from intrathecal injection to administration of first rescue analgesic was taken as total duration of analgesia. Pain was assessed with the help of VAS score at 15 min, 30 min and the at hourly intervals upto 12 hours. The last reading was taken at 24 h post spinal. Any patient with VAS score of four and more qualified for rescue analgesic (IV tramadol 2 mg/kg) and study was stopped.

Statistical analysis

Considering a 10 % increase in the duration of analgesia and a similar percentage of hemodynamic variations due to tNTG as an adjuvant to intrathecal neostigmine was compared with the previous studies (Ahmed et al.) calculated the sample size to be 60 with a total of two groups with alpha (type I error) = 0.05 and a beta(power of study)= 90%. Test for analysis among two groups was done by unpaired t test. A p value < 0.05 was considered as stastistically significant.

Table 1: Demographic profile in the groups

Demographic variables	N Group	P Group	p-values
Age (years)	40.4	42.36	0.247
Weight (kg)	58.7	59.3	0.893
Height (cm)	161.3	162.1	0.724
ASAI/II	20/10	20/10	1.0
Mean duration of surgery(min)	88	85	0.329

Table 2: Intraoperative Parameters

Intraoperative Parameters	N Group	P Group	p- value
Sensory Onset in min at T10 level	2.3±0.5	2.3±0.6	0.830
Motor onset in min (Bromage scale)	6.3 ± 1	5.8± 0.6 min	0.067

Table -3: **Comparison of hemodynamic parameters among the two groups (mean)**

Group	Pre op		Intra op		Post op	
	PR	MAP	PR	MAP	PR	MAP
N	85.3±8.4	92.5±6.9	75.6±6.9	83.1±7.3	78.3±5.1	90.2±4.9
P	87.2±9.2	93.1±8.3	77.3±5.7	85±8.1	79.3±6.2	86.4±5.7

MAP = Mean arterial pressure in mmHg, PR = Pulse rate

Table 4: Postoperative block characteristics between groups

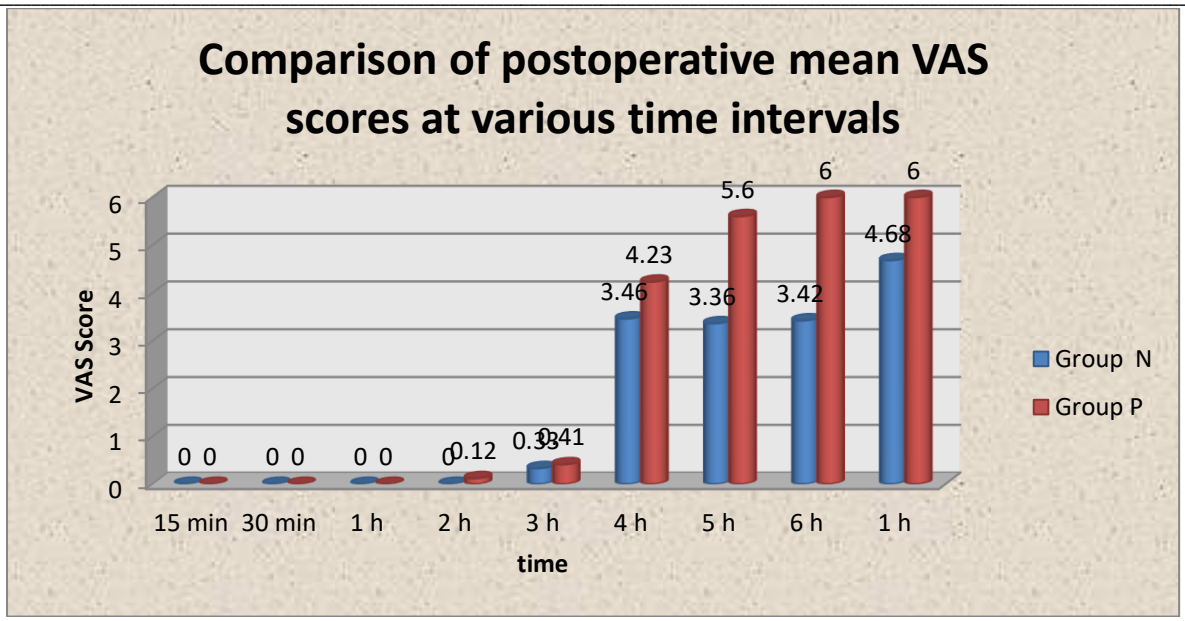
Postoperative parameters	Group N	Group P	p- values
Time for 2 segment regression (min)	77.5±2.4	76.0±2.9	0.082
Duration of motor blockade (min)	172.9±5.9	171.1±6.0	0.863
Duration of analgesia (min)	367.4 ± 16.7	218.7 ± 16.8 min	**<0.001**
Number of analgesics required in 24 h	1.83 ± 0.7	2.18 ± 0.9	0.038

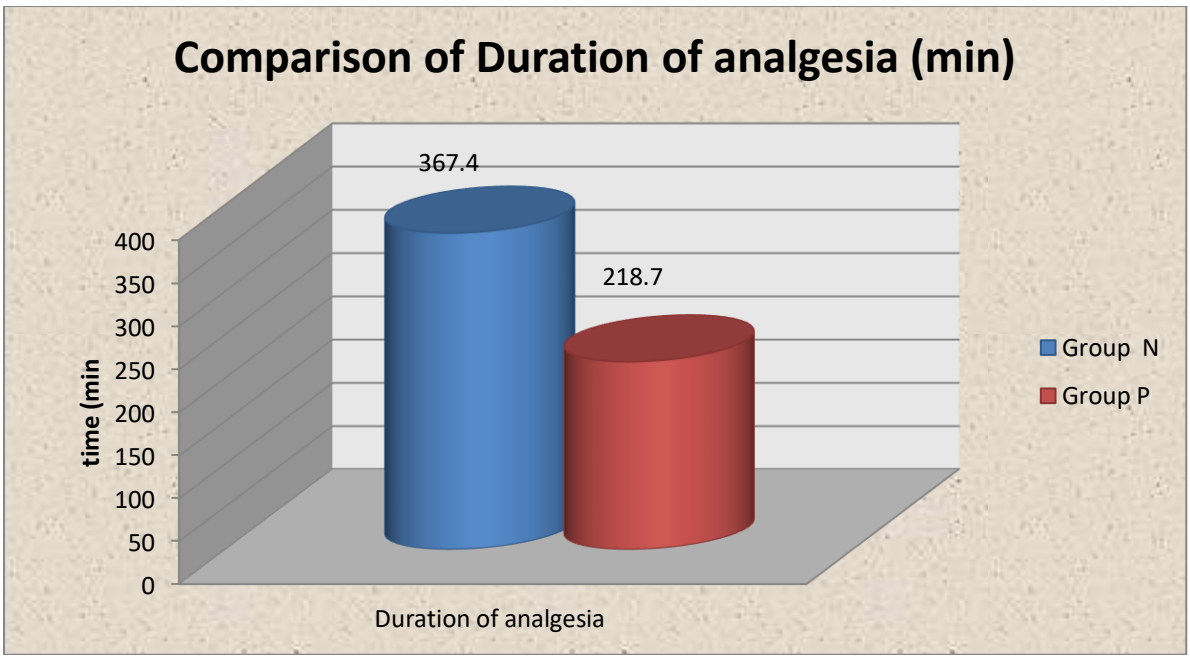
Table 5: Comparison of postoperative mean VAS scores at various time intervals

Post op time intervals	Group N	Group P	p-values
15 min	0	0	1.000
30 min	0	0	1.000
1 h	0	0	1.000
2 h	0	0.12±0.31	0.893
3 h	0.33± 0.4	0.41± 0.5	0.763
4 h	3.46 ± 0.56	4.23± 0.69	0.080
5 h	3.36± 0.53	5.6± 0.72	**<0.001**
6 h	3.42± 0.42	6.0±0.00	**<0.001**
8 h	4.68±0.35	6.00±0.00	-
24 h	-	-	-

Table 6: Comparison of the side effects of two groups

Side effects	Group N	Group P
Hypotesion	3 (5%)	4(6.7%)
Nausea and vomiting	2(3.3%)	3(5%)
Shivering	3(5%)	4(6.7%)





Results

There was no significant difference among the two study groups in respect of age, height, weight, ASA and duration of surgery (Table 1).

The onset of sensory block was 2.3 ± 0.5 and 2.3 ± 0.6 min in Group N and P respectively and there was no significant difference in two groups with regards to time to achieve grade 3 motor block 6.3 ± 1 and 6.1± 0.6 min in Group N and P respectively (Table 2).

Table 3 shows the comparative hemodynamic parameters i.e. mean arterial blood pressure (MAP) and pulse rate (PR) in two groups during the perioperative period. The differences in duration of two segment regression of sensory block and total duration of motor blockade in the groups were statistically insignificant (p>0.05). Duration of analgesia was significantly longer in Group N in comparison to Group P (367.4 ± 16.7 vs. 218.7 ± 16.8 min) which was clinically and statistically highly significant (p < 0.001). The mean consumption of rescue analgesic per patient was 2.18 ± 0.9 (P) and 1.83 ± 0.7 (N). This difference was statistically significant (p < 0.05) (Table 4).

VAS scores in Group P were persistently greater than that of Group N (Table 5), but the difference were statistically not significant, except at 5& 6 hours. Regarding complications, there was no significant difference among the groups in the frequency of nausea, vomiting and shivering, all these differences were clinically insignificant (Table 6).

Discussion

For early ambulation and recovery of the patient, postoperative pain management is essential. There are various methods of postoperative pain relief in patients. Intrathecal neostigmine causes dose dependent postoperative analgesia by inhibiting breakdown of acetylcholine in dorsal horn of spinal cord and spinal meninges. Acetylcholine causes pain suppression through direct action on spinal cholinergic

muscarinic receptors i.e. M1 and M3. Transdermal nitroglycerin patch has been associated to nitric oxide (NO) formation during degradation of organic nitrates and there is evidence that endogenous NO is necessary to inhibit nociceptive transmission. The enhancement of analgesic effect of transdermal nitroglycerin would be secondary to Nitric oxide action at primary afferent neuron and at the 2nd order neuron. Some researchers have identified that there is no prolongation of surgical anesthesia in patients receiving tNTG as an adjuvant to intrathecal neostigmine in different doses[7,8]. In our study also the prolongation of two segment regressions and duration of motor blockade was not statistically significant. As per Ahmed et al[2]. and Patel et al.[7], we used doses of 10µg of intrathecal neostigmine and transdermal nitroglycerin patch (5 mg/day). In past it was seen that a higher dose of neostigmine have been shown to produce many untoward side effects such as nausea, vomiting. Hence, as to reduce the dose of neostigmine and potentiate its analgesic property, other adjuvants such as opioids, clonidine and transdermal nitroglycerin (tNTG) patch have been added along with it[8]. In our study the duration of analgesia was significantly higher with tNTG group which goes along with other studies. Addition of 5 mg/day of tNTG to intrathecal neostigmine has increased the duration of analgesia[1,7,10,11]. To other studies showed there was no statistically significant difference in hemodynamic disturbances which is similar to our study[8,9]. The verbal analogue scale (VAS) is a simple and often used method for evaluating variations in pain intensity. Rescue analgesia was provided by IV tramadol 2mg/kg, when patient complains of pain or VAS 4 and above. In our results, we found that during initial 240 min, i.e. from baseline to 240 min, the difference was statistically insignificant ($p > 0.05$). Difference in VAS scores of two groups N and P becomes statistically significant at 250th to 360th min with p values < 0.05. VAS score was higher in neostigmine group requiring rescue analgesia at 220 min and maximum VAS scores at 240th-300th min, where as in nitroglycerin group VAS score started to increase only after 370th min and after that rescue analgesia given and study stop. Our results were similar to study conducted by Rameez et al,gurvinder et al and Shaikh SI et al[9,10,11]. which showed average VAS scores of combination (tNTG and neostigmine) group were significantly lower than neostigmine group.

From above discussion it can be clearly stated that transdermal nitroglycerin as an adjuvant to intrathecal neostigmine and bupivacaine prolongs duration of analgesia as compared to intrathecal neostigmine with bupivacaine alone.

Limitations

Transdermal NTG is a newer mode of analgesic use, and there are only few studies supporting its use for analgesia, more studies are needed to establish the safety and efficacy of this drug and further scope will be to design the study with different doses of neostigmine and nitroglycerin.

Conclusion

We conclude that transdermal nitroglycerin patch (5 mg/day) safely prolongs the duration of postoperative analgesia when it is used as an adjuvant to intrathecal low dose neostigmine 10 µg and bupivacaine 15 mg in patients undergoing inguinal hernioplasty surgeries.

Conflict of Interest: Nil Source of support: Nil

Conflict of interest

None

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