



Transdermal nitroglycerin as an adjuvant to intrathecal neostigmine and bupivacaine for prolongation of postoperative pain relief

Safiya I. Shaikh¹, Marutheesh Mallappa², Vikas Joshi³,
Roopa Sachidananda⁴

ABSTRACT

Objectives: Transdermal nitroglycerin patch is being used as an adjuvant to neostigmine for postoperative analgesia, besides its vasodilator effects on cardiovascular system. We aimed to evaluate the transdermal nitroglycerin for its capability to enhance analgesia when used as an adjuvant to intrathecal neostigmine and bupivacaine in elective lower abdominal surgeries.

Methodology: We enrolled 60 adult ASA-1 and 2 patients undergoing lower abdominal surgeries under spinal anesthesia. In this double blind randomized study, patients were assigned into two groups, Group NT received transdermal nitroglycerin patch (5 mg/24 h) and Group NE received placebo patch along with 5 µg of neostigmine and 15 mg of 0.5% hyperbaric bupivacaine. Spinal anesthesia 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 checked using pin prick method and motor block was assessed by 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 alpha of 0.05 and a power of 90 %. Test for analysis among two groups was done by ANOVA for quantitative and Chi-square test for qualitative data. A p < 0.05 was considered as significant.

Results: The characteristics of intraoperative block were comparable among two groups. The mean duration of analgesia in Group NT was significantly longer (p < 0.001) than in Group NE (476.9 ± 17.3 vs. 386.9 ± 17.2 min respectively). Group NE had higher VAS scores and the number of rescue analgesic requirement was significantly more in Group NE as compared to Group NT. Hemodynamic changes remained insignificant in both groups. Incidence of side effects were not significant in both the groups.

Conclusion: We conclude that the transdermal nitroglycerin used as an adjuvant to intrathecal neostigmine and bupivacaine prolongs postoperative analgesia.

Key words: Transdermal; Nitroglycerin; Neostigmine; Postop analgesia

Citation: Shaikh SI, Mallappa M, Joshi V, Sachidananda R. Transdermal nitroglycerin as an adjuvant to intrathecal neostigmine and bupivacaine for prolongation of postoperative pain relief. *Anaesth Pain & Intensive Care* 2018;22(4):463-467

¹Professor and HOD;

²Junior Resident;

³Senior Resident;

⁴Assistant Professor

Department of Anesthesiology,
Karnataka Institute of
Medical Sciences (KIMS),
Hubbali-580021, Karnataka,
(India)

Correspondence: Dr.
Marutheesh Mallappa,
Room No. 150, Viveka Hostel,
Vidyanagar, KIMS Campus,
Karnataka Institute of Medical
Sciences, Hubbali-580021,
Karnataka, (India)

Phone: 91-9743489482;
E-mail: marutheeshm90@gmail.
com.

Received: 28 Dec 2017

Reviewed: 25 May 2018

Corrected: 25 Jul 2018

Accepted: 7 Jan 2019

INTRODUCTION

Pain has been a major concern of humankind since medieval times and it has been the subject of

ubiquitous efforts to understand and to control it.

Spinal subarachnoid block is one of the most versatile regional anesthesia techniques available today as it is very economical and easy to administer with

transdermal nitroglycerin as spinal adjuvant

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.

Spinal 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 neuraxial 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 and potency of transdermal nitroglycerin patch with regard to its analgesic enhancing effects, when used as an adjuvant to intrathecal neostigmine and bupivacaine.

METHODOLOGY

The study was conducted at Karnataka Institute of Medical Sciences, Hubballi. After obtaining ethical committee approval, 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 lower abdominal surgeries were recruited for the study. Patients with previous spinal surgeries, spinal deformities, hemorrhagic disorders and cardio respiratory co-morbidities were excluded from the study.

All the patients received tablet diazepam 10 mg and tablet ranitidine 150 mg orally on the night before surgery. All of them 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 randomized into two groups of 30 each. Group NE received intrathecal injection of 15 mg (3 ml) of 0.5% hyperbaric bupivacaine, 5 µg of neostigmine diluted to 0.5 ml with 0.9% normal saline to make a total volume of 3.5 ml + transdermal placebo patch. Group NT received intrathecal injection of 15 mg (3 ml) of 0.5% hyperbaric bupivacaine, 5 µg of neostigmine diluted to 0.5 ml with 0.9% normal saline and transdermal nitroglycerin (tNTG) patch (5 mg/24 h). Each group received a total volume of 3.5 ml.

In the preanesthesia room, patients were premedicated with midazolam 0.05 mg/kg IV and preloaded with crystalloid 10 ml/kg. In the operation theatre, 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 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; able to move knees and feet, 2: Inability to raise extended leg and move knee; able to move feet, 3: Complete block of motor limb. Oxygen was administered by Hudson mask at the rate of 5 L/min. The transdermal patch (placebo or nitroglycerin) was applied on the thorax (ventral, T2-T4), in a non-anesthetized 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, respiratory depression, 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 below 60 beats per minute was treated with incremental doses of atropine 0.3 mg. Intra-operative nausea was treated with ondansetron 4 mg IV, Shivering was treated with 100% oxygen, warm fluids and adequate covering. No other sedation or analgesic drug was given to the patients. Time from subarachnoid injection to administration of first rescue analgesic was taken as total duration of analgesia.

Pain was assessed with the help of VAS at 15 min, 30 min and the at hourly intervals upto 12 hours. The

Table 1: Demographic profile in the groups

Demographic variables	Group NE	Group NT	p-value
Female / Male	14/16	16/14	0.606
Age (years)	40.7	41.37	0.833
Weight (kg)	59.2	58.1	0.476
Height (cm)	163.4	162.7	0.643
BMI	22.1	21.9	0.666
ASA I/II	23/7	23/7	1.0
Mean duration of surgery (min)	86.0	82.0	0.238

Table 2: Intraoperative parameters

Intra-operative parameters	Group NE	Group NT	p-value*
Sensory onset in min at T10 level	2.5 ± 0.6	2.5 ± 0.5	0.800
Motor onset in min (Bromage scale)	6.4 ± 1.0	5.9 ± 0.8	0.057

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

Group	Pre op		Intra op		Postop	
	PR	MAP	PR	MAP	PR	MAP
NE	83.8 ± 12.1	91.2 ± 7.5	77.35 ± 7.1	83.6 ± 8.1	78.4 ± 6.4	90.1 ± 5.1
NT	82.5 ± 9.1	92.4 ± 8.9	75.53 ± 9.2	81.2 ± 9.0	78.1 ± 6.8	87.3 ± 7.0

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

Table 4: Postoperative block characteristics between groups

Postoperative parameters	Group NE	Group NT	p-value*
Time for 2 segment regression (min)	77.8 ± 2.6	79.0 ± 2.4	0.078
Duration of motor blockade (min)	175.7 ± 6.2	176.1 ± 6.0	0.834
Duration of analgesia (min)	386.9 ± 17.2	476.9 ± 17.3	< 0.001
Number of analgesics required in 24 h	2.20 ± 0.7	1.83 ± 0.8	0.037

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

Postoperative time points	Group NE	Group NT	p-value Between group*
15 min	0.0	0.0	< 0.001
30 min	0.0	0.0	
1 h	0.0	0.0	
2 h	0.0 (0.0)	0.13 (0.35)	
3 h	0.40 (0.50)	0.73 (0.74)	
4 h	1.07 (0.69)	1.40 (0.56)	
5 h	2.23 (0.86)	1.93 (0.64)	
6 h	3.37 (1.12)	2.37 (0.56)	
7 h	0.53 (0.51)	3.37 (0.72)	
8 h	0.80 (0.61)	2.60 (2.0)	
12 h	2.67 (0.76)	2.60 (0.85)	
24 h	1.53 (0.82)	1.13 (0.63)	

Table 6: Comparison of the side effects of two groups

Side effects	Group NE N (%)	Group NT N (%)
Hypotension	0	6 (10.0%)
Nausea and vomiting	2 (3.3%)	4 (6.7%)
Shivering	3 (5.0%)	4 (6.7%)

last reading was taken at 24 h post spinal. Any patient with VAS score of four and more qualified for rescue analgesic (inj diclofenac 1.5 mg/kg IM).

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 of 0.05 and a power of 90%. Test for analysis among two groups was done by ANOVA for quantitative and Chi-square test for qualitative data. A $p < 0.05$ was considered as significant.

RESULTS

There was no significant difference among the two study groups in respect of age, sex, height, weight, BMI, ASA and duration of surgery

(Table 1).

The onset of sensory block was 2.5 ± 0.6 and 2.5 ± 0.5 min in Group NE and NT respectively and there was no significant difference in two groups with regards to time to achieve grade 3 motor block 6.4 ± 1 and 5.9 ± 0.8 min in Group NE and NT respectively (Table 2).

Table 3 shows the comparative hemodynamic parameters i.e. mean arterial pressure (MAP), 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. Duration of analgesia was significantly longer in Group NT in comparison to Group NE (476.9 ± 17.3 vs. 386.9 ± 17.2 min) which was clinically and statistically highly significant ($p < 0.001$). The mean consumption of rescue analgesic per patient was 2.20 ± 0.7 (NE) and 1.83 ± 0.8 (NT). This difference was statistically significant ($p < 0.05$) (Table 4). VAS scores in Group NE were persistently greater than that of Group NT (Table 5), but the difference were statistically not significant.

Regarding complications, there was no significant difference among the groups in the frequency of nausea, vomiting and shivering, Although statistically significant differences were seen in average MAP readings, all these differences were clinically insignificant (Table 6).

DISCUSSION

“The aim of the wise is not to secure pleasure, but to avoid pain” - Aristotle. Postoperative pain management is essential for early ambulation and recovery of the patient. Various methods of

transdermal nitroglycerin as spinal adjuvant

postoperative pain relief are available.

Intrathecal neostigmine causes dose dependent postoperative analgesia by inhibiting breakdown of acetylcholine in dorsal horn and spinal meninges. Acetylcholine causes analgesia through direct action on spinal cholinergic muscarinic receptors m1 and m3.

Transdermal nitroglycerin patch has been related 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 NO action at primary afferent and at the 2nd order neuron.

Almost all the 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.¹ and Patel et al.,⁷ we used doses of 5 μ g of intrathecal neostigmine and transdermal nitroglycerin patch (5 mg/day). 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 clonidine, opioids, 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}

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 intramuscular injection of diclofenac 75 mg, when patient complains of pain or VAS 4 and above. In our results, we found

that during initial 300 min, i.e. from baseline to 300 min, the difference was statistically insignificant ($p > 0.05$). Difference in VAS scores of two groups NE and NT becomes statistically significant at 360th to 480th min with p values < 0.05 . VAS score was higher in neostigmine group requiring rescue analgesia at 300 min and maximum VAS scores at 360th-420th min, where as in nitroglycerin group VAS score started to increase only after 420th min and maximum scores of VAS was seen at 480th-540th min. Nitroglycerin group had lower scores of VAS even at 12th and 24th hours. Our results were similar to study conducted by Rameez et al.⁹ which showed average VAS scores of combination (tNTG and neostigmine) group were significantly lower than neostigmine group.

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

LIMITATIONS

Limitation of our study is that, tNTG is a newer mode of peri-operative 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 5 μ g and bupivacaine 15 mg in patients undergoing below umbilical surgeries.

Conflict of interest: None declared by the authors

Authors' contribution:

SS & MM: Concept, conduc of the study work, literature search, statistical analysis and manuscript editing.

VJ & RS: conduct of study and manuscript editing.

REFERENCES

1. Morgan Jr. GE, Mikhail MS, Murray MJ, Larson Jr. CP. Clinical anaesthesiology. 4th ed. New York (NY): Lange; 2002.
2. Garg A, Chawla V, Khandelwal M, Ahmed F. Transdermal nitroglycerin enhances postoperative analgesia of intrathecal neostigmine following abdominal hysterectomies. *Indian J Anaesth.* 2010;54(1):24-8. [[PubMed](#)] DOI: [10.4103/0019-5049.60492](https://doi.org/10.4103/0019-5049.60492)
3. Raghavendra TR D. A clinical study of peri-operative effectiveness of adjuvant neostigmine with intrathecal bupivacaine for lower abdominal surgeries. *IOSR-JDMS.* 2012;2(3):35-9.
4. Elgohary M. Transdermal nitroglycerin potentiates the analgesic effect of patient controlled epidural analgesia after lower abdominal surgery. *Egyptian J Anaesth.* 2011;27(1):19-24. DOI: [10.1016/j.egja.2011.01.001](https://doi.org/10.1016/j.egja.2011.01.001)
5. Orbach-Zinger S, Lenchinsky A, Paul-Kesslin L, Velks S, Salai M, Eidelman LA. Transdermal nitroglycerin as an adjuvant to patient-controlled morphine analgesia after total knee arthroplasty. *Pain Res Manag.* 2009;14(2):109-12. [[PubMed](#)]
6. Lauretti GR, de Oliveira R, Ries MP, Prado WA, Pereira NL. Transdermal nitroglycerin enhances spinal sufentanil postoperative analgesia following orthopaedic surgery. *Anesthesiology* 1999;90(3):734-39. [[PubMed](#)]
7. Patel VP, Patel P, Mehta SS, Rathod GB. Effect of transdermal nitroglycerin patch on intrathecal neostigmine with bupivacaine for post-operative analgesia. *IAIM,* 2016;3(2):31-40. [[Free Full Text](#)]
8. Mammen MV, Tripathi M, Chandola HC, Tyagi A, Bais PS, Sanjeev OP. Comparison of enhancement of analgesic effect of intrathecal neostigmine by intrathecal clonidine and transdermal nitroglycerin patch on bupivacaine spinal anesthesia. *Anesth Essays Res.* 2017 Oct-Dec;11(4):993-7. DOI: [10.4103/aer.AER_68_17](https://doi.org/10.4103/aer.AER_68_17)
9. Rashid MR, Mushtaq S, Choudhary A, Mehta N. To study the role of transdermal nitroglycerin (tNTG) in enhancing the effect of low dose intrathecal neostigmine on post-operative analgesia in patients undergoing lower abdominal and lower limb surgery under spinal anesthesia with bupivacaine. *Sch J App Med Sci* 2015; 3(8C):2918-25. [[Free Full Text](#)]

