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A Study of Efficacy of Trans Dermal Nitroglycerine Patch in Enhancing Analgesia of Intrathecal Neostigmine Following Hyterectomies Under Bupivacaine Spinal Anaesthesia

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Abstract

Aim of the study: To evaluate and compare the efficacy, safety and adverse effects of combining intrathecal neostigmine with transdermal nitroglycerine patch for pain relief in patients undergoing hysterectomies under bupivacaine spinal anaesthesia. *Materials and Methods:* The study was conducted on 78 patients aged 30 to 60years of ASA grade I and II, planned for hysterectomies. Patients were allocated into 3 groups, each group containing 26 patients.

Group C: Patients received 15mg [3ml] of intrathecal bupivacaine.

Group N: Patients received 15mg [3ml] of intrathecal Bupivacaine and 25µg [1ml] of neostigmine.

Group P: Patients in addition to 15 mg [3ml] of intrathecal Bupivacaine and 25µg [1ml] of neostigmine, received transdermal NTG patch [5mg / 24hours] at chest wall in non- anaesthetized area 15 minutes after intrathecal administration of drug solution. Sensory level during anaesthesia, Postop VAS score and incidence of side effects were noted in all patients. *Observation and Results:* Duration of analgesia was longest in Group P (316.3 minutes) compared to other two groups. (Group N 211.3 minutes and Group C 150.4 minutes) which was statistically significant. Incidence of nausea and vomiting were higher in Group N and P compared to Group C. *Conclusion:* Addition of transdermal nitroglycerine patch [5mg/24hrs] and intrathecal 25µg neostigmine to 3ml of 0.5% bupivacaine spinal anaesthesia provided prolonged duration of analgesia but with increased incidence of nausea and vomiting.

Keywords: Nitroglycerine; Bupivacaine; Neostigmine; Spinal Anaesthesia.

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Introduction

Post-operative pain is a universal phenomenon experienced by millions of patients throughout the world, yet paradoxically after all the efforts taken to make intraoperative period pain and stress free, the patients is left to fend for himself in the postoperative period.

Neuraxial blockade is one of the answers to control post-operative pain. Neostigmine is the universally used neuromuscular block reversal agent whose post-operative pain relief property was first described by Naquib and Yaksh et al in1994. It inhibits the breakdown of acetylcholine which has been shown to cause analgesia by stimulating the synthesis of nitric oxide [NO] in the spinal cord. It blocks the activity of both true and

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pseudo cholineterase and thereby enhancing accumulation and binding of acetylcholine at various cholinergic sites.

But a higher dose of neostigmine produce many untoward side effect such a nausea, vomiting etc and lower does of neostigmine doesn't show much analgesic property. So as to reduce dose of neostigmine and potentiate its analgesic property other adjuvants like clonidine, opioids,transdermal nitroglyceine pathc etc, have been adden alone with it.

The transdermal nitroglycerine acts as a source for nitric oxide (NO). NO acts as a second messenger in the CNS and plays an important role in the mediation of pain. Intracellular cGMP levels are increased by NO by activation of enzyme guanyl cyclase. This Nitric oxide–cyclic GMP cascade in endothelial cells mediates acetylcholine induced vasodilatation as well as acetylcholine induced antinociception.

Aim of The Study

To evaluate and compare the efficacy , safety and adverse effects of combining intrathecal neostigmine with transdermal nitroglycerine patch for pain relief in patients undergoing hysterectomies under bupivacaine spinal anaesthesia.

Materials And Methods

After obtaining approval from Ethical committee, the study was conducted in *Raja Mirasdar Hospital, Thanjavur.*[Thanjavur Medical College] over a period of 5 months. Informed consent was obtained, the study was conducted on 78 patients aged 30 to 60years of ASA grade I and II, planned for hysterectomies. Patients were allocated into 3 groups, each group containing 26 patients.

Group C: Patients received 15mg [3ml] of intrathecal Bupivacaine.

Group N: Patients received 15mg [3ml] of intrathecal Bupivacaine and 25µg [1ml] of neotigmine.

Group P: Patients , in addition to 15 mg [3ml] of intrathecal bupivacaine and 25µg [1ml] of neostigmine, received transdermal NTG patch [5mg / 24hours] at chest wall in non-anaesthetized area 15 minutes after intrathecal administration of drug solution.

Visual analogue scale [VAS] was used as pain score, 0= no pain and 10= worst pain. After preloading the patient with Ringer lactate 10ml/kg, spinal anaesthesia was performed at L3-L4 level, with 25 gauge Quincke needle and 4 ml of drug volume was injected intrathecally.

Sensory level was assessed by pin prick . BP was recorded every 5 minute during the surgery. Inj. ephedrine 6mg iv was given when systolic BP decreases below 15% of base line. Pulse rate and SpO_2 were observed continuously. Fall in heart rate below 60 per minute was treated with Injection atropine 0.2mg IV. Intraoperative vomiting was treated with Injection metoclopramide 10 mg IV. Postoperatively VAS score was used to assess pain in subjects for every 30 minutes. Patients were given rescue analgesia at VAS score of 4.

Other adverse effects like vomiting, nausea, sedation, bradycardia, hypotension, sweating, headache and palpitation were also monitored.

Inj. pentazocine 30mg was administered intramuscularly as rescue analgesic. Duration of analgesia was calculated from the time of intrathecal drug administration till VAS score reaches 4.

Data thus obtained were analyzed using Microsoft excel software.

Statistical Tools

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using Epidemiological Information Package (EPI 2010) developed by Centre for Disease control, Atlanta.

Using this software range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Kruskul Wallis chi-quare test was used to test the significance of difference between quantitative variables and Yate's chi square test for qualitative variables. A 'p'value less than 0.05 is taken to denote significant relationship.

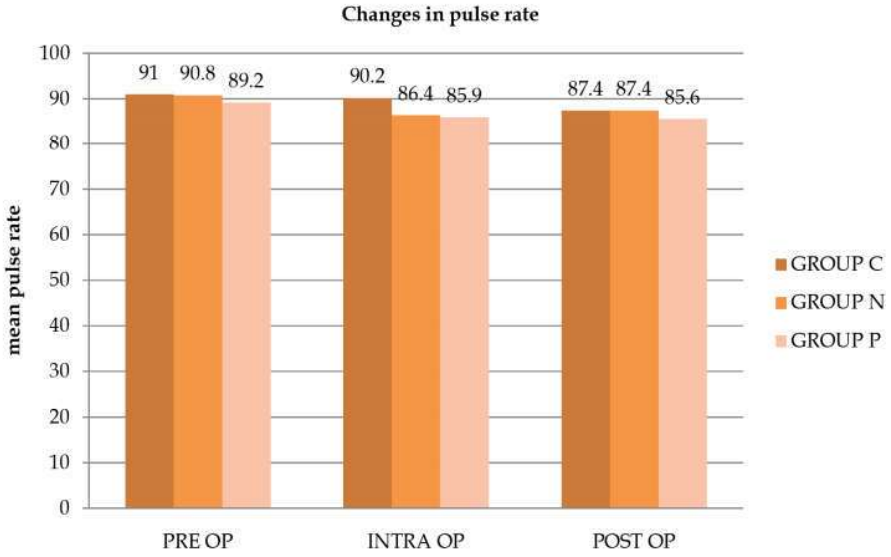
Results

Characteristics of Cases

The three groups were comparable with respect to the demographic variables such as age, weight & duration of surgery. There was no statistically significant difference between distribution of age, weight & duration of surgery among the three groups.

Table 1: Changes in Pulse rate

Pulse rate	Pulse rate						'p' value between Groups			
	Group C		Group N		Group P		C,N&P	C&N	C&P	N&P
	Mean	SD	Mean	SD	Mean	SD				
Pre operative	91	10.4	90.8	11.6	89.2	12.8	0.7195 Not significant	0.5701 Not significant	0.481 Not significant	0.6604 Not significant
Intra operative	90.2	11.1	86.4	10.7	85.9	12.7	0.1723 Not significant	0.0714 Not significant	0.156 Not significant	0.927 Not significant
Post operative	87.4	10.5	87.4	11.4	85.6	12.6	0.7125 Not significant	0.5704 Not significant	0.5159 Not significant	0.5518 Not significant
Decrease	3.5	2.4	3.3	5	3.6	7.3	0.7623 Not significant	0.4809 Not significant	0.5704 Not significant	0.9416 Not significant



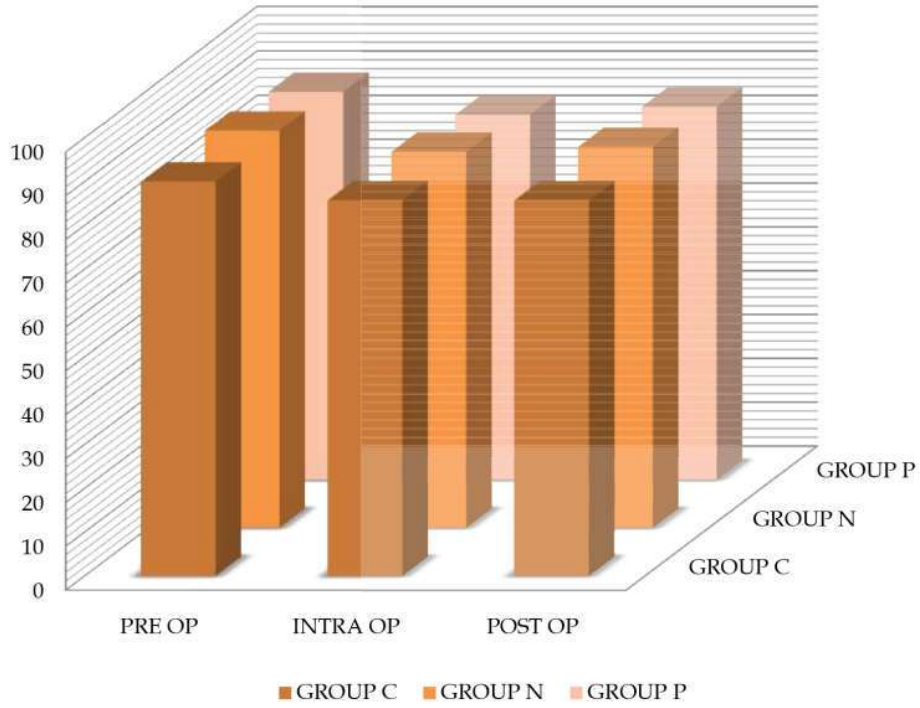
Graph 1: Changes in Pulse rate

There was no statistically significant difference in the heart rate among the three groups (Table 1 & Graph 1).

There was no statistically significant difference in the mean arterial pressure among the three groups (Table 2 & Graph 1).

Table 2: Changes in Mean arterial Pressure among the three groups

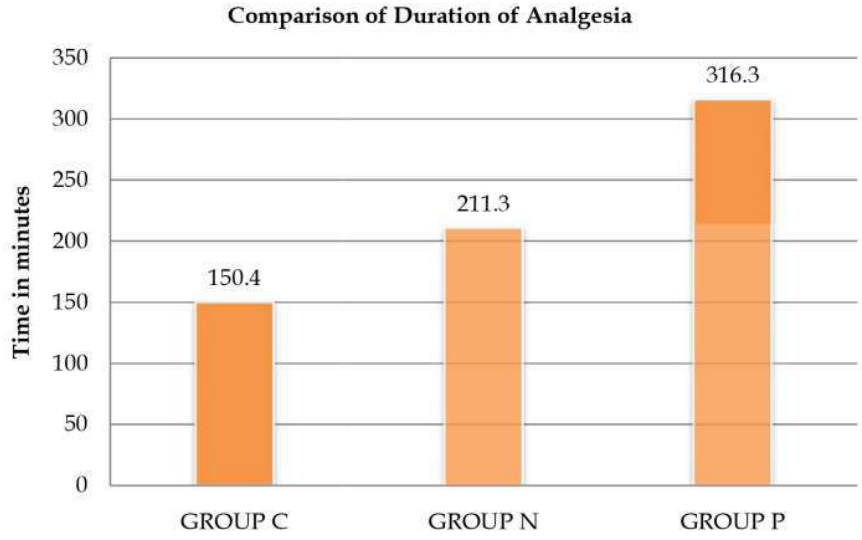
MAP	MAP of						'p' value between Groups			
	Group C		Group N		Group P		C,N&P	C&N	C&P	N&P
	Mean	SD	Mean	SD	Mean	SD				
Pre operative	90	5.2	90.7	5.2	88.5	6.8	0.4273 Not significant	0.3696 Not significant	0.558 Not significant	0.234 Not significant
Intra operative	85.7	5.5	85.8	5.4	83.3	6.7	0.2021 Not significant	0.8836 Not significant	0.148 Not significant	0.1033 Not significant
Post operative	85.7	5.6	86.9	4.6	85.1	6.6	0.7111 Not significant	0.4474 Not significant	0.9416 Not significant	0.5099 Not significant
Decrease	3.9	1.7	3.7	4.2	3.4	2.2	0.118 Not significant	0.9271 Not significant	0.1102 Not significant	0.4207 Not significant



Graph 2: Changes in MAP

Table 3: Comparison of duration of analgesia

Group	Duration of analgesia in minutes		
	Range	Mean	SD
Group C	120-180	150.4	15.7
Group N	180-250	211.3	22.8
Group P	200-400	316.3	48
'p' value between Groups C,N&P		0.0001 - Significant	
C&N		0.0001 - Significant	
C&P		0.0001 - Significant	
N&P		0.0001 - Significant	



Graph 3: Duration of analgesia

Duration of analgesia was longest in Group P in comparison to other two groups and this difference was statistically significant (p-0.0001) (Table 3).

Duration of analgesia was longer in Group N in comparison to Group C and this difference was also statistically significant (p-0.0001) (Graph 3).

Incidence of nausea and vomiting was higher in Group N and Group P when compared with Group C and this difference is statistically significant. There was no statistically significant difference in the incidence of nausea and vomiting among Group-P and Group-N (Table 4, 5 & Graph 4).

Discussion

Various drugs have been tried in the subarachnoid space along with local anaesthetics with the aim of improving the duration of post-operative analgesia. The cholinesterase inhibitor neostigmine is one among such adjuvants.

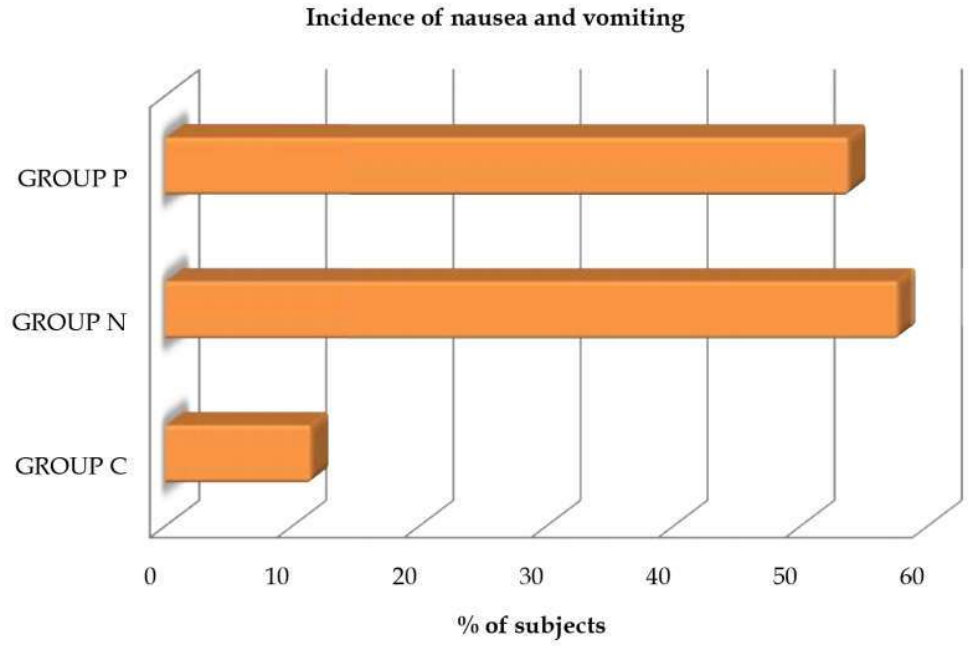
Even though neostigmine produces an increase in duration of analgesia, it was also associated with many unwanted side effects particularly nausea and vomiting, especially in higher doses. So to reduce the incidence of adverse effects and to

Table 4: Adverse effects

	Group - P	Group - N	Group - C
Nausea	8	8	2
Vomiting	6	7	1
Hypotension	3	2	3
Bradycardia	2	2	1

Table 5: Comparison of Adverse effects

Group	Nausea and Vomiting			
	Yes	%	No	%
Group C	3	11.5	23	88.5
Group N	15	57.7	11	42.3
Group P	14	53.8	12	46.2
'p' value between Groups				
C & N		0.0238 - Significant		
C & P		0.046 - Significant		
N & P		0.7822 - Not significant		



Graph 4: Incidence of nausea and vomiting

prolong the post operative analgesia other adjuvants have been used along with neostigmine.

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

Analgesic effect of intrathecally administered neostigmine is by release of acetylcholine in the spinal cord. Increased acetylcholine due to surgical stimuli and acetylcholine preserved from anticholinesterase activity of intrathecal neostigmine, binds to nicotinic and muscarinic nerve terminals in the spinal cord. Studies have proved that cholinergic agonist produce inhibitory effects on spinal dorsal horn neurons, including spinothalamic tract. This suggest that a spinal cholinergic system plays an important role in the modulation of pain pathways.

Since NO was shown to be a CNS neurotransmitter, there has been reports of relationship between nitric oxide and pain processing in the CNS. It is accepted that nitric oxide may occupy an important position in the mediation of pain. Acetyl choline induces analgesia by activation of the arginine- nitric oxide –cGMP pathway. Enzyme Guanylate Cyclase activity in the CNS is markedly stimulated by nitric oxide generated from L-arginine or provided through transdermal NTG, an exogenous source as in the present study. Nitric oxide formation occurs during degradation of organic nitrate from transdermal NTG.

This study was designed to find out whether the analgesic effect of intrathecal neostigmine will be enhanced by transdermal NTG, which act as an exogenous source of nitric oxide. In this study the duration of analgesia was analyzed as period from intrathecal drug administration till VAS score reaches 4. On statistical analysis, patient belonging to Group C complained of pain earlier than other groups, duration of analgesia being 2.5 hours. There was statistically significant delay in the onset of pain in Group N and Group P. Our study showed a mean duration of 3.5 hours in patients belonging to Group N and 5.2 hours in patients belonging to Group P.

Lauretti, Gabriela R. et al., in 2000 conducted a study to determine whether association of transdermal nitroglycerine would enhance analgesia from low dose of intrathecal neostigmine in patients undergoing gynaecologic surgery during spinal anaesthesia. They concluded that neither intrathecal 5µg neotigmine alone nor transdermal nitroglycerine alone (5mg/day) delayed the time to administration of first rescue analgesics, but the combination of both provided an average of 550min of effective postoperative analgesia after vaginoplasty. There was no significant difference in the incidence of adverse effect. They suggested that transdermal nitroglycerine and the central cholinergic agent neostigmine may enhance each other's antinociceptive effects which correlate with findings of our study. The increased incidence of adverse effects in our study may be due to usage of higher dose of neostigmine.

Gurvinder Kaur, Narheet Osahan, Lalita AFzal in 2007 conducted a study to examine the effect of transdermal NTG patch (5mg/24hour) in intrathecally administered neostigmine (5µg) along with 15mg Bupivacaine and incidence of untoward effect. They found that average duration of analgesia in intrathecal neostigmine group [Group I] was 6.5 hours and in neostigmine and transdermal nitroglycerine patch Group [Group II] wa 9.10 hours. Duration of analgesia was significantly higher in patients in Group II as compared t Group I. The incidence of nausea was higher in Group I than in Group II. The enhancement of analgesia of intrathecal neostigmine by transdermal NTG in this study correlates with our study. The increased incidence of nausea and vomiting in my study may be due to usage of higher dose of neostigmine.

Fareed ahmed et. Al 2010 conducted a study to determine the effect of trandermal nitroglycerine patch on intrathecal neostigmine. Patients were allocated into four group with Group I received 15 mg bupiuvacaine intrathecally, Group II received 15 mg of Bupivacaine with 5µg neostigmine intrathecally, patients in group III received 15 mg of Bupivacaine with 1 ml of normal saline intrathecally and transdermal NTG patch [5mg/ 24hours]. Patients in Group IV received 15mg bupivacaine with 5µg of neostigmine intrathecally and transdermal NTG patch [5mg/24 hours]. The mean duration of analgesia was 202.2 min, 407.6 min,207.8 min and 581.6min in Group [I], Group [II], Group [III], Group [IV] respectively.

In my study intrathecal Bupivacaine–transdermal nitroglycerine patch group was omitted since the above studies substantiated that transdermal nitroglycerine patch do not show analgesic potential of its own. The enhancement of analgesia by intrathecal neostigmine and potentiation of analgesic effect of intrathecal neostigmine by transdermal NTG patch correlates with the findings of our study. No change in perioperative hemodynamic parameters which was observed in this

study also correlates with our study. The increased incidence of nausea and vomiting in my study may be due to usage of higher dose of neostigmine.

Conclusion

On the basis of this study the following conclusions were drawn :

1. Spinal anaesthesia with 3ml 0.5% Bupivacaine provided 2.5 ± 0.26 hours of analgesia.
2. Addition of intrathecal 25µg neostigmine to bupivacaine spinal anaesthesia significantly prolonged the duration of analgesia [3.52±0.38 hrs]
3. Addition of transdermal nitroglycerine patch [5mg/24hrs] and intrathecal 25 µg neostigmine to bupivacaine spinal anaesthesia provided the longest duration of analgesia [5.27±0.8 hrs]
4. Addition of intrathecal neostigmine and transdermal nitroglycerine patch to bupivacaine spinal anaesthesia did not produce any significant change in hemodynamic parameters.
5. Addition of intrathecal 25 µg neotigmine to bupivacaine spinal anaesthesia significantly increased the incidence of nausea and vomiting.

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Indian Journal of Preventive Medicine	Semiannual	7000	6500	547	508
Indian Journal of Research in Anthropology	Semiannual	12500	12000	977	938
Indian Journal of Surgical Nursing	Triannual	5500	5000	430	391
Indian Journal of Trauma & Emergency Pediatrics	Quarterly	9500	9000	742	703
Indian Journal of Waste Management	Semiannual	9500	8500	742	664
International Journal of Food, Nutrition & Dietetics	Triannual	5500	5000	430	391
International Journal of Neurology and Neurosurgery	Quarterly	10500	10000	820	781
International Journal of Pediatric Nursing	Triannual	5500	5000	430	391
International Journal of Political Science	Semiannual	6000	5500	450	413
International Journal of Practical Nursing	Triannual	5500	5000	430	391
International Physiology	Triannual	7500	7000	586	547
Journal of Animal Feed Science and Technology	Semiannual	78500	78000	6133	6094
Journal of Cardiovascular Medicine and Surgery	Quarterly	10000	9500	781	742
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Journal of Orthopaedic Education	Triannual	5500	5000	430	391
Journal of Pharmaceutical and Medicinal Chemistry	Semiannual	16500	16000	1289	1250
Journal of Practical Biochemistry and Biophysics	Semiannual	7000	6500	547	508
Journal of Psychiatric Nursing	Triannual	5500	5000	430	391
Journal of Social Welfare and Management	Triannual	7500	7000	586	547
New Indian Journal of Surgery	Bi-monthly	8000	7500	625	586
Ophthalmology and Allied Sciences	Triannual	6000	5500	469	430
Otolaryngology International	Semiannual	5500	5000	430	391
Pediatric Education and Research	Triannual	7500	7000	586	547
Physiotherapy and Occupational Therapy Journal	Quarterly	9000	8500	703	664
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