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Original article:

EFFECT OF TRANSDERMAL NITROGLYCERIN PATCH ON INTRATHECAL NEOSTIGMINE WITH BUPIVACAINE FOR POST OPERATIVE ANALGESIA

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ABSTRACT:

Background: Spinal anesthesia is preferred over general anesthesia for various surgeries as it is simple to perform and economical. And produces rapid onset of anesthesia, analgesia with good muscle relaxation. Concept of post operative analgesia is gaining importance . Intrathecal neostigmine causes dose dependent post operative analgesia by inhibiting breakdown of acetylcholine in dorsal horn and spinal meninges. Acetylcholine produces analgesia indirectly through stimulation of release of nitric oxide in spinal cord. The transdermal nitroglycerine patch has been related to nitric oxide formation during degradation of organic nitrate and enhances the antinociception produced by low dose neostigmine intrathecally

Objective: to evaluate efficacy and potency of intrathecally administered bupivacaine with neostigmine (source of Acetylcholine) and bupivacaine and neostigmine with nitroglycerine patch (source of exogenous NO) on onset and duration of sensory and motor blockade, hemodynamic stability, duration of post operative analgesia and side effects in various surgeries.

Material &method: The study was conducted by taking 50 randomly selected patients for various surgeries. Patients belonged to ASA Grade I/II aged 18 to 60 years after excluding them according to exclusion criteria.Patient were divided into 2 groups.

Group-A : 0.5% heavy bupivacaine 3 ml (15 mg) + preservative free neostigmine 5 mcg.

Group-B : 0.5% heavy bupivacaine 3 ml (15 mg) + preservative free neostigmine 5 mcg + transdermal nitroglycerine patch (5 mg/24 hours), applied on a non anaesthetized area after 20 minutes.

Results: There was no statistically significant difference present regarding time of onset of sensory as well as motor blockade and hemodynamic parameters. There was highly significant difference between total duration of analgesia in both groups($p<0.01$)which was more in group B as compared to group A. Event of more hypotention noted in group B than group A and incidence of bradycardia was same in both groups.

Conclusion: From this study it can be concluded that transdermal nitroglycerine patch increases post-operative analgesia of low dose intrathecal neostigmine with bupivacaine in spinal anesthesia with less side effects.

Key words: spinal anaesthesia, neostigmine,nitroglycerine patch,post-operative analgesia

INTRODUCTION

The international association for the study of pain has defined pain as "An unpleasant and emotional experience associated with actual or potential tissue damage or described in terms of such damage"[6].

Spinal anesthesia is preferred over general anesthesia for various surgeries. All advantages of spinal anesthesia are offset by complain of postoperative pain when effect of local anesthesia wears off due to relatively shorter duration of action of local anesthetic drug. Concept of post operative analgesia is gaining importance.

Intrathecal neostigmine causes dose dependent post operative 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 and indirectly through stimulation of release of NO.Our objective was to evaluate efficacy and potency between two groups on onset and duration of sensory and motor blockade, hemodynamic stability, duration of post operative analgesia and side effects in various surgeries. The transdermal nitroglycerine patch has been related to nitric oxide formation during degradation of organic nitrate and enhances the antinociception produced by low dose neostigmine intrathecally.

MATERIAL AND METHOD

The study was conducted by taking 50 randomly selected patients for various surgeries. Patients belonged to ASA Grade I/II aged 18 to 60 years.

Exclusion criteria:

- Allergic to study medications.
- History of significant neurological, psychiatric, neuromuscular, cardiovascular, pulmonary, renal or hepatic disease.
- Alcohol or drug abuser
- Patient refused to give consent for this study.

Patient were divided into 2 groups.

Group-A : 0.5% heavy bupivacaine 3 ml (15 mg) + preservative free neostigmine 5 mcg.

Group-B : 0.5% heavy bupivacaine 3 ml (15 mg) + preservative free neostigmine 5 mcg + transdermal nitroglycerine patch (5 mg/24 hours), applied on a non anaesthetised area after 20 minutes.

Detailed pre anaesthetic check up with all routine investigations were done in pre operative room before surgery.Informed consent was taken and VAS scale explained to patient.

Inside the operation theatre intravenous line taken and each patient was preloaded with 10 ml/kg of ringer's lactate solution. Pulse oximeter, non invasive blood pressure and ECG monitors were applied and baseline readings were taken.

Inj. neostigmine 0.5 mg was diluted in 10 cc with normal saline and 1 cc is taken from it and again diluted in 10 cc and from it 1 cc (5mcg) was taken with 3cc(15 mg) of 0.5% hyperbaric bupivacaine. Total volume of 4ml was used. Under all aseptic and antiseptic precaution spinal anesthesia was performed in sitting/lateral position at L_2L_3 or L_3L_4 intervertebral space with 23G quincke spinal needle. After completion of procedure patients were immediately turned to supine position and time to subarachnoid injection was noted . Highest T6-T8 level achieved. O_2 was given by Hudson mask at the rate of 4 L/min by the anaesthesia machine. In group B after haemodynamic stabilisation the transdermal nitroglycerin patch was applied on the thorax (ventral, T2-T4), in a non-anaesthetised area, 20 minutes after spinal puncture. The total

nitroglycerin content of transdermal nitroglycerine patch was 25 mg; the total drug releasing area was 10 cm^2. It delivered nitroglycerine at the rate of 20-25 $\mu g/cm^2$.h or 5mg /24 hours.

Evaluation :

SENSORY BLOCK: was checked by using pin prick method with the tip of 24 G hypodermic needle

- Time of onset of sensory blockade in minutes.
- Time of two segment regression of sensory block in minutes.

MOTOR BLOCK: was assessed by modified Bromage scale.(0=none, 1=just able to move the knee but not the hip, 2=able to move foot only,3=unable to move knee or foot)

- Complete motor blockade: (it was defined as the time from intrathecal drug injection to time to attain modified Bromage grade 3)
- Duration of motor block: ((it was defined as time interval from intrathecal drug injection to when modified Bromage scale grade become 0 again)

(3) INTRA OPERATIVE VITAL PARAMETERS:

Pulse rate, Blood pressure and SPO2 were monitored at every 5 mins till first 30 minutes then every 10 min till 1 hr and then every 30 min till the end of surgery.

(4) INTRA OPERATIVE COMPLICATIONS:

Intraoperative complications like hypotension, respiratory depression, nausea, vomiting, shivering were treated as follow:

Hypotension greater than 15% below the baseline value was treated by the incremental dose of Injection mephenteramine 6 mg IV.. Any fall in the heart rate below 60 beats per minute was treated with incremental doses of Inj. atropine 0.3 mg IV. Intraoperative nausea was treated with Inj. Ondansetron 4 mg intravenous. shivering was treated with 100% oxygen, warm fluids and adequate covering. No other sedation or analgesic drug given to the patients .

(5) POST OPERATIVE PERIOD:

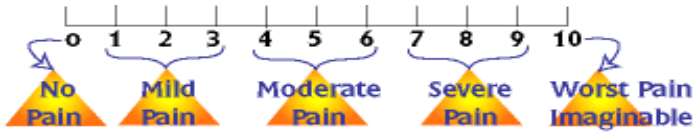
Time from subarchnoid injection to administration of first rescue analgesic was taken as total duration of analgesia.

Method of judging postoperative analgesia by VAS(Visual Analogue Scale). At this time, patients were given rescue analgesic Inj Diclofenac Sodium 1.5mg/kg IM. Vital parameters were recorded initially at 30 min interval for 1 hr then hourly for 7 hr then 2 hrly for 4 hrs (total 14 hrs).

PAIN ASSESSMENT:

It was done every 30 mins for initial 1 hr then hourly for 7 hr and then 2 hourly for 4 hr by using Visual Analogue Scale (VAS).

It is a 10 cm scale graded from 0-10 in such a way that 0 denotes no pain and 10 denote most excruciating pain. Patients were asked to mark the point on the scale that corresponded to their level of pain intensity at the time of observation.



Transdermal Nitroglycerine patch was removed after giving the rescue analgesia.

(6) POST OPERATIVE VITAL PARAMETERS:

Vital parameters were recorded initially at 30 min interval for 1 hr then hourly for 7 hr then 2 hrly for 4 hrs (total 14 hrs).

(7) POST OPERATIVE COMPLICATIONS

Postoperative complications like bradycardia , hypotension ,respiratory depression, nausea, vomiting, shivering, post dural puncture headache, backache were observed and treated accordingly.

The results of the study were tabulated & statistically compared among the two groups. The **Student t test** was used for quantitative data.Data were presented as mean and mean+SD.

The **p-value** was considered significant if it was <0.05.

OBSERVATION AND RESULTS

There were 25 patients in each group and their demographic characteristics are shown in following table.

Table 1 : Demographic Profile Of Groups With Mean And S.D Values

	Group A	**Group B**
Numbers of patients	25	25
ASA grade (I/II)	15/10	15/10
Age(Yrs)	37.24±12.3	37.64±11.82
Weight(kg)	55.12±3.59	55.60±4.04

Table 1 shows there was no statistically significant (P>0.05) difference among two groups in terms of demographic data like Age, Weight and ASA grade .

Table 2 Characteristics Of Sensory Block

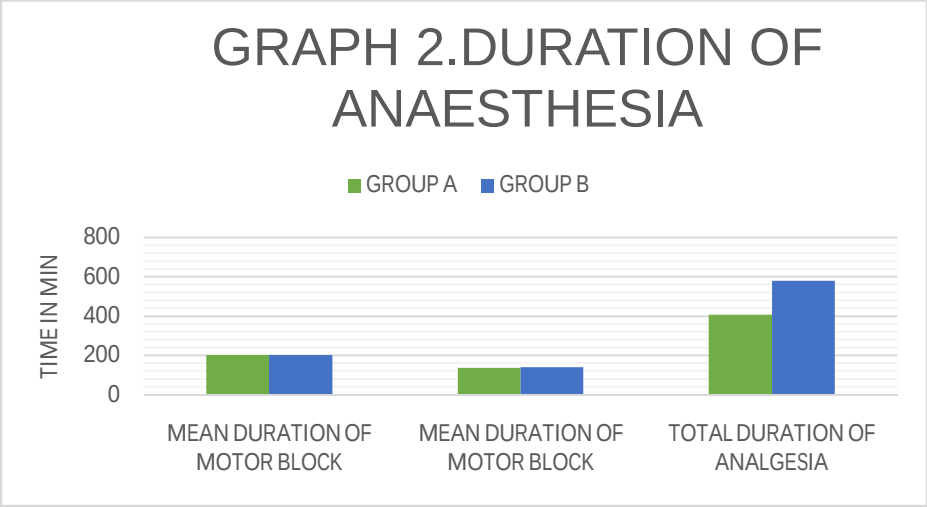
	Group A	**Group B**
Time to achieve sensory block (Mean ± SD) minutes	3.12± 0.60	3.52 ± 0.96
Duration of two segment regression of sensory block (Mean ± SD) minutes	137.36± 3.45	139.72± 3.57

Table 2 shows there was not significant difference in two groups with regards to duration of two segment regression of sensory block.

Table-3 Characteristics of Motor Blockade

	Group A	**Group B**
Time to achieve Grade 3 block (Mean ± SD) minutes	5.48± 0.87	5.52 ± 0.87
Time taken for Grade 3 to Grade 0 level (Mean ± SD)minutes	201.52 ± 7.41	200.16 ± 10.19

Table 3 shows there was not significant difference in two groups with regards to time to achieve grade 3 block and duration of grade 3 to grade 0 level($p>0.05$).



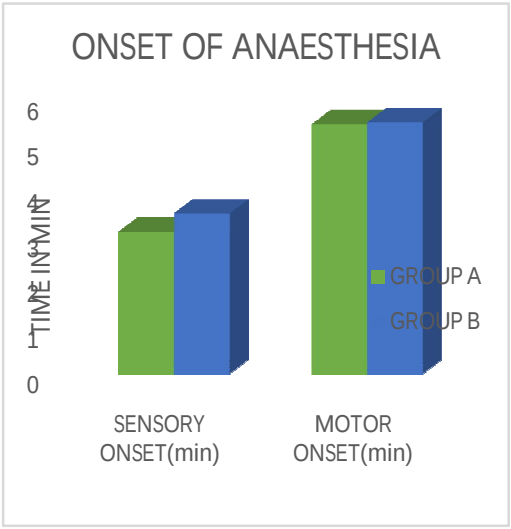


Table-4 Intraoperative Hemodynamic Monitoring (mean)

Time	Group-A			Group-B		
	Pulse (Per min)	Blood pressure (mm of Hg)		Pulse (Per min)	Blood pressure (mm of Hg)	
		Systolic	Diastolic		Systolic	Diastolic
5 min	83.88	124.88	77.92	85.0	125.92	78.96
10 min	81.92	121.36	77.60	82.04	121.28	77.52
15 min	80.40	114.32	72.16	80.36	113.84	72.24
20 min	77.28	108.72	67.68	76.52	108.64	67.72
25 min	73.88	106.48	64.88	75.12	105.92	65.44
30 min	71.08	107.12	66.64	74.36	101.68	62.56
40 min	73.08	109.2	68.88	73.08	106.08	67.92
50 min	72.08	110.16	71.2	72.08	110.16	71.2
60 min	72.72	112.48	73.04	72.72	112.24	72.24
90 min	73.84	116.56	72	73.84	116.32	71.52
120 min	77.76	118.64	75.28	77.76	118.64	75.28

Table 4 shows that there was statistically insignificant difference between two groups with regards to hemodynamic parameters.

Table-5 Postoperative Hemodynamic Monitoring

Time	Group-A			Group-B		
	Pulse (Per min)	Blood pressure (mm of Hg)		Pulse (Per min)	Blood pressure (mm of Hg)	
		Systolic	Diastolic		Systolic	Diastolic
150 min	73.84	116.56	72	77.4	120.08	75.92
180 min	77.76	118.64	75.28	78.72	119.84	76.4
240 min	77.4	120.08	75.92	80.68	120.96	75.6
300 min	81.84	122.08	78.08	81.68	121.76	77.84
360 min	82.88	122.8	77.68	82.84	122.48	77.44
420 min	84.16	123.12	77.92	84.2	122.88	77.84
480 min	84.92	123.44	77.92	84.96	123.6	78.08
540 min	83.12	125.52	78.4	82.96	125.28	78.48
600 min	82.68	126.88	80.8	82.52	126.64	80.48
720 min	83.92	124.88	82.0	83.6	124.72	81.6
840 min	84.56	124.64	83.12	84.32	124.48	82.64

Table 5 shows that there was statistically insignificant difference between two groups with regards to hemodynamic parameters.

Table-6 Total duration of analgesia

Time in Minutes	No. of Patients	
	Group A	**Group B**
300-350	2	0
351-400	6	0
401-450	17	0
451-500	0	0
501-550	0	5
551-600	0	13
601-650	0	7
Mean time $\pm$ S.D.	408 $\pm$ 30.27	580.8 $\pm$ 34.87

Table 6 shows highly significant difference between total duration of analgesia in both groups($p<0.01$).

Table-7 Peri Operative Complications

Complications	**No. of Patients**			
	Group-A		**Group-B**	
	Intra-Op.	**Post-Op.**	**Intra-Op.**	**Post-Op.**
Nausea / Vomiting	0	0	0	0
Hypotension	5(20%)	0	9(36%)	0
Bradycardia	5(20%)	0	5(20%)	0

Respiratory depression	0	0	0	0
Shivering	0	0	0	0

Table 7 shows that more hypotention noted in group B than group A and incidence of bradycardia was same in both groups.

DISCUSSION

Effective control of post operative pain remains one of the most important and pressing issues in the field of surgery and anesthesia with significant impact on our health care system.

The aim of this study was to evaluate that nitroglycerine patch (source of exogenous NO) would enhance the analgesic efficacy of intrathecal neostigmine (source of acetylcholine) with bupivacaine.

The study was conducted by taking 50 randomly selected patients for various surgeries. Patients were divided into 2 groups.

Group-A : 0.5% heavy bupivacaine 3 ml (15 mg) + neostigmine 5 mcg.

Group-B : 0.5% heavy bupivacaine 3 ml (15 mg) + neostigmine 5 mcg + transdermal nitroglycerine patch (5 mg/24 hours).

Naguib M et al[5] in 1997 studied increased level of acetyl choline binds to muscarinic and nicotinic receptors in the spinal cord dorsal horn and neostigmine increase level of acetylcholine in cerebrospinal fluid and acetylcholine bioavailability at cholinergic nerves within the spinal cord. Acetylcholine causes analgesia through direct action on spinal cholinergic muscarinic receptors M1, M3 and indirectly through the second messenger Nitric Oxide in spinal cord.

- The objective of our study was to observe effect of transdermal nitroglycerine patch on the efficacy of low dose of intrathecal neostigmine with bupivacaine.

Characteristics Of Sensory Blockade:

- **Ahmed et al[1] in 2010** studied that onset of sensory block was faster in neostigmine using groups. There was no statistically significant difference was present regarding duration of regression time of sensory block by two segments.
- In our study there was no statistically significant difference present regarding time of onset of sensory blockade as it was 3.12+0.60 min in Group A and 3.52+0.96 min in Group B (P>0.05).There was no statistically significant difference present regarding time of two segment regression of sensory block as it was 136± 35.08 min in Group A and 139.72± 3.57 min in Group B (P>0.05).

Characteristic Of Motor Blockade :

- **Ahmed et al[1] in 2010** studied that there was no significant difference between onset and duration of motor block in neostigmine using group as compared to other groups.
- In our study we did not find any significant difference between two groups regarding time to achieve complete motor blockade as it was 5.48+0.87 min in Group A and 5.52+0.87 min in Group B (P>0.05). we did not find any significant difference between two groups regarding duration of motor block as it was 200 ± 6.75min in Group A and 201± 6.84 min in Group B (P>0.05).

Hemodynamics Monitoring :

Gabrriela et al[3] in (2000) observed no bradycardia and hypotension in their study.

- In our study we observed bradycardia in both groups in intraoperative period. There was significant fall in blood pressure noted after 25 min in Group B**(**106.32± 4.44,65.68 ±4.02 mins) as compare to Group A (107.52± 4.87, 64.8±5.22 mins)patiets. Thereafter blood pressure was comparable in both the groups. There was no significant difference between two groups regarding postoperative hemodynamic monitoring in both groups upto 12 hrs.

Total Duration Of Analgesia :

- **Anand et al[2] in 2008** studied that duration of analgesia was longer in intrathecal neostigmine(50 mcg) group (322.2+25.76 min) as compare to bupivacaine(15

mg) group(185.8+10.90min).

- In our study there was significant difference between total duration of analgesia as it was longer duration in Group B (580±34.87 mins) as compare to Group A (408±30.27 mins) (P<0.05).

Peri operative Complications :

- In our study incidences of hypotension were more in Group B (36%)as compare to Group A (20%).
- In our study 5 patients in each group had bradycardia.
- Any other complications like nausea, vomiting, respiratory depression and shivering were not present in both the groups.

CONCLUSION

In our study of 50 patients we observed that intrathecal neostigmine 5 mcg with bupivacaine 15 mg with transdermal nitroglycerine patch(5 mg/day) markedly prolong duration of post operative analgesia than intrathecal neostigmine with bupivacaine alone. Intraoperative complication like bradycardia do occur but it was not significant, and other complication like hypotension occur with both groups but more in group B which requires monitoring .

So from this study it can be concluded that transdermal nitroglycerine patch increases post operative analgesia of low dose intrathecal neostigmine with bupivacaine in spinal anesthesia with less side effects.

CONFLICT OF INTEREST:None

SOURCE OF SUPPORT: Nil

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