Brief Communications

Transdermal nitroglycerine enhances the post-operative analgesic effect of intrathecal clonidine in abdominal hysterectomies

INTRODUCTION

Clonidine is frequently used as an adjuvant in spinal anaesthesia to enhance the quality and duration of post-operative analgesia,[1-3] transdermal nitroglycerine (tNTG) has been found to be useful for enhancing the post-operative analgesic effect of intrathecal (IT) sufentanil[4] and neostigmine[5] by release of nitric oxide (NO). This NO increases the intracellular concentration of cyclic guanosine monophosphate (cGMP), which produces pain modulation in the central and peripheral nervous system.[6,7] We have carried out this study to evaluate the effect of tNTG on IT clonidine.

METHODS

This was a prospective, randomized, placebo-controlled, double-blind study. Ethical approval was taken from the local ethical committee. ASA grade I or II patients scheduled for elective total abdominal hysterectomy, aged between 30 and 50 years and weighing between 45 and 65 kg were included. Patients with a contraindication to spinal anaesthesia and major neurological, cardiovascular, metabolic, respiratory, hepatic, renal disease or coagulation abnormalities were excluded from the study.

Patients were randomized by a computer into one of four groups (group B, BN, BC and BCN), consisting of 30 subjects each. Pain was assessed by the Visual Analog Score (VAS) scale. Heart rate and blood pressure were recorded at baseline and periodically.

After lumbar puncture, patients in the four groups (group B, BN, BC and BCN) received different combination of drugs [Table 1]. Fifteen degree head-down tilt was given after intrathecal drug administration. The nitroglycerin patch (Nitroderm TTS; Novartis Pharma, Global headquarters-Basel, Switzerland) was applied on non-anaesthetized area which has a total nitroglycerin content of 25 mg per patch and delivered nitroglycerin at 20–25 μg/cm^2.h. The placebo patch was prepared by cutting the ECG electrode in the same shape as the tNTG patch. The drug combinations and placebo patch were prepared by the first anaesthesiologist; however, various observations were made by a second anaesthesiologist who was involved after the procedure had been performed. The cephalad spread of analgesia and the degree of motor blockade of the lower limbs was recorded every minute. The level of sensory blockade was assessed by loss of sensation to pin prick. Motor blockade was determined according to the Bromage scale.[8]

Patients were allowed to receive rescue analgesics on demand. Duration of analgesia was measured as time from intrathecal drug administration to the patient's first request for analgesic. Rescue analgesia was provided by injection diclofenac sodium 75 mg intramuscular (IM) in the gluteal region and requirement was recorded for 24 h. The duration of motor block was calculated from the time of attainment of Bromage Grade IV motor blockade (onset of motor block) till the reversal to Bromage Grade II. The tNTG patch or placebo patch was removed after 24 h.

Statistical analysis was done using analysis of variation (ANOVA). P value<0.05 was considered statistically significant. Data were presented as mean value±SD.

RESULTS

A total of 120 patients were enrolled in the study. The time interval from intrathecal drug administration to 2-segment sensory regression was significantly prolonged in group BC (36±19 min) and BCN (139±21 min) as compared with group B (80±19 min) and BN (88±17 min) ($P<0.0001$) [Table 2]. Duration of motor blockade was 115±13 min, 116±11 min, 160±19 min and 164±18 min in the B, BN, BC and BCN groups, respectively [Table 2]. Statistical significance was found in group BC and group BCN as compared with group B and group BN.

Table 1: Different combinations of drugs received by the four groups

Groups	Group B (n=30)	Group BN (n=30)	Group BC (n=30)	Group BCN (n=30)
Bupivacaine (intrathecal)	15 mg hyperbaric bupivacaine	15 mg hyperbaric bupivacaine	15 mg hyperbaric bupivacaine	15 mg hyperbaric bupivacaine
Saline or clonidine (intrathecal)	0.5 mL of saline	0.5 mL of saline	50 μg of clonidine	50 μg of clonidine
Transdermal patch	Placebo patch	tNTG patch	Placebo patch	tNTG patch

Table 2: Characteristics of sensory and motor blockade				
Groups	**Group B (*n*=30)**	**Group BN (*n*=30)**	**Group BC (*n*=30)**	**Group BCN (*n*=30)**
%Time for 2 segment regression (min.)	80±19	88±17	136±19	139±21
#Total duration of analgesia (min.)	120±21	136±19	302±54	464±48
@Onset of motor block (min.)	9±1.06	8.23±1.2	8.4±1.3	8.6±1.4
$Total duration of motor block (min.)	115±13	116±11	160±19	164±18
¥No. of IM diclofenac in 24 hrs	3.20 (3–4)	3.17 (3–4)	1.63 (1–2)	1.30 (1–2)

%Statistical significance between Gp. B & Gp. BN (P<0.05)**; Gp. B & Gp. BC(P<0.0001)***; Gp. B & Gp. BCN (P<0.0001)***; Gp. BN & Gp. BC (P<0.0001)***; Gp. BN & Gp. CN (P<0.0001)***; Gp. BC & Gp. BCN (P<0.0001)**; #Statistical significance between Gp. B & Gp. BN (P<0.05)**; Gp. B & Gp. BC (P<0.0001)***; Gp. B & Gp. BCN (P<0.0001)***; Gp. BC & Gp. BCN (P<0.0001)***; Gp. BN & Gp. BC(P<0.0001)***; Gp. BN & Gp. BCN (P<0.0001) ***; ¥Statistical significance between Gp. B & Gp. BN (P>0.05)*; Gp. B & Gp. BC (P<0.0001)***; Gp. B & Gp. BCN (P<0.0001)***; Gp. BC & Gp. BCN (P<0.0001) ***; Gp. BN & Gp. BC(P<0.0001)***; Gp. BN & Gp. BCN (P<0.0001)***; Foot notes: Gp-group, *P>0.05 (Non-Significant); **P<0.05 (Significant); ***P<0.0001 (Highly Significant); @Bromage Grade IV; $ Return to Bromage Grade II

Table 3: Sedation score	
0	Awake, alert
1	Mild sedation, easy to rouse
1S	Asleep, easy to rouse
2	Moderate sedation, unable to remain awake
3	Difficult to rouse

Table 4: Characteristics of haemodynamics and incidence of side-effects (intra-operative and early post-operative period)				
Groups	**Bradycardia**	**20% fall in MAP**	**PO headache**	**PO nausea and vomiting**
Group B	2	3	0	2
Group BN	3	1	2	0
Group BC	1	11	1	3
Group BCN	0	12	0	0

PO: Post-operative; MAP: Mean arterial pressure; #Fall of BP>20% from base level; $HR<60 min. It was statistically not significant between the groups

Mean time to rescue analgesia was significantly prolonged in group BCN (464±48 min) as compared with group BC (302±54 min) (P<0.0001). In groups BC and BCN, the mean VAS score at 2 h was zero (no pain), and it rose to 29.2±4 and 28.3±3, respectively, at the time of giving rescue analgesia. The total number of intramuscular diclofenac requirements in 24 h was less in group BC (mean 1.63) and group BCN (mean 1.30) (P<0.0001). On comparison of group B (120±21 min) with group BC (302±54 min), the mean time for rescue analgesia was found to be statistically significant. The VAS score at 2 h in group B and group BN was 27.5±6 and 26.3±5, respectively. It rose to 29.4±7 and 28.5±6 at the time of giving rescue analgesia. The number of IM diclofenac in 24 h was higher for group B (mean 3.20) and group BN (mean 3.17).

As per the sedation score [Table 3], 18 patients were sedated in group BC and 16 patients in group BCN. None of the patients were sedated in groups B and BN.

Post-operative nausea, vomiting, headache, bradycardia and hypotension were not statistically significant in the different groups [Table 4].

DISCUSSION

In the present study, addition of tNTG patch to 0.5% heavy bupivacaine and 50 μg IT clonidine significantly prolonged the time to rescue analgesia in the immediate post-operative period without significant side-effects. Thus, it decreased the requirement of IM diclofenac injections. Studies have been done in the past to investigate the effect of tNTG on IT sufentanil, fentanyl and neostigmine. In a study of orthopaedic surgery, the time to first rescue analgesia was longer for the sufentanil-NTG group (785±483 min) as compared with the other groups.[4] In our previous study, we showed that tNTG patch enhanced the analgesic effect of IT fentanyl in gynaecological surgeries.[9]

Combination of both intrathecal neostigmine and tNTG was found in an average of 14 h of effective analgesia after vaginoplasty, but neither alone.[5] tNTG prolonged the mean duration of post-operative analgesic effect of neostigmine in patients with abdominal hysterectomies in our previous study.[10] tNTG also enhances the antinociceptive effect of epidural S (+) ketamine.[11] In the present study, tNTG along with IT bupivacaine delayed the time to rescue analgesia but it did not change the requirement of IM diclofenac injections significantly as compared with bupivacaine alone.

The possible mechanism of analgesia by IT clonidine is through release of acetylcholine, which may act directly on spinal cholinergic receptors subtypes as well as indirectly through the stimulation of release of the second messenger NO in the spinal cord. tNTG could have enhanced the analgesic effect of clonidine by providing NO source.

CONCLUSION

In this study, tNTG has enhanced the post-operative analgesic effect of IT clonidine without any significant

alteration of haemodynamics and increase in incidence of nausea and vomiting. The effect was synergistic and possibly mediated through NO.

Mamta Khandelwal, Fareed Ahmed, Ashish Garg, AP Verma, Aquil, CS Chatterjee

Department of Anesthesiology, SMS Medical College, Jaipur, Rajasthan, India

Address for correspondence:
Dr. Mamta Khandelwal,
A-7, Vaishali Nagar, Near Police Station, Jaipur, Rajasthan, India.
E-mail: drmamtakhandelwal@gmail.com

REFERENCES

1. Eisenach JC, De Kock M, Klimscha W. Alpha (2)-adrenergic agonists for regional anaesthesia. A clinical review of clonidine (1984–1995). Anesthesiology 1996;85:655-74.
2. Dobrydnjov I, Axelsson K, Samarutel J, Holmstrom B. Postoperative pain relief following intrathecal bupivacaine combined with intrathecal or oral clonidine. Acta Anaesthesiol Scand 2002;46:806-14.
3. Bonnet F, Buisson VB, Francois Y, Catoire P, Saada M. Effects of oral and subarachnoid clonidine on spinal anesthesia with bupivacaine. Reg Anesth 1990;15:211-4.
4. Lauretti GR, de Oliveira R, Reis MP, Mattos AL, Pereira NL. Transdermal nitroglycerin enhances spinal sufentanil postoperative analgesia following orthopedic surgery. Anesthesiology 1999;90:734-9.
5. Lauretti GR, Oliveira AP, Julião MC, Reis MP, Pereira NL. Transdermal nitroglycerin enhances spinal neostigmine postoperative analgesia following gynecological surgery. Anesthesiology 2000;93:943-6.
6. Duarte ID, Lorenzetti BB, Ferreira SH. Acetylcholine induces peripheral analgesia by the release of nitric oxide from l-arginine. In: Moncada S, Higgs EA, editors. A bioregulatory system. Amsterdam: Elsevier; 1990. p. 165-70.
7. Zhuo M, Meller ST, Gebhart GF. Endogenous nitric oxide is required for tonic cholinergic inhibition of mechanical transmission. Pain 1993;54:71-8.
8. Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. Acta Anaesthesiol Scand 1965;16:55-9.
9. Garg A, Ahmed F, Khandelwal M, Chawla V, Verma AP. The effect of transdermal nitrogycerine on intrethecal fentanyl with bupivacaine for post operative analgesia following gynaecological surgery. Anaesth Intensive Care 2010;38:285-90.
10. Ahmed F, Garg A, Chawla V, Khandelwal M. Transdermal nitroglycerine enhances post operative analgesia of intrathecal neostigmine following abdominal hysterectomies. Indian J Anaesth 2010;54:24-8.
11. Lauretti GR, Oliveira AP, Rodrigues AM, Paccola CA. The effect of transdermal nitroglycerin on epidural S (+)-Ketamine antinociception following orthopedic surgery. J Clin Anesth 2001;13:576-81.

Access this article online	
Quick response code	Website: www.ijaweb.org
	DOI: 10.4103/0019-5049.93352