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Research Article

Transdermal nitroglycerine potentiates the analgesic effect of patient controlled epidural analgesia after lower abdominal surgery

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KEYWORDS

Transdermal nitroglycerine;
Combined general epidural anesthesia

Abstract *Background:* This study was designed to evaluate the effect of pre-emptive use of transdermal nitroglycerine (NTG) patch as an adjuvant to combined general epidural anesthesia (CGEA) in patients undergoing lower abdominal surgery.
Method: Forty patients (ASA I or II) were randomly allocated to two equal groups; control group (group C) and nitroglycerine group (group NG). Nitroderm patch, 5 mg, was applied to patients in group NG, 2 h before surgery. All patients received epidural bolus of 18 ml of 0.25% bupivacaine with fentanyl 2 μg/ml followed by continuous infusion at the rate of 5 ml/h combined with general anesthesia. Patients used patient controlled analgesia (PCA) device to receive bolus dose of 5 ml of patient controlled epidural analgesia (PCEA) solution containing bupivacaine 0.125% and fentanyl 2 μg/ml after surgery. Perioperative mean arterial blood pressure (MAP) and heart rate (HR), time to first rescue analgesic, postoperative bupivacaine and fentanyl consumption, and VAS pain scores were measured for 24 h postoperatively. Patient satisfaction score was also recorded.
Results: Postoperative MAP and HR increased significantly to both baseline and the other group at 2 h in group C and at 4 h in group NG ($p < 0.05$). The time to first rescue analgesic was significantly longer in group NG (238.62 ± 54.3 min) than in group C (126.75 ± 35.1 min) ($p < 0.05$). Pain scores were significantly higher compared to the other group at 2 h in group C and at 4 h in group NG ($p < 0.05$). Postoperative bupivacaine and fentanyl consumption were significantly

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lower in group NG (74.91 ± 26.34 mg and 121.83 ± 32.5 μg, respectively) than in group C (118.68 ± 29.4 mg and 194.21 ± 45.31 μg, respectively). Patient satisfaction was significantly better in group NG than in group C ($p < 0.05$).

Conclusion: Pre-emptive application of 5 mg transdermal nitroglycerine patch as adjuvant to CGEA provided significant prolongation of the postoperative analgesia and reduction of the postoperative bupivacaine and fentanyl consumption.

1. Introduction

Nitric oxide (NO) or NO donors have been reported to contribute to the analgesia produced by morphine through activation of cyclic guanosine monophosphate (cGMP). There is evidence that endogenous NO is necessary to inhibit nociceptive transmission [1–3].

Because of the multiple mechanisms involved in postoperative pain, a multimodal analgesic regimen could be used to enhance analgesic efficacy and reduce unwanted side effects [4].

Data from the literature suggest that in humans high dose nitroglycerine (NTG) patches (NO donor), such as 30 mg daily, are hyperalgesic, whereas doses less than 6 mg/day are analgesic under different circumstances [5,6]. Transdermal NTG patches improved oral morphine and ketamine analgesia for cancer pain management [7].

The use of NTG patches for intraoperative and postoperative pain control has been studied [8,9].

Several researches stated that NTG patch application in addition to neuroaxial S(+)-ketamine, neostigmine or sufentanil [9,10,5], enhance postoperative analgesia and reduce the need for other analgesic medication.

The present study was designed as a randomized double blinded controlled study to evaluate the efficacy of pre-emptive usage of transdermal patch 5 mg as adjuvant to combined general epidural anesthesia in patients undergoing lower abdominal surgery. Perioperative hemodynamics, postoperative local anaesthetic and fentanyl requirements and postoperative analgesia were studied.

2. Materials and methods

After obtaining Ethics and Research Committee approval and informed written consent, 40 patients aged 20–60 years, ASA physical status I or II, scheduled for lower abdominal surgery under combined general/epidural anaesthesia (CGEA) were studied. Exclusion criteria included cerebrovascular, neurological disorder, history of major back disease or known allergy to amide local anaesthetics. The night before surgery all patients were instructed on the use of patient controlled epidural analgesia (PCEA) device and how to assess their pain using a 10-cm visual analogue score (VAS), with 0 representing no pain at all and 10 representing the worst imaginable pain.

Patients were randomly allocated using computer-generated randomization to two equal groups ($n = 20$), control group (group C) and nitroglycerine group (group NG). Two hours before surgery, an assistant anaesthetist not involved in data collection applied a transdermal nitroglycerine patch, 5 mg (Nitroderm® TTS 5, Novartis Pharma, AG Basle, Switzerland) at the patients' chest wall and covered it with a sterile gauze and tape in group NG or applied a sterile gauze of same size and shape only in group C. All patients were premedicated with i.v. 0.02 mg/kg midazolam in the holding room.

On arrival to the operating room (OR) standard monitors were applied (Viralert 2000, North American Dräger) and heart rate (HR), mean arterial blood pressure (MAP) and oxygen saturation were recorded.

Before induction of general anesthesia (GA), all patients received fluid preload consisting of 10 ml/kg i.v. lactated Ringer's solution. Then, an epidural puncture was performed under complete aseptic condition with a 18-gauge Tuohy needle inserted at the L2–3 or L3–4 interspace using loss of resistance to saline technique. A 20-gauge catheter was inserted cephalad 4–5 cm into the epidural space. After negative aspiration of blood and cerebrospinal fluid, the proper placement was tested using 3 ml lidocaine 2% containing 1:200,000 epinephrine then, the catheter was secured. An epidural loading dose of 18 ml of bupivacaine 0.25% plus 2 μg/ml fentanyl was administered to achieve a sensory level at T10. The effect of somatosensory blockade was tested bilaterally at the midclavicular line after 15–30 min by dull and sharp end of safety pin and alcohol-soaked swab. The block was maintained with continuous infusion of 0.25% bupivacaine with fentanyl 2 μg/ml at the rate of 5 ml/h, started 1 h after the loading dose until the end of surgery.

After preoxygenation, general anaesthesia was induced in all patients with intravenous fentanyl 2 μg/kg and propofol 2–3 mg/kg. Vecuronium 0.08 mg/kg was used to facilitate tracheal intubation. General anaesthesia was maintained with isoflurane (0.5–1 minimum alveolar concentration) in 100% oxygen and vecuronium. All patients were mechanically ventilated to maintain end-tidal carbon dioxide between 35 and 40 mmHg. The anesthesiologist involved in data collection was blinded to the group assignment.

Hypotension (defined as a drop of MAP more than 20% of preoperative value) was treated with a fluid challenge of 300 ml of lactated Ringer's solution followed by boluses of 5 mg ephedrine if necessary.

MAP and HR were recorded before epidural anaesthesia (base line T0), before induction of general anaesthesia (T1), immediately after induction (T2) and every 10 min intraoperatively till the end of surgery [mean intraoperative value (T3)].

At completion of surgery inhalational anaesthetic was discontinued, residual neuromuscular block was antagonized with atropine 0.02 mg/kg and neostigmine 0.08 mg/kg.

After extubation, patients were transferred to the surgical intensive care unit (SICU). All patients received oxygen via nasal catheter at FIO_2 0.4. Each patient was reminded of how to operate the PCEA device after receiving an initial dose of 5 ml of PCEA solution containing bupivacaine 0.125% and fentanyl 2 μg/ml at the first trigger. The subsequent PCEA was set to deliver a bolus dose of 5 ml with lock-out of 15 min and a 4 h limit of 40 ml without continuous basal infusion. If

analgesia was inadequate (VAS pain score > 3), 5 ml bolus was given. The time interval from PACU admission to first PCEA trigger, total bupivacaine and fentanyl consumption in the first postoperative 24 h were recorded for all patients.

Sedation score, VAS pain score, MAP and HR were recorded at 1, 2, 4, 8, 12 and 24 h postoperatively. Sedation was assessed using five point scoring system: 0 = aware, 1 = drowsy, 2 = asleep/easily respond to verbal command, 3 = asleep/difficult response to verbal command, 4 = asleep/no responses to verbal command [11].

The degree of motor blockade was assessed using modified Bromage scale (I = free movement of legs and feet, II = just able to flex the knee with free movement of the feet, III = unable to flex the knee but with free movement of the feet, IV = unable to move legs or feet) [12].

Incidence of postoperative side-effects [e.g. nausea and vomiting, respiratory depression (defined as RR < 10 breath/min), hypotension, pruritis, constipation, urinary retention, dizziness and drowsiness, Bromage score > 0] were recorded and managed as necessary. Ondansetron 0.1 mg/kg i.v. was given as an anti-emetic if required in the postoperative period.

At 24 h postoperative, patient satisfaction with their postoperative analgesia was assessed using a 101-point verbal rating scale (VRS), with 0 = highly dissatisfied to 100 = completely satisfied.

2.1. Statistical analysis

Assuming that a difference of 20% or more in postoperative fentanyl consumption would be of clinical interest, a sample size of 20 patients/group was calculated to achieve a power of 80% and a significance level of 0.05.

Statistical analysis was performed using SPSSwin statistical package version 15 (SPSS Inc., Chicago, IL). Data was presented as mean (SD), median (range) or number (%) as appropriate. Comparison between the two groups was performed using unpaired Student's *t*-test. Sedation scores were compared between the two group using Mann–Whitney test. Intragroup comparison relative to baseline was performed using repeated measure analysis (ANOVA) with post hoc Dunnet's test if ANOVA results were significant. Categorical variables were compared using Chi-square test (Fisher's exact test) as appropriate. A p value <0.05 was considered significant.

3. Results

Fifty-two patients were assessed for study eligibility, five patients failed to meet the inclusion criteria and seven were excluded due to study violations. The remaining 40 patients were able to complete the entire study and their data were included in the final analysis. Both groups were comparable with respect to age, sex, ASA physical status, and duration of surgery (Table 1).

Intraoperative MAP and HR showed significant reduction at T2 and T3 compared to baseline in both groups with no intergroup difference. Postoperatively, MAP and HR were significantly higher at T5 in the group C and at T6 in group NG compared to baseline and to the other group ($p < 0.05$) (Figs. 1 and 2).

Time from SICU admission to first analgesic demand (PCEA) were significantly longer in group NG than the group C ($p < 0.01$). Total bupivacaine and fentanyl consumed in the first postoperative 24 h were significantly less in group NG compared to group C ($p < 0.01$) (Table 2).

In the control group VAS pain scores were significantly higher at 2 h postoperatively compared to the nitroglycerine group while at 4 h a significantly higher score was observed in group NG than in the group C ($p < 0.05$). Subsequently, both groups showed comparable pain scores till the end of the study period (Fig. 3). Sedation scores were comparable in both groups at all time intervals (Table 3).

Incidence of postoperative nausea, vomiting, pruritis and usage of anti-emetic treatment were less frequent in group NG than in group C but the difference was statistically insignificant ($p > 0.05$). Two patients in group NG experienced transient motor block (Bromage score > 0) compared to four patients in group C ($p > 0.05$) (Table 4).

Postoperative oxygenation was satisfactory in all patients during the study period (none of the patients had respiratory depression in both groups).

Patient satisfaction with their postoperative pain management was significantly greater in group NG than in group C ($p < 0.01$) (Table 2).

Table 1 Demographic data of both groups [mean ± SD, number or ratio].

	Group C $n = 20$	Group NG $n = 20$
Age	42.3 ± 12.3	43.6 ± 9.7
Male/female	8/12	9/11
ASA (I/II)	13/7	12/8
Weight (kg)	73.4 ± 8.5	69.7 ± 9.1
Height (cm)	161.7 ± 6.7	163.4 ± 5.3
Duration of surgery (min)	151.6 ± 28.3	149.7 ± 32.4

ASA = American Society of Anaesthesiologists.
Group C = control group; group NG = nitroglycerine group.

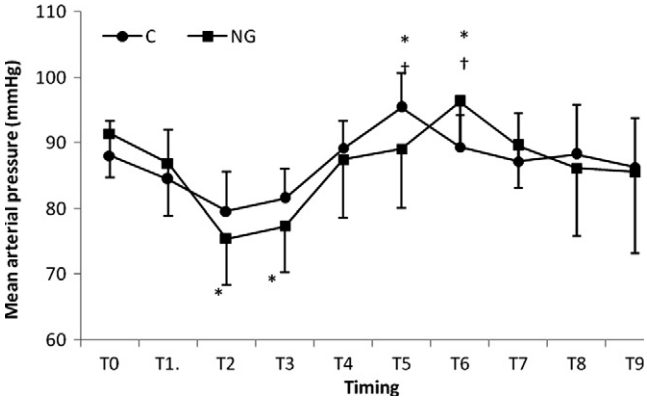

Figure 1 Perioperative mean arterial blood pressure (MAP) values of both groups. Values are means and error bares represent standard deviation. C = control group; NG = nitroglycerine group. T0: before epidural anaesthesia (base line); T1: before induction of general anaesthesia; T2: immediately after induction; T3: mean intraoperative value; T4–T9: 1, 2, 4, 8, 12 and 24 h postoperatively. $^{*}p < 0.05$ compared to baseline. $^{\dagger}p < 0.05$ compared to the other group.

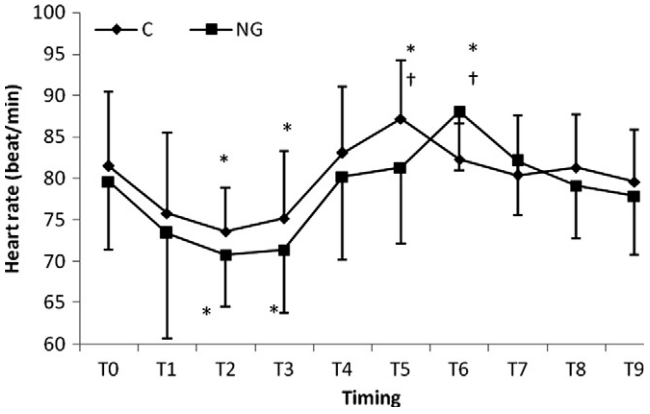

Figure 2 Perioperative heart rate (HR) values of both groups. Values are means and error bares represent standard deviation. C = control group; NG = nitroglycerine group. T0: before epidural anaesthesia (base line); T1: before induction of general anaesthesia; T2: immediately after induction; T3: mean intraoperative value; T4–T9: 1, 2, 4, 8, 12 and 24 h postoperatively. $^{*}p < 0.05$ compared to baseline. $^{\dagger}p < 0.05$ compared to the other group.

Table 2 Postoperative data of both groups [mean ± SD].

	Group C $n = 20$	Group NG $n = 20$	p value
Time to 1st analgesic dose (min)	126.75 ± 35.1	238.62 ± 54.3*	<0.001
Total bupivacaine consumption in 24 h (mg)	118.68 ± 29.4	74.91 ± 26.34*	<0.001
Total fentanyl consumption in 24 h (μg)	194.21 ± 45.31	121.83 ± 32.5*	<0.001
Patient satisfaction VRS	85.5 ± 7.6	91.3 ± 5.6*	0.009

Group C = control group; group NG = nitroglycerine group.
* $p < 0.01$ compared with control group.

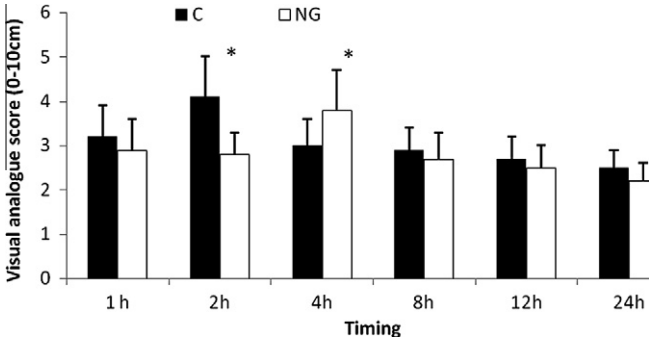

Figure 3 Postoperative visual analogue scale in both groups. Values are means and error bars represent standard deviation. C = control group; NG = nitroglycerine group. $^{*}p < 0.05$ compared to the other group.

Table 3 Sedation score of both groups [median (range)].

	Group C $n = 20$	Group NG $n = 20$
1 h	2 (1–2)	2 (0–2)
2 h	2 (1–2)	1 (0–2)
4 h	2 (1–2)	2 (0–2)
8 h	1 (0–2)	1 (0–2)
12 h	1 (0–2)	0 (0–1)
24 h	1 (0–2)	0 (0–1)

Group C = control group; group NG = nitroglycerine group.

Table 4 Incidence of postoperative complications of both groups [number (%)].

	Group C $n = 20$	Group NG $n = 20$
Nausea	6 (30%)	3 (15%)
Vomiting	3 (15%)	1 (5%)
Pruritis	4 (20%)	1 (5%)
No. of patients required anti-emetic	5 (25%)	2 (10%)
Bromage score		
I	16 (80%)	18 (90%)
II	3 (15%)	2 (10%)
III	1 (5%)	0

Group C = control group; group NG = nitroglycerine group.

4. Discussion

The current study shows that, pre-emptive usage of 5 mg transdermal nitroglycerine patch (NO donor) in patient undergoing lower abdominal surgery using combined general epidural anesthesia (CGEA) resulted in significant prolongation of postoperative analgesia, decreased postoperative analgesic consumption and reduced postoperative related side effect than the control group.

The aim of combining different analgesic drugs and techniques is to obtain synergistic or additive action which allows the use of a smaller dose of each agent, hence improving the safety profile and reducing related side effects [13].

As regarding the intraoperative analgesia, no significant changes occurred on adding nitroglycerine. This was evidenced by insignificant differences in intraoperative hemodynamics which could be explained by adequacy of analgesia provided by other modalities of analgesics used in both groups.

Transdermal nitroglycerine patch application as adjuvant to PCEA in the present work enhanced postoperative analgesia for 24 h after surgery. It was evidenced by delayed first analgesic rescue and significantly less PCEA bupivacaine/fentanyl consumption in nitroglycerine group vs. the control group.

The time recorded to first analgesic trigger was significantly shorter in the (group C) than in the (group NG) [126.75 ± 35.1 vs. 238.62 ± 54.3 min, respectively]. This coincided with the postoperative changes in hemodynamics and VAS scores. This may be due to fading effect of epidural analgesia by that time in (group C) and the synergistic effect of nitroglycerine patch in (group NG).

The comparable postoperative VAS pain scores in both groups at 6 h postoperatively and till the end of the study period could be attributed to the usage of PCEA. However, patients in the (group NG) required a significant less amount of bupivacaine/fentanyl to achieve this analgesic effect than (group C).

These findings are in accordance with Yamangushi and Naito [14] who stated that NO interacts synergistically with morphine after intravenous or spinal administration. Other studies of acute postoperative pain reported that transdermal nitroglycerine patch prolonged postoperative analgesia when combined with intrathecal sufentanil or neostigmine [5,10]. Previous researches also showed that daily application of 5 mg transdermal nitroglycerine patch enhanced the analgesic effect of oral morphine analgesia in chronic cancer pain without increasing the frequency of adverse effects [7,15]. Lauretti et al. [9] stated that the association of 5 mg transdermal nitroglycerine patch prolonged the analgesic action of 0.1 mg/kg epidural S(+)-ketamine). In another study, Garg et al. [16] demonstrated an increase in total effective analgesia in patients undergoing gynaecological surgery using intrathecal bupivacaine and fentanyl with transdermal nitroglycerine.

The mechanism by which NO enhances analgesia is not clear. NO is a molecule with different effects; although it is essential in nociception, it is also an important messenger in tonic cholinergic pain inhibition [17]. NO-cyclic guanosine monophosphate (cGMP) cascade is involved in acetylcholine- or morphine-induced peripheral antinociception [3].

The activation of descending pain pathway has been shown to involve the participation of NO through a mechanism of action that is likely to include activation of second messengers such as cGMP [18]. Wide-dynamic-range neurons in the superficial dorsal horn and high-threshold cells in the superficial or deep layers show reduced response after exposure to (cGMP) [17].

Intrathecal or epidural fentanyl acts mainly on neurons with opioid receptors in lamia III of the dorsal horn as well as in lamina V and VII, producing a segmental antinociceptive effect [19]. Neurons containing nitric oxide synthase have been found in lamina I–III of the dorsal horn [20].

Other investigators have described the activation of adenosine triphosphate (ATP) sensitive potassium channels by NO resulting in peripheral antinociception [21].

Another possible mechanism is NO peripheral effect. Its vasodilator action on the venous system decreases the vasoconstrictor tone induced by the inflammatory process and further reduces the oedema formation [6]. NO generators also induce anti-inflammatory effects and analgesia by blocking hyperalgesia and neurogenic components of inflammatory oedema [22].

Basic research demonstrated that nitroglycerine activated varied sets of brain nuclei following systemic administration via the intervention of selected neurotransmitters and neuromediators. This could support the possibility that nitroglycerine may act as non-opioid analgesic [23].

The lower incidence of postoperative nausea, vomiting and itching in (group NG) compared to the (group C) recorded in the present work could be explained by significantly lower postoperative fentanyl consumption in the nitroglycerine group than in control group.

In conclusion, pre-emptive usage of transdermal nitroglycerine 5 mg (NO generator) 2 h before surgery as adjuvant to CGEA as a part of multimodal analgesia in lower abdominal surgery provided significant prolongation of postoperative analgesia, reduction of postoperative bupivacaine and fentanyl requirements with reduced related side effects and high patients satisfaction.

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