

Transdermal Nitroglycerine Enhances Spinal Sufentanil Postoperative Analgesia following Orthopedic Surgery

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Background: Sufentanil is a potent but short-acting spinal analgesic used to manage perioperative pain. This study evaluated the influence of transdermal nitroglycerine on the analgesic action of spinal sufentanil in patients undergoing orthopedic surgery.

Methods: Fifty-six patients were randomized to one of four groups. Patients were premedicated with 0.05–0.1 mg/kg intravenous midazolam and received 15 mg bupivacaine plus 2 ml of the test drug intrathecally (saline or 10 µg sufentanil). Twenty to 30 min after the spinal puncture, a transdermal patch of either 5 mg nitroglycerin or placebo was applied. The control group received spinal saline and transdermal placebo. The sufentanil group received spinal sufentanil and transdermal placebo. The nitroglycerin group received spinal saline and transdermal nitroglycerine patch. Finally, the sufentanil–nitroglycerin group received spinal sufentanil and transdermal nitroglycerine. Pain and adverse effects were evaluated using a 10-cm visual analog scale.

Results: The time to first rescue analgesic medication was longer for the sufentanil–nitroglycerin group (785 ± 483 min) compared with the other groups ($P < 0.005$). The time to first

rescue analgesics was also longer for the sufentanil group compared with the control group ($P < 0.05$). The sufentanil–nitroglycerin group required less rescue analgesics in 24 h compared with the other groups ($P < 0.02$) and had lesser 24-h pain visual analog scale scores compared with the control group ($P < 0.005$), although these scores were similar to the sufentanil and nitroglycerin groups ($P > 0.05$). The incidence of perioperative adverse effects was similar among groups ($P > 0.05$).

Conclusions: Transdermal nitroglycerine alone (5 mg/day), a nitric oxide generator, did not result in postoperative analgesia itself, but it prolonged the analgesic effect of spinal sufentanil (10 µg) and provided 13 h of effective postoperative analgesia after knee surgery. (Key words: Arthroscopy; knee surgery; nitric oxide donor.)

SUFENTANIL is a potent analgesic used to manage perioperative pain associated with spinal block. The onset of analgesia is quicker than with morphine or fentanyl, but the duration of a single injection is shorter.¹ Thus, a continuous infusion or a combination of pharmacologically distinct analgesics is needed.

Previously we observed that patients with past histories of angina who had spinal block, in which the nitroglycerin transdermal patch (a nitric oxide [NO] generator²) was applied prophylactically, required fewer analgesics after operation. Data from the literature suggest that in humans, high-dose nitroglycerin patches, such as 30 mg daily, are hyperalgesic,³ whereas doses less than 6 mg per day are analgesic under different circumstances.^{4–6} The goal of this study was to determine whether a combination of transdermal nitroglycerine would enhance analgesia from a single intrathecal sufentanil administration in patients undergoing orthopedic surgery under intrathecal anesthesia. If clinically demonstrated, the combination of sufentanil and transdermal nitroglycerine would enhance postoperative analgesia while maintaining proper cardiac blood flow, which is already described in the literature.^{7,8}

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Table 1. Group Data

	Control Group (n = 13)	Sufentanil Group (n = 15)	Nitroglycerine Group (n = 13)	Sufentanil/Nitroglycerine Group (n = 15)
Intrathecal (3 ml)	Bupivacaine (15 mg)	Bupivacaine (15 mg)	Bupivacaine (15 mg)	Bupivacaine (15 mg)
Intrathecal supplement (2 ml)	Saline	Sufentanil (10 µg)	Saline	Sufentanil (10 µg)
Transdermal test drug	Placebo	Placebo	Nitroglycerine (5 mg/24 h)	Nitroglycerine (5 mg/24 h)

Methods

The ethics committee of the University of São Paulo's Teaching Hospital, Ribeirão Preto, approved the study protocol. After giving informed consent, 56 patients classified as American Society of Anesthesiologists (ASA) physical status I and II and scheduled for minor orthopedic procedures (arthroscopy or meniscectomy) were randomized by computer to one of four groups and prospectively studied using a placebo-controlled, double-blinded design to examine analgesia and adverse effects. The number of patients was based on preliminary experimental data. We hypothesized that use of intrathecal sufentanil would increase the time to first rescue analgesic by 20% in the population studied, and that use of a transdermal nitroglycerin patch would increase the time to first rescue analgesic by 100% compared with the control group. If we estimated a 40% standard deviation for this prospective power analysis and an alpha value of 0.05, these assumptions would require five patients in each group to yield a 100% increase in the time to the first rescue analgesic. To increase further the power, we observed at least 12 patients in each group. A visual analog scale (VAS), which consisted of a 10-cm line with 0 equaling "no nausea" (VAS N) or "no pain at all" and 10 equaling "worst possible nausea" or "the worst possible pain" was introduced before surgery.

Patients were premedicated with 0.05 to 0.1 mg/kg intravenous midazolam in the holding room. Hydration consisted of 10 ml/kg lactate solution before operation and $10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ after spinal anesthesia. Spinal anesthesia was administered in the operating room at the L3-L4 interspace with the patient in the sitting position. A total volume of 5 ml was injected at 1 ml per 7 s through a 25-gauge spinal needle. The intrathecal drugs were 15 mg hyperbaric bupivacaine (3 ml) plus the test drug (2 ml). Patients were placed supine immediately after spinal injection. The transdermal patch was applied at the thorax, in a nonanesthetized area, 20 to 30 min after the spinal puncture (after hemodynamic stabilization). The drugs (intrathecal and transdermal) were prepared by one anesthesiologist. The second anesthesiolo-

gist who was blinded to the drug selection stayed during the operation and checked the patient after operation. Table 1 describes the control group, sufentanil group, nitroglycerin group, and sufentanil-nitroglycerin group.

Intraoperative sensory loss assessment included the pinprick test 5, 10, and 15 min after the injection. Blood pressure was monitored noninvasively every 5 min during surgery, and heart rate and oxyhemoglobin saturation were monitored continuously during surgery. A decrease in the mean arterial pressure more than 15% below the preanesthetic baseline level was treated by 4-mg incremental doses of ephedrine given intravenously. Decreases in heart rate to less than 50 beats/min were treated with 0.25-mg incremental doses of atropine given intravenously. Intraoperative nausea was scored by the patient using the 10-cm VAS N. The number of patients having nausea (of any degree) or vomiting at any point during operation was noted. Nausea greater than VAS 2/10 cm at any time or vomiting during the study were treated initially with 10 mg intravenous metoclopramide followed by 0.5 mg intravenous droperidol, if necessary. The VAS scores were averaged for patients with more than one episode of nausea.

Postoperative assessment included pain scores, adverse effects, and the duration of motor block, measured from anesthetic injection until the time a Bromage 2 score was achieved.⁹ Patients were free to request rescue analgesics, and someone from the anesthesiology staff was always available to administer the analgesic when it was requested. Intramuscular diclofenac (75 mg) was available. Pain was assessed at the time of first rescue analgesic and 24 h after the spinal puncture by the anesthesiologist who was blinded to the treatment. Nausea and the occurrence of vomiting were assessed during operation and 24 h after the spinal puncture by the same anesthesiologist who was blinded to the treatment. The duration of effective analgesia was measured as the time from intrathecal drug administration to the patient's first request for analgesic administration in the recovery room or the infirmary, and it was recorded in minutes. The VAS at the time of first rescue analgesic

Table 2. Demographic Data

Group	ASA (I/II)	Gender (M/F)	Age (yr)	Weight (kg)	Height (cm)
CG	9/3	8/4	28 ± 13	77 ± 17	173 ± 8
SG	8/7	7/8	39 ± 17	67 ± 13	168 ± 10
NG	7/6	5/8	37 ± 20	65 ± 11	166 ± 11
SNG	10/5	8/7	42 ± 22	69 ± 16	164 ± 10
P	0.7727	0.9999	0.5663	0.3897	0.3588

Data are mean ± SD.

CG = control group; SG = sufentanil group; NG = nitroglycerine group; SNG = sufentanil/nitroglycerine group.

medication was measured using the 10-cm VAS. The 24-h VAS pain score and VAS N reflected the patient's overall impression of the 24 h after spinal injection.

Statistical Analysis

The normality of the distributions was assessed using the Shapiro-Wilk test. Groups were compared for demographic data (age, weight, height) and duration of surgery by one-way analysis of variance. The incidence of adverse events, gender, ASA status, and adjuvant drug use were compared among the groups by chi-squared analysis corrected for multiple comparisons. $P < 0.0125$ was considered significant. Blood pressure, heart rate, level of anesthesia (pinprick), and VAS scores were compared among groups by two-way analysis of variance for repeated measures.¹⁰ Tukey analysis was applied to decrease the probability of type 1 errors. The time to first rescue analgesics was compared using the Kruskal-Wallis test, which was applied along with a nonparametric multiple comparison procedure, the Wilcoxon rank sum test. The nonparametric tests, however, confirmed the findings of the parametric approach. $P < 0.05$ was considered significant. Data are expressed as the mean ± SD unless otherwise stated.

Results

Fifty-five patients were evaluated. One patient from the control group was excluded from the final evaluation be-

cause the first spinal block failed. The four groups showed no differences regarding ASA status, gender, age, weight, and height ($P > 0.05$; table 2). The level to pinprick at 5, 10, and 15 min, surgical and anesthetic time, and intraoperative ephedrine consumption were similar among groups ($P > 0.05$; table 3). The mean blood pressure and pulse rate 5, 10, 15, 20, 30, and 40 min after the spinal injection were also the same in all groups ($P > 0.05$).

Table 4 presents postoperative data. The pain VAS score at the time of first rescue analgesic medication was similar among the four groups ($P = 0.1120$). The time to first rescue analgesic medication was longer for the sufentanil-nitroglycerin group compared with all other groups ($P < 0.005$), and it was longer for the sufentanil group compared with the control group ($P < 0.05$). Figure 1 describes the data plots for each patient. The number of intramuscular diclofenac dose injections in 24 h was smaller for the sufentanil-nitroglycerin group compared with all other groups ($P < 0.02$). The sufentanil-nitroglycerin group 24-h pain VAS scores were lesser compared with the control group ($P = 0.0026$) but similar to the other groups (sufentanil group and nitroglycerin group) ($P > 0.05$).

There were no differences regarding the incidence of perioperative adverse effects ($P > 0.05$). During operation, none of the patients reported nausea or vomiting. One patient from the sufentanil-nitroglycerin group had

Table 3. Intraoperative Data

Group	Pinprick (5 min)*	Pinprick (10 min)*	Pinprick (15 min)*	Surgical Time (min)	Anesthetic Time (min)	Ephedrine (mg)
CG	8.4 (4-10)	6.7 (5-10)	6.4 (4-10)	107 ± 37	157 ± 32	2 ± 3
SG	9.3 (8-10)	7.5 (7-8)	7.1 (6-8)	97 ± 41	148 ± 31	2 ± 4
NG	10.2 (10-10)	7.7 (6-8)	7.2 (6-8)	95 ± 34	151 ± 33	7 ± 9
SNG	10 (10-10)	7.2 (6-8)	6.4 (5-8)	103 ± 41	179 ± 40	7 ± 5
P	0.5294	0.4851	0.6312	0.8295	0.1118	0.1422

Pinprick = dermatome anesthesia to a pinprick on the skin; CG = control group; SG = sufentanil group; NG = nitroglycerine group; SNG = sufentanil/nitroglycerine group.

* Median (25-75% percentile confidence). Other data are mean ± SD. No statistically significant differences were observed.

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Table 4. Postoperative Data

	CG	SG	NG	SNG	P
Time to first rescue analgesic (min)	231 ± 49	325 ± 108	269 ± 82	785 ± 483	*
VAS at first rescue analgesic	6.5 ± 1.2	7.7 ± 1.5	6.5 ± 1.1	6.5 ± 2	0.1120
Number of im diclofenac dose injections in 24 h*	2.5 (2-3)	2.3 (2-3)	2 (1-3)	1 (0-2)	†
Overall 24-h VAS pain†	1.7 ± 1.4	1 ± 1.1	1 ± 81.1	0.3 ± 0.6	‡
Overall 24-h VAS N/V	0.5 ± 1	0.4 ± 1.5	0.5 ± 1	0.7 ± 1.6	0.9999

VAS = visual analogue scale; im = intramuscular; N/V = nausea and vomiting; CG = control group; SG = sufentanil group; NG = nitroglycerine group; SNG = sufentanil/nitroglycerine group.

Number of im diclofenac expressed as median (25-75% percentile confidence). Other data are mean ± SD.

* SNG > SG > CG = NG. SNG > CG ($P = 0.003704$); SNG > SG ($P = 0.001471$); SNG > NG ($P = 0.001873$); SG > CG ($P = 0.028063$).

† SNG < CG = SG = NG. SNG < CG ($P = 0.000722$); SNG < SG ($P = 0.001261$); SNG < NG ($P = 0.019273$).

‡ CG = SG = NG ($P > 0.05$); SNG < CG ($P = 0.0026$).

bradycardia (43 beats/min) and hypotension 30 min after the spinal puncture, coincident in time with the transdermal patch application. The patient was treated successfully with intravenous ephedrine. Three patients from the sufentanil group and two from the sufentanil-nitroglycerin group reported perioperative pruritus of their hands, nose, and thorax. One patient each from the sufentanil and the nitroglycerin groups reported postoperative headache (VAS 5 and 6, respectively). One patient from the sufentanil group had urinary retention.

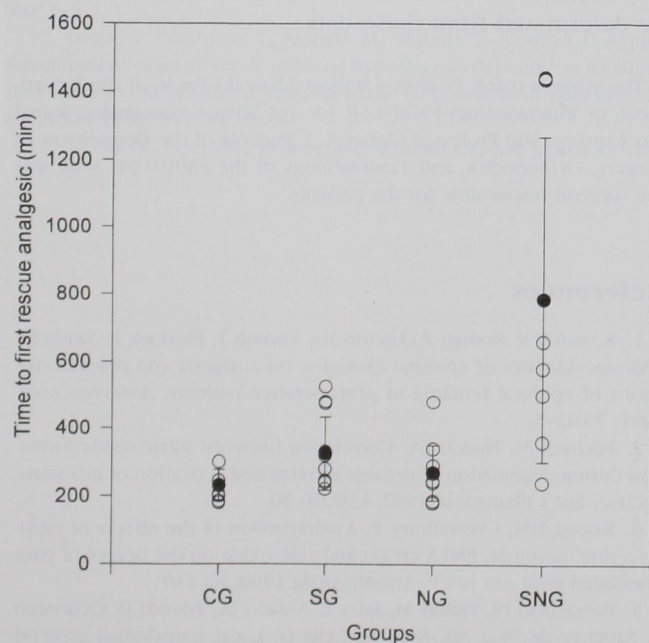


Fig. 1. A normal dot plot for each patient. ● Mean ± SD. CG = control group, SG = sufentanil group, NG = nitroglycerine group, SNG = sufentanil-nitroglycerine group. P values for the Shapiro-Wilk test: CG, $P < 0.0376$; SG, $P < 0.0055$; NG, $P < 0.0435$; SNG, $P < 0.0018$.

Finally, one patient from the sufentanil-nitroglycerin group reported postoperative lumbar pain (VAS 6), and another reported postoperative epigastralgia (VAS 2), nausea (VAS 4), and headache (VAS 6). The mean overall 24-h nausea VAS scores were control group (0.5 ± 1) = sufentanil group (0.4 ± 1.5) = nitroglycerin group (0.5 ± 1) = sufentanil-nitroglycerin group (0.7 ± 1.6) ($P = 0.9999$).

Discussion

The results indicate that 10 μ g intrathecal sufentanil resulted in 5.4 h of analgesia after the spinal puncture, or 3 h from the end of the spinal block, but resulted in the same analgesic postoperative consumption compared with the control group, in accordance with findings reported in the literature. Spinal sufentanil, compared with morphine, has been shown to produce a faster and more intense analgesia but of shorter duration. Patients requested additional analgesics within 3 h of the end of the anesthesia, and their morphine consumption during the first 24 h after surgery was similar to that found after general anesthesia.¹¹ A dose-response curve for intrathecal sufentanil during labor suggested that the median effective dose (ED_{50}) for intrathecal sufentanil was 2.5 μ g and that the ED_{95} between 7.5 and 10 μ g.¹¹

Our results also showed that 5 mg transdermal nitroglycerine alone did not result in postoperative analgesia, but a 5-mg transdermal nitroglycerin patch enhanced the sufentanil analgesic effect. Their combination resulted in 13 h of postoperative analgesia after arthroscopy and meniscectomy. Nitric oxide has been shown to interact synergistically with morphine after intravenous or spinal administration.¹² Recent animal studies showed that pe-

riperally administered NO had no analgesic effect, but it enhanced the analgesic effect of peripherally administered morphine during experimental inflammation in rats.¹³ In addition, systemic morphine increased spinal cord NO metabolite concentrations, and behavioral analgesia in healthy animals from systemic morphine is blocked by NO synthase inhibitors.¹⁴ How NO would enhance sufentanil analgesia is not known, and at least four explanations are possible: a supraspinal, spinal, or peripheral mechanism, or molecular pharmacology.

Nitric oxide derived from transdermal nitroglycerine may enhance the antinociceptive effect produced by intrathecal sufentanil through the supraspinal mechanism. Intrathecal injection of L-arginine and NO-releasing compounds produced hyperalgesia in the tail-flick test,¹⁵ formalin pain model,¹⁶ and neuropathic pain model.¹⁷ In contrast, intracerebroventricular administration of L-arginine or dibutyl cyclic guanosine monophosphate (cGMP) produced antinociception *via* the NO-cGMP pathway in the tail-flick procedure.¹⁸⁻²⁰ According to the data described, NO exerts a dual role in acute nociceptive processing. Intrathecal NO plays a role in thermal hyperalgesia, whereas intracerebroventricular NO plays a role in thermal antinociception.

Conversely, NO derived from transdermal nitroglycerine may enhance the antinociceptive effect produced by intrathecal sufentanil through the spinal mechanism. The analgesic effect after opioid administration is mediated in part through activation of inhibitory descending pain pathways that will involve the participation of NO, which mechanisms of action are likely to include activation of second messengers such as cGMP.²¹ Spinal activation of the NO-cGMP signal transduction system contributes to sensitization of wide dynamic range neurons located in the deep dorsal horn. In contrast, wide dynamic range neurons in the superficial dorsal horn and high-threshold cells in the superficial or deep layers show a reduced response after exposure to cGMP.²² Thus, NO may exert a dual role in acute nociceptive processing. The analgesia would be a result of a predominant analgesic action on superficial spinal layers, and thus the nociceptive effect would be a result of a predominant action on deep layers.

Peripherally, NO produces neither nociceptive nor antinociceptive effects on the receptors.²³ However, it modulates the antiinflammatory process and edema formation. Its vasodilator action on the venous system decreases the vasoconstrictor tone induced by the inflammatory process and further reduces the edema formation.⁴ Nitric oxide also produces platelet desegre-

gation, impeding the platelet adhesion to the endothelium of the injured vessel.²⁴ In addition, NO generators induce antiinflammatory effects and analgesia by blocking hyperalgesia and the neurogenic component of the inflammatory edema.²⁵ Another possible mechanism includes an analgesic effect through the direct stimulation of peripheral fibers mimicking the actions of locally applied acetylcholine.²⁶

Finally, the molecular pharmacology modulation also may be proposed for the mechanism of synergistic interaction between μ -opioid receptors and NO. Nitric oxide may act directly at the μ -opioid receptor for the positive modulation and enhance its function. Nitric oxide has been reported to have direct modulatory effects on N-methyl-D-aspartate receptors²⁷ and gamma-aminobutyric acid-A receptors.²⁸ However, the molecular nature of the action of NO at the μ -opioid receptor has not been clarified.

In conclusion, although transdermal nitroglycerine alone (5 mg/day), an NO generator, did not result in effective postoperative analgesia, its association with intrathecal sufentanil provided 13 h of postoperative analgesia after minor knee surgery, suggesting that NO and μ -opioid receptors may enhance their antinociceptive effects on the dose studied. Whether this represents a synergistic action or some other mechanism could not be determined from these data.

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