Transdermal nitroglycerin as an adjuvant to patient-controlled morphine analgesia after total knee arthroplasty

Sharon Orbach-Zinger MD[1], Artium Lenchinsky MD[1], Lesley Paul-Kesslin MD[1], Steven Velks MD[2], Moses Salai MD[2], Leonid A Eidelman MD[1]

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BACKGROUND: Nitroglycerin (NTG) has been shown to be a useful adjunct for pain treatment without increasing adverse side effects. The effects of NTG on postoperative morphine consumption after knee replacement were evaluated.
METHODS: After undergoing total knee replacement, patients receiving patient-controlled morphine analgesia were randomly assigned to receive either an NTG or a placebo patch. The blinded investigator assessed each patient using a visual analogue scale at rest and while moving, as well as the patient's morphine requirements, sedation score, sleep quality, nausea and vomiting, vital signs and postoperative bleeding.
RESULTS: Two of the patients in the NTG group suffered postoperative myocardial infarctions after removal of the patch. Because of these two serious adverse effects, the study was stopped prematurely. In the subset of patients studied, NTG conferred no advantage over placebo in pain control (visual analogue scale at rest or during movement) and in satisfaction scores.
CONCLUSIONS: The use of NTG patches conferred no advantage over the use of placebo in patients receiving patient-controlled morphine analgesia after total knee replacement. Two myocardial infarcts occurred in this group. Therefore, the safety of postoperative NTG patch use for pain control must be questioned.

Key Words: *Nitroglycerine patch; Patient-controlled analgesia; Total knee replacement*

La nitroglycérine transdermique comme adjuvant à l'analgésie par la morphine contrôlée par le patient après une arthroplastie totale du genou

HISTORIQUE : Il est démontré que la nitroglycérine (NTG) est utile pour le traitement d'appoint de la douleur sans pour autant accroître les réactions indésirables. Les auteurs ont évalué les effets de la NTG sur la consommation de morphine après une arthroplastie du genou.
MÉTHODOLOGIE : Après une arthroplastie totale du genou, les patients qui recevaient une analgésie à la morphine qu'ils contrôlaient eux-mêmes ont été divisés au hasard pour recevoir soit un timbre de NTG, soit un timbre de placebo. En aveugle, le chercheur a évalué chaque patient au moyen d'une échelle analogique visuelle au repos et en mouvement, ainsi que les besoins en morphine du patient, son indice de sédation, la qualité de son sommeil, ses nausées et vomissements, ses signes vitaux et les saignements postopératoires.
RÉSULTATS : Deux des patients du groupe de NTG ont souffert d'un infarctus du myocarde postopératoire après le retrait du timbre. En raison de ces deux réactions indésirables graves, on a prématurément mis un terme à l'étude. Dans le sous-groupe de patients étudiés, la NTG ne procurait aucun avantage par rapport au placebo pour ce qui est du contrôle de la douleur (échelle analogique visuelle au repos ou pendant le mouvement) et des indices de satisfaction.
CONCLUSIONS : Le recours aux timbres de NTG ne procurait aucun avantage par rapport au placebo chez les patients qui recevaient une analgésie qu'ils contrôlaient eux-mêmes après une arthroplastie totale du genou. Deux infarctus du myocarde se sont produits au sein de ce groupe. Par conséquent, il faut remettre en question l'innocuité des timbres de NTG pendant la période postopératoire pour contrôler la douleur.

Nitroglycerin (NTG) is a vasodilatory drug most commonly used for anginal pain. However, studies have been recently published showing its analgesic activity for nonanginal pain. Recent articles have described its efficacy for use in shoulder pain (1), chronic post-thoracotomy pain (2) and diabetic neuropathy (3). In addition, the use of NTG in cancer patients suffering from chronic intractable pain has been described (4,5). Transdermal NTG patches improved morphine analgesia in cancer pain patients without increasing adverse side effects (4). Likewise, in patients treated with a combination of oral morphine and oral ketamine, transdermal NTG patches have been found to be a useful adjuvant for cancer pain management (5). The use of NTG for intraoperative and postoperative pain control has also been recently explored (6). The addition of NTG to lidocaine for intravenous regional anesthesia improved sensory and motor block, reduced tourniquet pain and provided better postoperative analgesia than lidocaine alone (6). Systemic NTG administration was found to be a useful addition to spinal anesthesia. Postoperatively, visual analogue scale (VAS) scores were lowered and the need for other analgesic medications was reduced when NTG patches were administered in addition to spinal ketamine (7), spinal neostigmine (8) and spinal sufentanil (9).

To date, the effect of NTG on postoperative morphine consumption has not been studied. Our primary study goal was to assess whether a postoperative NTG patch reduced pain both

[1]*Department of Anesthesia;* [2]*Department of Orthopedics, Rabin Medical Center, Beilinson Campus, Petach Tiqvah, Israel*
Correspondence: Dr Sharon Orbach-Zinger, Department of Anesthesia, Rabin Medical Center, Beilinson Campus, Petach Tikvah, Israel. Telephone 972-50-406-5523, fax 972-39-376-851, e-mail sharonorbach@yahoo.com

TABLE 1
Demographic data

Data	Placebo group (n=14)	Nitroglycerin group (n=15)	P
Age, years, mean ± SD	71±11.7	70.3±4.1	0.82
Sex, n (%)	Men: 11 (88.6)	Men: 9 (60)	0.3
	Women: 3 (21.4)	Women: 6 (40)	
ASA score			0.33
1	n=0	n=0	
2	n=4	n=7	
3	n=10	n=8	
4	n=0	n=0	

ASA American Society of Anesthesiologists

at rest and while moving after total knee replacement. Secondary goals were assessment of morphine-sparing effect and patient satisfaction, and evaluation of side effects.

METHODS

Design and setting

A prospective, double-blind, randomized comparative design was used. The present study was conducted in a major tertiary centre (Rabin Medical Center, Beilinson Campus, Petach Tiqvah, Israel). The protocol was approved by the local institutional ethics committee, and all participants provided written informed consent.

Patients

The planned study sample included patients undergoing total knee replacement under general anesthesia. Exclusion criteria included NTG allergy, morphine allergy, severe asthma, sleep apnea, refusal to undergo general anesthesia, history of migraine headaches or inability to comprehend the use of patient-controlled analgesia (PCA).

Procedure

The patients were divided into two groups according to a computer-generated randomization list to receive either an NTG or a placebo patch. Patients were given premedication of 5 mg of midazolam 1 h before surgery. General anesthesia was induced with fentanyl 0.2 µg/kg, propofol 1 mg/kg to 1.5 mg/kg and rocuronium 0.6 mg/kg. All patients were intubated. Anesthesia was maintained with isoflurane and fentanyl. Morphine 1 mg/kg was given 1 h before the end of surgery. After the surgery was completed, but before the patient awakened, an NTG or placebo patch was placed on the patient's scapula.

Postoperatively, all patients received 1 mg/kg morphine in the recovery room and were attached to PCA delivering a morphine bolus of 1 mg with a lockout period of 8 min. The maximal 4 h dose was 25 mg with no background infusion. The patients were carefully instructed on the use of the device and were familiarized with the VAS scoring system. Oxygen was delivered via nasal prongs and saturation was monitored continuously with a pulse oximeter according to the hospital policy. Patients who had a VAS above 5 were given an additional bolus of 5 mg of morphine.

Demographic data, American Society of Anesthesiologists (ASA) status, associated diseases and length of surgery were recorded. Heart rate, blood pressure and respiratory rate were measured every 4 h after surgery. Postoperatively, a researcher blinded to the patch type (NTG versus placebo) recorded the VAS at the end of surgery and the following data every 6 h for the first 24 h:

1. VAS (0 to 10) at rest and on movement.
2. Sedation, on a four-point scale: 0 = awake, 1 = drowsy, 2 = somnolent but arousable to verbal commands and 3 = unarousable sleep.
3. Nausea, on a four-point scale: 0 = no nausea, 1 = mild nausea not requesting pharmacological rescue, 2 = nausea amenable to pharmacological treatment and 3 = nausea resistant to pharmacological rescue.
4. Satisfaction on a scale of 0 to 10. Patients were asked to rank the satisfaction they felt with the pain control they received, where 0 was not satisfied at all and 10 was completely satisfied.
5. Sleep quality (1 to 4): 1 = undisturbed sleep, 2 = occasional disturbance of sleep, 3 = usual disturbance of sleep and 4 = total inability to sleep.
6. Need for analgesic supplementation.
7. Total morphine consumption.
8. Blood loss.

Sample size calculation

To calculate a change in VAS of 10 points with 85% power and an alpha of 5%, it was estimated that a minimum of 21 patients were needed in each group. To compensate for possible drop-outs, enrollment of 50 patients was planned.

Statistical analysis

Results for continuous variables are shown as mean ± SD. To compare categorical variables between the groups, a χ^2 test and *t* test or repeated measure for continuous variables were used. $P<0.05$ was considered statistically significant.

RESULTS

Only 29 patients were enrolled in the present study because of the premature termination due to patient complications. Fourteen of these patients received placebo, while 15 received the NTG patch. One patient in the NTG group suffered respiratory depression 4 h after attachment to the PCA device. He required naloxone therapy. Afterward, he received only oral analgesics. Because of the intent to treat, his data were included until the time of discontinuation from PCA.

There were no significant differences between the groups in demographic data (Table 1). There were no significant differences in VAS at rest or during movement between the two groups over time (Figures 1 and 2). There were no statistically significant differences seen in blood pressures, heart rates or respiratory rates between the groups at any time period. Likewise, no significant differences in morphine consumption, need for additional analgesic supplementation, sleep quality, or level of nausea and vomiting between the groups were seen (Table 2). Finally, no significant difference in intraoperative and first 24 h postoperative blood loss was seen between the two groups (placebo 899±414.5 mL, NTG 1087.5±446.9 mL, P=0.27).

Two patients in the NTG group suffered serious adverse events. Both patients suffered from myocardial infarction 12 h

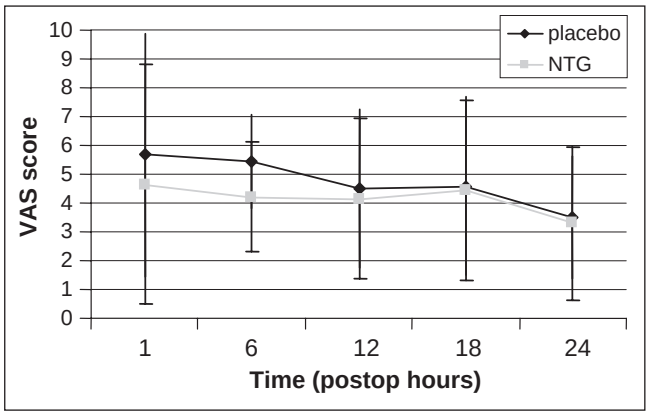

Figure 1) *Visual analogue scale (VAS) score at rest. NTG Nitroglycerin; Postop Postoperative*

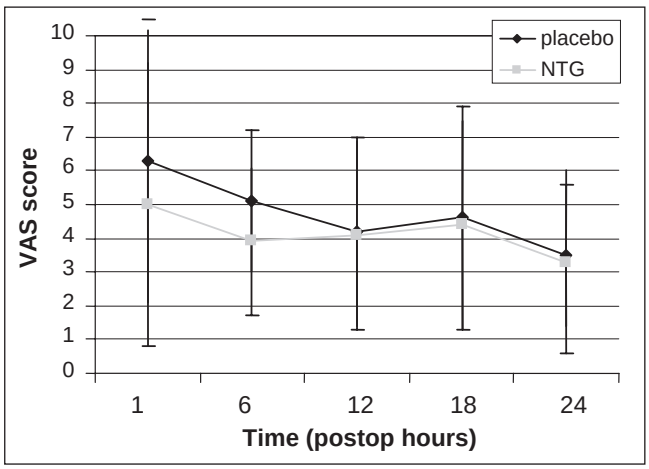

Figure 2) *Visual analogue scale (VAS) score during movement. NTG Nitroglycerin; Postop Postoperative*

after removal of the NTG patch. One patient in the NTG group, a 71-year-old man with a history of heart disease and four cardiac catheterizations, although asymptomatic at the time of surgery, underwent uneventful surgery and had a NTG patch placed. Twelve hours after its removal, the patient suffered from dyspnea and chest pain followed by an episode of syncope and severe hypotension. He underwent intubation and cardiopulmonary resuscitation. A subsequent electrocardiogram showed the pattern of an inferior wall myocardial infarction. Blood tests taken at the time showed a troponin level of 0.89 µg/L and a decrease in hemoglobin of 40 g/L. Transthoracic echocardiography showed severe right heart dysfunction and mild left heart dysfunction. He was transferred to the cardiac intensive care unit where he received treatment for cardiogenic and hemorrhagic shock (noradrenaline and blood transfusion) with subsequent stabilization. However, during his stay in the cardiac intensive care unit, he developed severe sepsis and subsequent multiorgan failure that led to his demise three weeks later.

The second patient, a 76-year-old man with no history of heart disease, underwent surgery and was randomly assigned to the NTG patch group. Postoperatively, there was a decrease in hemoglobin of 30 g/L which was treated with a unit of blood. Fourteen hours after patch removal the patient suffered from chest pain. A physical examination at that time showed

TABLE 2
Postoperative data

Data	Placebo group (n=14)	NTG group (n=15)	P
Patient satisfaction (0–10)	6.4±1.8	6.3±1.8	0.69
Postoperative nausea score (0–3)	0.8±0.9	0.6±0.6	0.47
Systolic blood pressure, mmHg	129.3±9.9	134.2±17.2	0.40
Diastolic blood pressure, mmHg	67.2±6.7	69.7±8.9	0.50
Heart rate, beats/min	81.3±8.0	76.6±13.3	0.29
Respiratory rate, breaths/min	15.7±5.9	15.0 ±3.2	0.62
Sedation score (0–3)	0.6±0.3	0.7±0.3	0.54
Sleep quality score (1–4)	1.7±0.4	1.7±0.6	0.82
Total PCA morphine consumption, mg	33.5±17.3	30.6±15.9	0.66
Total length of surgery, min	82.1±31.5	94.8±32.2	0.27

Data presented as mean ± SD. NTG Nitroglycerin; PCA Patient-controlled analgesia

tachycardia, tachypnea and signs of right heart failure. An electrocardiogram at the time showed ST depressions in leads V3 to V6 and blood tests demonstrated elevation of cardiac enzymes. A chest x-ray showed mild pulmonary edema. Cardiac echocardiography showed mild left ventricular dysfunction. Because of these findings, the patient was diagnosed as having a perioperative myocardial infarction and was treated with nitrates, low molecular weight heparin, angiotensin-converting enzyme inhibitors and blood transfusions. With this treatment, the patient improved and was subsequently released from the hospital.

These events were reported to the institutional review board. When the rates of cardiac events in the study group were compared with the average rate of cardiac events after total knee replacement surgery in the Rabin Medical Center, the difference was very statistically significant (P<0.001). Because of these serious adverse effects, the study was discontinued.

DISCUSSION

The present study, which was discontinued prematurely because of serious cardiac events in the study group, was unable to draw conclusions about the use of NTG patches as an analgesic supplement in postoperative pain, as was previously suggested (10-19).

The present study is the first to test NTG combined with intravenous morphine given as PCA postoperatively. Previous studies have shown that NTG is an effective analgesic supplement in shoulder pain (1), chronic thoracotomy pain (2) and cancer pain (4,5), as well as for spinal anesthesia (7-9). The efficacy of morphine PCA for pain control after total knee replacement remains controversial (20-24). Indeed, in our study, pain scores were high and satisfaction scores were low in both groups.

In previous studies of NTG as an analgesic (1-9), no serious side effects were noted. The use of NTG in our study was associated with two major cardiac events. Although we can not prove causality, we fear that NTG may have been a contributing factor because the cardiac event rate was significantly higher in the study group than in the general population undergoing the same surgery. A few studies have shown that abrupt cessation of

NTG may cause a 'rebound phenomenon' of myocardial ischemia after patch removal (25-27). In the Second Transdermal Intermittent Dosing Evaluation Study (TIDES II) (27), patients suffered more ischemic episodes during patch-off hours after use of intermittent transdermal NTG. Another study showed that in patients with stable angina pectoris using intermittent NTG therapy, there was a decrease in anginal threshold in patients during the nitrate-free period (28). A possible explanantion is that NTG withdrawal may cause an increase in endothelium-dependent vasomotor response to acetylcholine (25).

CONCLUSION

We were unable to reach significant conclusions about the use of NTG patches as an analgesic supplement to morphine PCA in a postoperative setting. Our study's patients were, in general, older and sicker than patients in previous studies. Perhaps further research for NTG as an analgesic supplement should be with younger patients without history of heart disease. Further studies should consider gradual weaning from patch, cardiac monitoring on patch removal and possible collaboration with a cardiologist.

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