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Reduced morphine consumption and pain severity with transdermal fentanyl patches following total knee arthroplasty

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Abstract
Purpose To determine the effects of transdermal fentanyl patches (TFPs) for postoperative analgesia in patients undergoing total knee arthroplasty (TKA) surgery.
Methods A randomized, double-blind, controlled trial study of 40 ASA I–III patients undergoing TKA surgery was performed under general anaesthesia. Patients were randomly divided into two groups. Group I ($n = 20$) received two 25 μg TFPs placed on the laterals of chest wall approximately 12 h before induction of general anaesthesia. Group II, the control group ($n = 20$), received placebo patches of identical size. Postoperative pain at rest was assessed with visual analogue scale (VAS) at 0, 30 min and 2, 4, 6, 12, 24, 48 and 72 h. Total rescue consumption of morphine was estimated with patient control analgesia during the first 72 h after operation. The degree of active knee flexion and incidence of side effects were also evaluated.
Results The VAS scores at 2, 4, 6, 12, 24, 48 and 72 h were significantly less in the group I compared to the group II ($p < 0.05$). Total morphine consumption was significantly less in group I than in group II ($p < 0.05$). No significant differences were found between the groups in the postoperative active knee flexion (n.s.). Side effects were similar between the groups.
Conclusions Transdermal fentanyl patches provide effective pain relief and decrease total rescue morphine consumption during the first 72 h after operation without additive side effects in patients undergoing TKA surgery.
Level of evidence I.

Keywords Transdermal fentanyl patch · Patient control analgesia · Morphine · Postoperative analgesia

Introduction

Total knee arthroplasty (TKA) is a major orthopaedic operation, associated with moderate (approximately 30 %) to severe (approximately 60 %) postoperative pain [4]. There are different techniques and medications used to achieve good pain relief and early mobilization. At present, analgesic modalities include intravenous opioids, patient-controlled analgesia (PCA), epidural analgesia, peripheral nerve block and local intra-articular or periarticular analgesic injection [2, 6, 8, 9, 14, 17, 18, 22]. All of these methods are relatively effective, but TKA postoperative pain management is still an unsolved challenge.

Transdermal fentanyl patch (TFP) is a selective μ receptor opioid agonist, commonly used for chronic cancer pain [11]. Previous studies have also shown that it can be applied as an effective analgesic for postoperative pain particularly in abdominal and gynaecological surgeries [16,

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19, 24, 25]. Recently, Minville et al. [20] reported that TFP decreases the postoperative pain score and rescue morphine consumption compared with PCA in patients undergoing total hip arthroplasty.

In this randomized, double-blind, controlled trial study, the objectives were the assessment of efficacy of TFP on postoperative pain score and rescue morphine consumption as well as the degree of active knee flexion and incidence of side effects in patients undergoing TKA. It was hypothesized that TFP as a safe and potent opioid would reduce systemic and additional opiate requirement and also could improve early knee joint range of motion by providing improved analgesia after TKA surgery.

Materials and methods

The study protocol was approved by the research ethics committees in Shahid Sadoughi University of Medical Sciences. All patients gave written informed consent to participate in the study. Forty patients were selected according to inclusion criteria including age ≥18 and ASA physical status ≤III. Exclusion criteria were allergy and contraindication to TFP and morphine, dependence or addiction to narcotics, major organ disease, pregnancy or breastfeeding and morbid obesity [body mass index (BMI) ≥ 40].

The patients were randomized in two groups by using sealed envelopes method. In the group I ($n = 20$), patients received two TFPs (Duragesic 25 μg/h, Fentanyl 4.2 mg per transdermal patch, JANSSEN-CILAG) placed on the laterals of chest wall approximately 12 h before induction of general anaesthesia. Group II or control group ($n = 20$) received placebo patches of identical size. Patients did not receive any premedication. Standard monitoring techniques including electrocardiography, pulse oximetry, non-invasive blood pressure and capnography were applied to all patients. All operations were performed under general anaesthesia. Anaesthesia was induced with propofol (2 mg/kg) intravenously. Tracheal intubation was facilitated with atracurium (0.5 mg/kg), and anaesthesia was continued with 50 % N_2O–50 % O_2 breathing and propofol infusion (8–10 mg/kg/h). The surgeries were performed using a standard surgical technique by a single surgeon.

After the surgery, patients were transferred to the postanaesthesia care unit. Postoperative pain severity at rest was assessed with 100-mm visual analogue scale (VAS) (subjective measurement, with 0: no pain, to 100: worst pain possible) [28] by questioning the patients at 0, 30 min and 2, 4, 6, 12, 24, 48 and 72 h. Additional morphine (rescue morphine consumption) was administered by PCA (Ace Medical Co. Korea) set up to deliver incremental doses of 1 mg morphine and lockout of 15 min with no background infusion for both groups. Also, the degree of knee flexion was measured with goniometer for the first three postoperative days. The TFPs were removed at the end of third day after surgery. The occurrence of side effects such as nausea, vomiting, pruritus, sweating, respiratory depression (rate ≤ 10 breaths/min), hypotension (systolic blood pressure less than 90 mmHg) and retention of urine was recorded regularly three times a day (based on hospital shifts) by nurses. Demographic data including age, gender, weight, height, BMI and intraoperative data such as surgery and anaesthetic times were also recorded.

Statistical analysis

As an initial assessment about effects of TFP on postoperative analgesia for patients undergoing TKA, a pilot study was conducted on 16 patients based on rescue morphine consumption (group I: 30.6 ± 9.0, group II: 39.2 ± 6.4, mean ± SD). Then the sample size was calculated 14 per group using α error 0.05 and β error 10 % (90 % power), but the sample size was set at 20 per group, as the initial study. The data between the groups were analysed by Mann–Whitney U test for quantitative data and chi-square for qualitative data. Statistical analysis was performed using the SPSS 18.0 software, and a value of $p < 0.05$ was considered statistically significant. Data were presented as mean ± SD.

Results

There was no significant difference between the two groups in demographic and intraoperative data (Table 1). VAS scores decreased significantly in the group I compared to the group II at 2, 4, 6, 12, 24, 48 and 72 h after operation ($p < 0.05$). VAS score measured before operation did not differ significantly between the groups (Table 2).

Total rescue morphine consumption was significantly less in group I than in group II during the 72 postoperative hours (33.0 ± 8.6 vs. 40.0 ± 6.8, $p = 0.01$) (Fig. 1). No

Table 1 Demographic and intraoperative data

	Group I ($n = 20$)	Group II ($n = 20$)
Age (year)	61.2 ± 8.2	58.8 ± 8.1
Gender (female/male)	17/03	14/06
Knee (right/left)	10/10	11/09
Weight (kg)	73.5 ± 10.2	75.6 ± 11.0
Height (cm)	159.7 ± 10.3	162.0 ± 8.0
BMI (kg/m^2)	28.9 ± 3.7	28.8 ± 4.1
Surgery time (min)	143.0 ± 33.4	127.5 ± 24.3
Anaesthesia time (min)	169.3 ± 34.3	151 ± 26.7

Table 2 Pain scores (VAS, 0–100 mm), presented as mean ± SD

	Group I ($n = 20$)	Group II ($n = 20$)	p value
Preoperative			
VAS	21.2 ± 11.5	19.1 ± 9.4	n.s.
Postoperative			
VAS 0 min	36.5 ± 28.1	47.0 ± 29.9	n.s.
VAS 30 min	61.0 ± 27.1	59.0 ± 19.1	n.s.
VAS 2 h	61.0 ± 22.6	81.5 ± 12.4	0.002
VAS 4 h	56.8 ± 24.1	73.2 ± 17.7	0.016
VAS 6 h	53.5 ± 24.9	67.2 ± 15.9	0.035
VAS 12 h	39.4 ± 20.2	64.5 ± 13.9	0.000
VAS 24 h	36.5 ± 20.8	57.0 ± 14.2	0.002
VAS 48 h	26.7 ± 13.5	50.7 ± 11.9	0.000
VAS 72 h	26.5 ± 17.3	44.2 ± 14.1	0.002

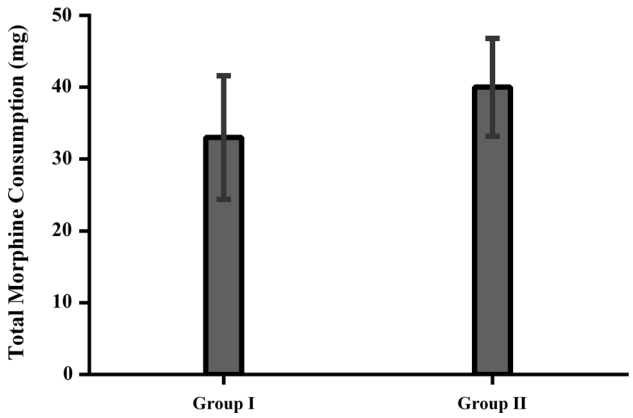

Fig. 1 Total rescue morphine consumption during the 72 postoperative hours, mean ± SD

significant differences were found between the groups in the preoperative and postoperative active knee flexion (n.s.) (Table 3).The groups were similar with respect to incidence of side effects (n.s.) (Table 4).

Discussions

The most important finding of the present study was that TFPs provide effective pain relief and decreases total rescue morphine consumption during the first 72 h after operation without additive side effects in the TKA surgery. The postoperative degree of active knee flexion increased in the TFP group, but it was not significant statistically.

In fact, due to slow absorption and prolonged effects, TFP is used as an effective and safe opioid in chronic pain reduction in cancer patients [7, 11, 26]. TFP studies were initially performed in the late 1980s, as a postoperative analgesic [12, 13]. Sandler et al. [24] indicated that TFP (50–75 μg/h) is associated with less consumption of

Table 3 The degree of active knee flexion, presented as mean ± SD

	Group I ($n = 20$)	Group II ($n = 20$)	p value
Preoperative			
Active flexion	97.7 ± 38.9	72.3 ± 43.1	n.s.
Postoperative			
First-day active flexion	17.2 ± 13.1	11.3 ± 10.8	n.s.
Second-day active flexion	28.7 ± 26.6	17.1 ± 11.2	n.s.
Third-day active flexion	35.6 ± 25.3	20.7 ± 13.0	n.s.

Table 4 Postoperative side effects, presented as number and percentage

	Group I ($n = 20$)	Group II ($n = 20$)
Nausea n (%)	11 (55 %)	13 (65 %)
Vomiting n (%)	5 (25 %)	9 (45 %)
Pruritus n (%)	4 (20 %)	2 (10 %)
Sweating n (%)	2 (10 %)	4 (20 %)
Respiratory depression n (%)	1 (5 %)	0 (0 %)
Hypotension n (%)	1 (5 %)	2 (10 %)
Urine retention n (%)	2 (10 %)	3 (15 %)

supplementary morphine and significant decrease in VAS pain score in patients undergoing abdominal hysterectomy. Similar results were also seen in the study of Miguel et al. [19] after gynaecologic exploratory laparotomy. However, both studies found increased rates of respiratory depression in the active groups. Amr et al. [1] compared TFP (50 μg/h, applied 10 h before surgery) with placebo for the management of postmajor abdominal surgery pain. They found that there was significant reduction in the pain intensity and rescue morphine consumption with normal oxygen saturation in the TFP group when compared with the placebo group. They also recorded longer time for request the rescue morphine consumption in the TFP group.

In studies that have been conducted in the orthopaedic field, Caplan et al. [5] reported that TFP (75 μg/h for 24 h) produces an agreeable, safe and effective analgesia after major shoulder surgeries and is superior to conventional therapy with morphine. Van Bastelaere et al. [27] also indicated that TFP (75 μg/h for 72 h) improves postoperative pain and decreases morphine consumption in the orthopaedic surgeries, along with increased risk of respiratory depression. Recently, Minville et al. [20] showed that TFP (50 μg/h for 24 h) decreases pain severity and rescue morphine consumption in patients undergoing total hip arthroplasty. Lauretti et al. [15] reported that TFP (25 μg/h) provides a lower pain and lesser rescue analgesic consumption after posterior laminectomy. Also Barrera et al. [3] assessed the safety and efficacy of TFP (50 μg/h)

for postoperative analgesia in dorsal and lumbar spine arthrodesis. They indicated that TFP significantly decreases pain intensity and rescue analgesic requirement when compared with the placebo group.

The result of this research similar to other studies describes TFP as a suitable narcotic for pain relief after surgery, thus for reducing the amount of additional analgesics for the first time among patients who had undergone TKA surgery.

In fact, fentanyl is a highly potent opioid, approximately 75–100 times more potent than morphine [21]. The high lipophilicity of fentanyl can lead to high absorption of transdermal form in which it provides an acceptable plasma concentration (during the 72-h continuous diffusion). Although increased plasma concentration induces clinical complications, like respiratory depression, they are rapidly reversible by naloxone [21]. Respiratory depression in some studies reported the only drawback of using TFP as an analgesic after surgery, which was the only one case observed in this study. So, for a more detailed examination of the analgesics effects and side effects of TFP, it was recommended to measure serum levels of fentanyl in various times in future studies. In addition to analgesia, fentanyl is an anxiolytic and sedative compound which is also used as premedication for anaesthesia [10].

Overall, with an appropriate dose based on the type of surgery, TFP can be used for relief postoperative pain as an effective, easy and relatively inexpensive method [20, 23].

The limitation of this study is that these results cannot be generalized to the other surgical procedures. The comparison of TFP with other analgesic methods after TKA surgery is also recommended.

Of clinical relevance of this study, it can be said that TFP provides desired analgesia and decreases additional anodyne consumption without serious side effect induction in patients undergoing TKA surgery.

Conclusion

This study indicates that 50 μg transdermal fentanyl patch provides effective pain relief and less rescue morphine consumption during the first 72 h after operation without additive side effects in patients undergoing total knee arthroplasty surgery.

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Conflict of interest None.

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