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TRANSDERMAL FENTANYL PATCH FOR ACUTE PAIN CONTROL AFTER SHORT INTRAHOSPITAL STAY

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Keywords: analgesia, enhanced recovery, opioids, transdermal application, surgery, NSAID.

Summary

Transdermal fentanyl patch (TFP) is used for alleviation of chronic pain, while scientific evidence regarding its use for acute pain is insufficient.

Purpose. To compare the effects of pain control by non-steroidal anti-inflammatory drug (NSAID) and TFP and the restrictions in daily activities in patients following elective minor surgical interventions.

Patients and methods. Prospective, randomised, case-controlled study included patients aged ≥18 years who underwent elective cholecystectomy, gastric fundoplication or inguinal hernia repair. All randomised patients (fentanyl prescription group, FG, and control group, CG, 62 cases each) were administered dressing plasters for the first three post-operative days; the FG patients received 50mcg/h TFP under the plaster. Within the 4 post-operative days, the patients of both groups received diclofenac on demand. Post-operative pain at rest and during movement was evaluated using the Visual Analogue Scale on the 1st, 2nd, 3rd, 4th post-operative days. Daily activities using the Functional Activity Score were scored as 0 - no limitations, 1 - some limitations, 2 - severe limitations.

Results. Pain both at rest and during movement on the first three post-operative days was lower in the FG; CG patients received 5 times more doses of diclofenac on demand on the 1st day after the surgery, with the higher need of NSAID during the next two days ($p<0.05$). The total number of NSAID doses per patient administered on demand was 3.11±0.59 in the CG and 0.73±0.16 in the FG ($p<0.05$). The influence of pain on daily activities on the 2nd post-operative day was scored as 0 by 92% patients and as 1 by 8% patients of the FG, versus 60% and 40% patients of the CG ($p<0.05$).

Conclusion. Patients with TFP experienced significantly more effective pain control leading to less restricted daily activities and used less doses of NSAID within the first few post-operative days.

Plain Language Summary. Could a single long-lasting dose of transdermal fentanyl patch serve as an alternative to uncontrolled consumption of non-steroid anti-inflammatory drugs when dealing with early post-operative pain in patients following a hospital discharge after an elective minor surgery? Our conclusion suggests that the answer is “yes”, if the risk-benefits balance is evaluated.

Introduction

Today it is obvious, both from evidence-based literature as well as clinical practice, that uncontrolled post-operative pain results in the development of post-surgical complications, poor healing and functioning, and impaired quality of life [1-3]. Early post-operative pain triggers the development of chronic pain in 10%-60% of patients following common surgical procedures, that persists for months after the surgery [4,5]. In order to reduce the incidence and intensity of acute pain immediately after the surgery as well as to prevent its progression into chronic pain, more aggressive analgesic measures are required [3,6-8].

Transdermal fentanyl application (FTA) is widely used for the alleviation of chronic pain [9-12]. Fentanyl is slowly released and absorbed through the skin where it reaches the blood flow. FTA ensures prolonged analgesic effect and thus may help prevent repeated doses of non-steroidal anti-inflammatory medication (NSAID). Scientific evidence regar-

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ding the use of FTA for acute pain management is controversial and insufficient [13-18]. We hypothesized that FTA might help to control post-operative acute pain and to improve early mobilization after elective minor surgery.

The aim of this study was to compare the effects of pain control by conventional NSAID and FTA in the acute period in patients who underwent pre-planned *minor* surgical interventions, as well as to compare restrictions in daily activities in both groups.

Material and methods

The study was conducted at the Department of Surgery of the Hospital of Lithuanian University of Health Sciences. This prospective, randomised, case-controlled study included 124 patients operated between May 1, and December 31, 2018. Ethical approval of this study has been provided by the Bioethics Center of Lithuanian University of Heath Sciences according to the protocol No. BEC – MF – 161 (December 21, 2017).

Inclusion criteria: 18 years of age or older; an elective type of surgery that allowed hospital discharge on the next day after the operation – either a cholecystectomy, a gastric fundoplication, an inguinal hernia repair using a laparoscopic technique, or an inguinal hernia repair by Shouldice or Lichtenstein; were not already taking opioid pain medication at the time of inclusion; willing to participate in this study. Exclusion criteria were any conditions of chronic pain, also the use of opioid painkillers at the time of inclusion. All eligible patients were informed about the purpose and the design of the study, were free to decide about their participation and confirmed their approval by signing the Informed Consent Forms. For purposes of randomisation, an equal number of envelopes had been prepared: 62 for the fentanyl prescription group (FG) and 62 for the control group (CG). The envelopes were opened randomly for each patient by the surgical trainees responsible for the randomization. At the end of the surgery all patients were administered a 5x5 cm dressing plaster for the next three consecutive days; the FG patients received 50 mcg/h transdermal fentanyl patch (TFP) under the dressing plaster. None of the patients knew the type of the plaster they had received. Also, at the end of the surgery, all patients received paracetamol 1 g and ketoprofen 100 mg intravenously. On the first day after surgery, for pain management on demand, the patients of both groups received intramuscular injections of diclofenac 75 mg/3mL, and 75 mg of oral diclofenac for the following 3 days.

All information concerning post-operative pain at rest and during movement was collected and recorded, either directly during the patients' stay at the hospital on the first day after the surgery, or by phone after the discharge. The latter interview also included questions on the patients' functional activities.

The intensity of post-operative pain was evaluated using the Visual Analogue Scale (VAS, where 0 represented "no pain", 1-3 points represented "mild pain", 4-6 points represented "medium pain", 7-8

Table 1. Demographic and surgical data of the study groups

	Fentanyl group N (%)	Control group N (%)	Total N (%)	p
Patients	62 (50)	62 (50)	124 (100)	
Female	35 (56.5)	38 (61.3)	73 (59)	p>0.05
Male	27 (43.5)	24 (38.7)	51 (41)	p>0.05
Age (years)	58.30±16.12	58.87±15.04	57.58±15.55	p>0.05
Surgical procedures:	62 (100)	62 (100)	124 (100)	p>0.05
Laparoscopic cholecystectomy	30 (48.4)	28 (45.2)	58 (46.8)	p>0.05
Laparoscopic hernia repair	12 (20.0)	8 (13.0)	20 (16.1)	p>0.05
Open hernia repair	13 (20.3)	20 (32.2)	33 (26.6)	p>0.05
Laparoscopic gastric fundoplication	7 (11.3)	6 (9.6)	13 (10.5)	p>0.05

Table 2. The intensity of pain on the first day after the surgery, at rest
Abbreviations: *VAS - Visual Analogue Scale*

VAS of pain at rest (from 0 to 10)			
Post-operative days	Fentanyl group	Control group	p
1	0.5±0.11	1.28±0.13	p<0.05
2	0.29±0.93	1.44±0.12	p<0.05
3	0.21±0.07	0.80±0.08	p<0.05
4	0.21±0.07	0.18±0.06	p>0.05

Table 3. The intensity of pain on the first day after the surgery, during movement
Abbreviations: *VAS - Visual Analogue Scale*

VAS of pain during movement (from 0 to 10)			
Post-operative days	Fentanyl group	Control group	p
1	1.11±0.17	2.54±0.15	p<0.05
2	0.61±0.14	2.57±0.15	p<0.05
3	0.52±0.13	1.85±0.12	p<0.05
4	1.05±0.15	0.85±0.09	p>0.05

points meant "severe pain" and 9-10 points meant "unbearable pain") following 8 hours after the surgery as well as on the subsequent 2nd, 3rd and 4th post-operative days both at rest and during movement.

Limitations in daily activities were recorded using the Functional Activity Score (FAS) in the following manner: 0 meaning "no limitations", 1 - "some limitations", and 2 - "severe limitations", ie difficulties or need for assistance with basic daily activities that one is expected to perform independently - personal hygiene, getting dressed, feeding, getting in and out of bed, etc [19].

Statistical analysis was performed using SPSS 17.0 package, Mann-Whitney U and exact Chi square test. For the testing of statistical hypotheses, $p < 0.05$ was used as statistically significant.

Results

The demographic and surgical characteristics of both groups are presented in Table 1.

Patient groups were comparable by mean age, gender and the type of surgery. The types of the surgery performed were as follows: 13 (10.5%) laparoscopic gastric fundoplications, 58 (46.8%) laparoscopic cholecystectomies, 20 (16.1%) laparoscopic hernioplasties, 33 (26.6%) open hernioplasties (Shouldice or Lichtenstein methods).

Pain both at rest (Table 2) and during movement (Table 3) on the 1st, 2nd and 3rd post-operative days, according to the VAS, was statistically lower in the FG as compared to the CG. On the 4th post-operative day, pain intensity at rest and during movement did not differ between the two groups.

Due to more severe post-surgical pain the CG patients had greater demand for additional analgesia and received 5 times more doses of diclofenac on the first day after the surgery (Table 4). The need for NSAID for the CG patients remained also significantly higher for the next two post-operative days ($p<0.05$); this need appeared to be comparable with the FG patients on the 4th post-operative day only. The total number of NSAID doses used per patient on demand was 3.11±0.59 in the CG, and 0.73±0.16 in the FG ($p<0.05$).

The influence of pain on daily activities at home on the 2nd post-operative day was scored as "no limitation" by 57 (92%) patients and as "some limitation" by 5 (8%) patients of the FG, while "no limitation" was scored by 37 (60%) patients and as "some limitation" by 25 (40%) patients of the CG ($p<0.05$) (Table 5).

Some adverse events were recorded in the FG patients only: 4 (6.45%) patients experienced dizziness, 1 (1.61%) had syncope, and 3 (4.83%) suffered from nausea. All of them had their body mass index >25, were aged 67-83 years and were on regular antihypertension medications.

Table 4. Need for non-steroidal anti-inflammatory drugs following surgery
Abbreviations: *NSAID - non-steroidal anti-inflammatory drug*

NSAID doses received by patients (mean)			
Post-operative days	Fentanyl group	Control group	p
1	0.19±0.05	0.92±0.05	p<0.05
2	0.19±0.07	1.16±0.08	p<0.05
3	0.11±0.05	0.80±0.10	p<0.05
4	0.23±0.06	0.23±0.59	p>0.05
Total doses per patient	0.73±0.16	3.11±0.59	p<0.05

Table 5 Distribution of functional activity scores after the discharge from the hospital on the 2nd-4th post-operative days (FAS 0-2)
Abbreviations: *FAS - Functional Activity Scores*
Notes: **p<0.05*

FAS	Fentanyl group, patients N (%)			Control group, patients N (%)		
	2-nd day	3-rd day	4-th day	2-nd day	3-rd day	4-th day
0 (no activity limitation)	57 (92)	57 (92)	61 (98)	37 (60)	49 (79)	60 (97)
1 (some activity limitation)	5 (8)*	5 (8)	1 (2)	25 (40)*	13 (21)	2 (2)
2 (severe activity limitation)	0	0	0	0	0	0

Discussion

An early discharge from the hospital is feasible when rapid recovery can be expected and when the risk of surgery-related and anaesthesia-related adverse effects (ie pain, nausea, fatigue) is low. The patients must feel fit enough, and symptom intensity must be so low that safe self-care can be ensured [20].

Despite our ability to control pain during and immediately after the surgery with the help of local anaesthetic agents, opioids, and cyclo-oxygenase (COX) inhibitors, the pain that persists after the surgical

wound has healed remains a major clinical problem [21].

Given the rise in ambulatory and one-day surgeries worldwide, greater effort has been taken to assess post-operative recovery with the focus on analgesia and early mobilisation [22]. The fear of post-operative pain scares many patients awaiting surgery. Gan et al. published the results of a US National survey: before surgery, post-surgical pain was the most prominent concern among patients surveyed, with 80% of responders expressing concern about this issue. After the surgery, which in 50% of cases was performed in an outpatient setting, these concerns appeared to be true in 85.7%, and 75.5% of these patients scored their pain as moderate, severe or extreme; 87.9% of inpatients and 79.2% of outpatients reported pain after hospital discharge [23]. Presence and intensity of acute post-operative pain are major risk factors for the development of chronic post-operative pain that occurs in 10%-50% of patients, which is both distressing and reduces the quality of life [8,21,22].

Opioid analgesia remains the mainstay of acute post-operative pain management, providing high-quality effective pain relief despite its potential side effects. Opioid abuse, however, has reached epidemic proportions in the United States, raising awareness of opioid abuse as a public health issue. Dealing with an opioid epidemic firstly requires that responsible use of opioids is medically warranted [24-27].

The use of non-opioid medication is often enough for functional relief of pain [4,28-30]. Non-opioids play an ever-increasing role in the treatment of post-operative pain; either on their own for mild to moderate pain management, or in combination with other analgesic approaches, in particular opioids, when the pain is severe. According to the practice recommendations, unless contraindicated, patients should receive an around-the-clock regimen of NSAID for acute post-operative pain control as post-operative pain is the type of acute pain due to surgical damage of the tissue with an inflammatory reaction [31]. However, patients are not always satisfied with analgesic effects of NSAID, and NSAID appear to be a common cause of adverse drug events (ADEs), accounting for 25% of ADEs reported in the United Kingdom and 21% in the United States [32]. NSAID could lead to the occurrence of acute kidney or liver injury, cardiovascular complications and gastrointestinal disturbances such as dyspepsia, heartburn, nausea, vomiting, bleeding or perforation as well as various neurological abnormalities, etc. [33-40].

TFP is an alternative to i/v or oral opioids. These patches provide continuous medication for 2 to 3 days which leads to fewer opioid-related adverse events and pain control compared to intravenous opioids. Specificity of the transdermal route includes the slow desired effect as levels of fentanyl concentration in the plasma reach a plateau approximately 12-24 hours after the application of the patch and decline slowly following the removal of the patch (at 72h). The increase of fentanyl concentration in the plasma occurs slower in elderly patients [6,41-42]. The idea to use TFP was based on the personal experience of one of the authors in dealing with post-operative pain following a hospital discharge even after a minimal surgery. The analgesic effects of NSAID are short-lived, therefore additional doses, even exceeding the daily recommended doses, or the use of over-the-counter (OTC) analgesia is required. Widespread availability of OTC analgesics and the limited knowledge of analgesic risk by consumers and thus improper use of these drugs could potentially present a serious health risk [43,44].

A rather alarming population-based cross-sectional study from the Netherlands showed that OTC NSAID were used by 30% of the general population, and 13% of high-risk patients with gastrointestinal, cardiovascular or renal disorders. Moreover, at least 333,000 Dutch adults use OTC NSAID in dosages exceeding the maximum at any given time [45]. Evidence of such high levels of uncontrolled use of OTC NSAID as shown by the above study raises concerns regarding potential epidemic risks of damaging OTC NSAID side effects across other populations.

By applying TFP, we expected to achieve longer lasting analgesia following the discharge from the hospital. Our patients who were administered TFP immediately post-surgery experienced significantly lower intensity of pain on the three consecutive post-operative days both at rest and during movement as compared to the control group.

Because of more intense pain, patients of the control group were likely to require more additional doses of NSAID (although their pain rating according to VAS may be evaluated as “mild”): on the 1st day following the surgery they received nearly 5 times more doses of NSAID, on the 2nd day they needed over 6 times more doses, and on the 3rd day they were administered 7.3 times more doses of NSAID as compared to the fentanyl group patients; only on the 4th day the number of additional NSAID doses levelled across both groups.

Our study demonstrated that analgesia by applying TFP after *minor* surgical procedures and during short-term hospital stays allowed for sufficient analgesia within the initial few days following the surgery and helped to reduce the number of additionally required NSAID doses by 4.3 times.

Six patients in the fentanyl group experienced adverse effects (dizziness, nausea, syncope); all of these patients were 67 years or older. This raises the hypothesis that elderly patients may need TFP of a lower release. Analgesic effects as well as adverse effects when using TFP may be dose-de-

pendent, as demonstrated by Gupta et al., who applied TFP 3 hours prior to the surgery in order to assess the difference in mean duration and the quality of post-spinal analgesia in patients who underwent elective abdominal hysterectomy [46]. Patients of Group I received placebo patch, Group II - 25 mcg/h TFP, Group III - 50 mcg/h TFP. The mean difference of VAS pain score was significantly lower in Group III and Group II. The requirement of rescue analgesic dose was significantly lower in Group II, and no rescue analgesic was needed in Group III (p=0.00), with side effects of nausea and vomiting in one patient from Group II and in three patients from Group III (p>0.05)

There are some limitations to our study. Firstly, we did not measure the fentanyl plasma levels. But the results of our study regarding the timing of the analgesic effects of the fentanyl transdermal patch are consistent with the results of a study from South Korea[41]. The authors used TFP (25 mcg/h) for alleviation of post-surgical pain following laparoscopic cholecystectomies. They applied TFP 14 hours prior to surgery which allowed them to reach a peak (3.27+-0.34 nanog/mL) in the plasma fentanyl levels of their study group one hour following the operation. The authors conclude that FTA 12-14 hours prior to surgery ensures maximum fentanyl plasma levels immediately after the surgery which are then maintained at slightly lower levels for 48 hours post-surgery. Our aim was to ensure sufficient analgesia after the patient is discharged from the hospital, and, similar to the authors of the above-mentioned study, we observed favourable analgesic effects for around 60 hours when the risk of post-operative pain is at its peak, as observed in our control group.

Secondly, our study populations were not homogeneous in terms of the type of surgery, although all of them can be attributed to the *minor* surgery group - laparoscopic repair of inguinal hernia, gastric fundoplication, cholecystectomy as well as *open* repair of inguinal hernia. Moreover, the size of our study group was too small to allow reliable data analysis based on performed surgical procedure. Large-scale prospective studies might help to confirm the safety and efficacy of a single FTA dose as a part of multimodal analgesia during the early post-operative period after different elective *minor* surgeries.

Conclusion

Patients administered with FTA experienced significantly more effective pain control leading to less restricted daily activity within the first few post-operative days. Although NSAID could not be avoided entirely, the consumption of these drugs proved significantly lower in the group of patients administered with TFP. TFP should be used with caution in elderly patients due to potential risk of adverse effects.

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Patient consent for publication

Informed Consent.

Ethics Approval

Center of Bioetics of Lithuanian University of Health approved this study on December 21, 2017 No. BEC-MF-161.

Data Availability Statement

Data is available upon reasonable request.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The author reports no conflicts of interest in this work.

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ŪMINIO SKAUSMO MALŠINIMAS TRANSDERMINIU FENTANILIO PLEISTRU PO TRUMPALAIKIO POOPERACINIO LAIKOTARPIO LIGONINĖJE

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Raktažodžiai: analgezija, opioidai, transderminis fentanilio pleistras, chirurgija, nespecifiniai vaistai nuo uždegimo.

Santrauka

Transderminis fentanilio pleistras (TFP) vartojamas malšinti stiprų ilgalaikį skausmą, tačiau moksliniais tyrimais pagrįstos informacijos apie jo panaudojimo galimybes ūminio skausmo malšinimui nėra daug.

Tikslas. Palyginti pooperacinio nesteroidinių vaistų nuo uždegimo (NSAID) ir TFP efektyvumą mažinant skausmą ir jo sukeliamus kasdienės veiklos apribojimus po planinių „mažųjų“ pilvo operacijų.

Pacientai ir metodai. Perspektyvinio, atsitiktinių imčių tyrimo metu buvo tiriami 18 metų ir vyresni pacientai, kuriems buvo atliktos planinės laparoskopinės tulžies pūslės šalinimo, skrandžio antirefliuksinės (gastrofundoplikacijos) ar kirkšnies išvaržos šalinimo operacijos laparoskopu ar „atviru“ būdu. Į tyrimą įtraukti pacientai buvo suskirstyti į dvi grupes – 62 asmenys sudarė fentanilio grupę (FG), kiti 62 - kontrolinę grupę (CG). Abiejų grupių pacientams pabaigus operacijas buvo užklijuojamas pleistras trims pooperacinėms paroms, bet FG grupėje po šiuo pleistru buvo priklijuojamas 50mcg/val transderminis fentanilio pleistras. Per pirmąsias keturias dienas pooperacinio skausmo malšinimui pacientams pagal poreikį buvo skiriamas diklofenakas. Šiuo laikotarpiu kasdien buvo vertinamas skausmo intensyvumas ramybės metu, bei pacientams judant, naudojantis vizualine analogine skausmo skale. Kasdienės veiklos aktyvumo apribojimai vertinti naudojantis funkcinio aktyvumo balų sistema: 0 – nėra apribojimų, 1 – nežymūs apribojimai, 2 – ryškūs apribojimai.

Rezultatai. Pirmųjų trijų pooperacinių dienų metu FG pacientai atžymėjo mažesnio intensyvumo skausmą ir ramybėje, ir judesių metu; tuo tarpu CG pacientai suvartojo 5 kartus daugiau diklofenako dozių per pirmąją pooperacinę dieną, bei poreikis didesniam NSAID vartojimui buvo stebėtas ir kitas dvi dienas ($p<0.05$). Bendras pagal poreikį suvartotų NSAID dozių skaičius sudarė 3.11 ± 0.59 kontrolinės grupės pacientams, tuo tarpu FG jis siekė 0.73 ± 0.16 ($p<0.05$). Skausmo įtaką kasdienei veiklai antrą pooperacinę dieną 0 balų įvertino 92% FG pacientų bei 1 balu - 8%; atitinkamai kontrolinės grupės pacientų įvertinimai nuvo 60% ir 40% ($p<0.05$).

Išvados. Pacientai po „mažųjų“ pilvo operacijų su TFP ankstyvuoju pooperaciniu laikotarpiu jautė efektyvesnį nuskausminimą, tuo pačiu ir mažiau ribotą kasdienį aktyvumą bei mažesnį papildomo nuskausminimo NSAID poreikį.

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