TRANSDERMAL FENTANYL PATCH FOR ACUTE PAIN CONTROL AFTER SHORT INTRAHOSPITAL STAY

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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. Postoperative 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-steroidal 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-
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 Health 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 laparoscopic 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-
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.

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

<table>
<thead>
<tr>
<th>NSAID doses received by patients (mean)</th>
<th>Fentanyl group</th>
<th>Control group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-operative days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.19±0.05</td>
<td>0.92±0.05</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>2</td>
<td>0.19±0.07</td>
<td>1.16±0.08</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>3</td>
<td>0.11±0.05</td>
<td>0.80±0.10</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>4</td>
<td>0.23±0.06</td>
<td>0.23±0.59</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Total doses per patient</td>
<td>0.73±0.16</td>
<td>3.11±0.59</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>FAS</th>
<th>Fentanyl group, patients N (%)</th>
<th>Control group, patients N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-nd day</td>
<td>57 (92)</td>
<td>57 (92)</td>
</tr>
<tr>
<td>3-rd day</td>
<td>57 (92)</td>
<td>61 (98)</td>
</tr>
<tr>
<td>4-th day</td>
<td>37 (60)</td>
<td>49 (79)</td>
</tr>
<tr>
<td>2-nd day</td>
<td>37 (60)</td>
<td>49 (79)</td>
</tr>
<tr>
<td>3-rd day</td>
<td>49 (79)</td>
<td>60 (97)</td>
</tr>
<tr>
<td>4-th day</td>
<td>60 (97)</td>
<td></td>
</tr>
</tbody>
</table>

Notes: *p<0.05
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-
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.

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.

Acknowledgments

We thank Mrs Aiste Smith for English language proofreading and editing services.

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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Išvados.

Pacientai ir metodai. Perspektyvinio, atsitiktinių imčių tyrimo metodika. Tyrimas vyko abejojančios išvados pooperacinių pažeidimų, naudojant transderminį fentanilio pleistrą, chirurgija, nespecifiniai vaistai nuo uždegimo.

Pacientai po "mažųjų" pilvo operacijų su TFP ankstyvoje pooperacine medicinoje malšinimui per pooperacinę parą, bet FG grupėje po šiuo pleistru buvo prikabintina pooperacineje paroje. Čia paaiskėjo didesnėks apribojimų, 2 – ryškūs apribojimai. Pooperacine skausmo malšinimo vartojamoje medžiagoje (NSAID) ir TFP efektyvumą mažinant skausmą ir jo sukęjimus kasdienės veiklos apribojimais po planinėje "mažųjų" pilvo operacijų. Tikslas. Transderminis fentanilio pleistras (TFP) vartojimas mažinti pooperacinius pažeidimus ir skausmą po operaciją.


