



## Reconsidering Post-Operative Application of Transdermal Fentanyl in Day Surgery Adult Patients: Benefits and Detriments

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### Short Communication

Acute postoperative pain remains a major problem despite the safety of the drugs used in perioperative settings and the guidelines available for correct management of postoperative pain [1]. With day or ambulatory surgery, nowadays hospital stay for up to 24 h after surgery is quite common [2]. Early discharge demands a rapid recovery, also low incidence and intensity of surgery and anesthesia related side effects, such as pain, nausea and fatigue. The patients must be fit enough and symptom intensity so low that self-care is feasible in order to secure the quality of care [2].

Many patients suffer from postoperative pain. A survey of 250 patients demonstrated that around 80% of patients experienced acute pain after surgery; of these patients, 86% had moderate, severe, or extreme pain, with more patients experiencing pain after discharge than before discharge [3]. In a national US survey of 300 adults who had undergone surgery within the previous 5 years, 75% of those who reported pain during the immediate postoperative period in an outpatient setting described its severity as moderate (42%), severe (25%), or extreme (4%) [3].

In a systematic review and meta-analysis of 33 studies, the following preoperative predictors were found to be negatively associated with pain control immediately after surgery: Young age, female sex, smoking, history of depressive or anxiety symptoms, sleep difficulties, obesity, presence of preoperative pain and the use of preoperative analgesia [4]. During the preoperative visit, identification of patients who may be prone to developing pain during or following surgery may allow for physical, emotional, and psychological preparations to mitigate surgical stress [3].

It is obvious that uncontrolled postoperative pain results in the development of postsurgical complications, poor healing and functioning, and impaired quality of life [3,5]. Moreover, presence and intensity of acute postoperative pain are major risk factors for the development of chronic postoperative pain due to a combination of factors emerging as contributors, most notably inflammatory processes, tissue and nerve damage, and central sensitization [6]. Persistent pain occurs in 10% to 50% of patients, which is both distressing and reduces the quality of life; also may result in prolonged opioid use [2,3,7,8]. It may limit mobility leading to muscle wasting, thrombi formation and a risk for the development of pulmonary complications; sleep deprivation due to pain may additionally contribute to anxiety and depression in patients, and delirium in the elderly [3,4,9].

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Regarding the type of surgery, numerous studies of patients have demonstrated that the presence and intensity of acute postoperative pain (moderate, severe, or evaluated as 'high scores') are significant predictive risk factors for the development of chronic pain: Severe pain on the 1<sup>st</sup> or 3<sup>rd</sup> postoperative day in cardiac surgery, sternotomy or thoracotomy, on the 1<sup>st</sup> to 10<sup>th</sup> days in orthopedic surgery, or within the 1<sup>st</sup> week in laparoscopic cholecystectomy and groin-hernia repair [3]. Following other minor abdominal surgical procedures, postoperative pains have also shown procedure-related individual patterns requiring procedure-specific analgesic treatment regimens [3,10,11]. In order to reduce the incidence and intensity of acute pain immediately after the surgery and for the subsequent few days as well as to prevent its progression into chronic pain, more aggressive targeted analgesic measures are required [3,5].

Intravenous opioids are effective analgesic agents that remain the mainstay of postoperative pain management [12]. However, they have substantial short-term and long-term adverse effects such as respiratory depression, nausea and vomiting, ileus, somnolence, hypotension; development

of tolerance, hyperalgesia, cognitive dysfunction, hormonal changes, immune dysmodulation, and some patient subgroups are especially vulnerable (e.g. patients who are older, obese, smoke, have sleep apnea or are using certain concomitant medications) [1,3,7,12-15]. Besides, opioid dependence and abuse has become a major concern and has caused dramatic increase in opioid overdose deaths [15- 20].

Perioperative multimodal analgesia by combining analgesic drugs with different modes of action helps reduce postoperative opioid consumption and thus avoid their adverse effects [7,9,12-13]. It may contain multiple methods (local or regional anesthesia) and drugs, including non-opioids (NSAIDs, acetaminophen, COX2 inhibitors, NMDA-receptor antagonists, gabapentin or pregabalin, glucocorticoids, alpha-2 adrenergic agonists) and opioids [2,3,7,9,11-14]. The Enhanced Recovery after Surgery (ERAS) perioperative pain management guidelines have been developed and used for different types of surgery [7,13]. Yet, although multimodal analgesic therapy has significant benefits over opiate therapy alone [9,12], the literature on multimodal analgesia often shows variable degrees of success, even with studies utilizing the same adjuvant medication. Besides, the adverse effects of non-opioid drugs should be also taken into account [1,9,14]. No new adjuvants have appeared in the last years that would robustly reduce opioid consumption [2-3]. Thus, although prophylactic use of opioids in preventing postoperative pain should be avoided [14], opioids still play their role in the management of postoperative pain immediately after surgery as 'rescue analgesics' and are often prescribed thereafter [2,9,11,13,21].

Even small exposures to opioids can result in addiction and chronic use [17]. Around 6% of patients switched to chronic opioid use following postoperative opioids, regardless of the type of surgery (minor or major), as compared to only 0.4% of the non-surgical control group [22]. A study by Shah et al. [23] showed that the probability of long-term opioid use increased most sharply in the first days of therapy, particularly after an opioid prescription from 5 days to 1 month. The rate of long-term use was relatively low (6.0% on opioids 1 year later) for persons with at least 1 day of opioid therapy, but increased to 13.5% for persons whose first episode of use was  $\geq 8$  days and to 29.9% when the first episode of use was  $\geq 31$  days; transitions from acute to long-term therapy can begin to occur quickly: The chances of chronic use begin to increase after the third day supplied and rise rapidly thereafter; prescribing  $<7$  days (ideally  $\leq 3$  days) of medication when initiating opioids could mitigate the chances of unintentional chronic use [23]. Risk factors found to be associated with new persistent opioid use are preoperative tobacco, alcohol and substance abuse, mood disorders, and preoperative pain disorders (back, neck, joint, and centralized pain) [22]. Therefore, the management of chronic pain with opioids necessitates a meticulous balance between the risks of opioid misuse or diversion and the benefits of adequate pain relief [1].

Thus, analgesia is mostly needed within the initial few days after surgery, depending on the surgery type. While hospitalized, patients have the opportunity to receive effective analgesia on demand. After discharge, the choice of analgesic agents becomes more limited: oral NSAIDs, COX inhibitors, paracetamol, gabapentinoids, opioids, all used under poor control and with high risks of overdosing, may result in adverse effects (gastric, hematological complications, dizziness, respiratory problems) or, finally, addiction. A single application of Fentanyl Transdermal Patch (FTP) applied on the operative day may stay effective within the next 3 days when the postoperative pain is

most likely and may help avoid additional painkillers [24]. Having in mind that the risk of addiction also increases with  $>3$  days of opioid use, the one-dose application of FTP before discharge might help avoid oral opioid prescription and provide effective analgesia for the next 3 days, with low risk of subsequent addiction.

Levels of slow-release fentanyl concentration in the plasma reach a plateau approximately 12 h to 24 h after the application of the patch and remain relatively constant for the remainder of the 72-h application period, declining slowly following the removal [15,25]. FTP has advantages over i/v opioids as it provides a steady-state plasma level of fentanyl for 3 days with the use of one patch, helping to avoid the peak-related complications which results in reduced risk of adverse effects and longer pain control compared to intravenous opioids [21].

FTP is approved and widely used for the alleviation of chronic pain that requires continuous long term opioid administration, restricted to 'severe' in the EU and to both 'moderate' or 'severe' in the USA [15,26]. FTP has not been approved for alleviation of acute pain, and in the light of the opioid crisis and potential dangers the opinion on the use of FTP for acute pain management remains controversial [21].

However, well-designed, multicentre clinical studies have proved FTP to be an effective and generally well-tolerated method of managing acute postoperative pain and achieving faster recovery in patients following abdominal, thoracic or orthopedic surgery compared to i/v opioids or non-opioid analgesics [21,27]. If selected carefully, minding the possible risks of opioid adverse effects in certain patient populations and the type of surgery (by the likelihood of development of chronic pain), as well as taking additional safety measures, the use of FTP for the alleviation of postoperative pain in adults deserves reconsideration.

Studies regarding the effects of FTP for postoperative pain suggest the application of FTP a few hours prior to surgery in order to achieve fentanyl peak levels for sufficient analgesia right after surgery [13,21]. However, additional heating during the surgery and the use of perioperative medications may lead to increased opioid blood levels and respiratory distress [15,21]. Postoperative FTP might help to avoid these intraoperative complications, and more studies are required to test this hypothesis.

FTP may not be indicated for patients who are at a high risk of severe side effects or may require dose adjustments: Patients with fever, any significant lung, renal or hepatic impairment; elderly, cachectic, or debilitated patients who have a tendency toward altered metabolism of the FTP due to their poor body fat stores, muscle wasting, or altered clearance; those with concomitant use of mixed opioid agonist/antagonists, general anesthetics, tranquilizers, alcohol, sedative-hypnotics, monoamine oxidase inhibitors, serotonergic drugs, all CYP3A4 inhibitors;  $<18$  years of age; lactating, and patients with myasthenia gravis [15,21].

Although FTP allows avoiding long term opioid prescription, there are dangers related to the misuse of FTP, including intentional fentanyl extraction from FTP in order to be administered intravenously, insufflated or inhaled after volatilization or by mistake, or intoxication due to defective membrane and fentanyl leakage. Patients with drug dependency and potential for abuse should not receive FTP [15,22]. Safer commercially available fentanyl patches might minimize the potential for abuse and misuse of FTP.

## Conclusions

The advantages of a single dose of FTP for the management of acute postoperative pain in a day-surgery setting for adults include: 1) Analgesic effects that last throughout the period when pain severity and the risk of its evolution into persistent pain is most expressed, and when the risk of addiction is relatively low; 2) convenient route of administration, pre-programmed delivery (no risk of programming errors/incorrect dosage); 3) stable opioid plasma levels, low risk of overdosing and adverse effects; 4) no need for additional opioid prescription. The dangers include the risk of unpredictable plasma levels resulting in adverse effects in certain patient subgroups (those having chronic lung, renal, hepatic disorders; using concomitant sedative and other aforementioned medications; elderly or exposed to an increased body temperature); risks of accidental or intentional misuse. FTP application prior to surgery, although it may help to achieve sufficient fentanyl plasma levels faster, is related to the procedure-related risk of overheating and drug interactions leading to respiratory problems.

In combination with other modes of analgesia, the administration of FTP after one-day surgery may be beneficial and safe for carefully selected adult patients: those who are exposed to a high risk of developing chronic pain (young, female, smokers, suffering from mood or sleep disorders or obesity), those with low opioid-related risks, also based on the type of surgery (having in mind the likelihood of chronic pain). Safe forms of FTP and patient education may serve as additional measures in this setting.

More studies are needed to reveal the benefits and risks of short-term FTP use after minor surgery in clinical setting.

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