ORIGINAL RESEARCH

Efficacy of fentanyl transdermal patch in impacted mandibular third molar surgery- A original research

[1]Dr. K Pratyusha, [2]Dr (Lt Col) Sunil R, [3]Dr. Ashmeet Kaur, [4]Dr. Saurabh. S. Pillai, [5]Dr. Bathini Dilip Chakravarthy, [6]Dr Tharini Satheesh, [7]Dr. Rahul VC Tiwari

[1]Assistant Professor, Department of Anaesthesia, Government General Hospital, Suryapet, Telangana, India
[2]Department of Oral and Maxillofacial Surgery, Al Azhar Dental College and Hospital, Thodupuzha, Kerala, India
[3]PG Resident, Department of Oral and Maxillofacial Surgery, NIMS Dental College, Jaipur, Rajasthan, India
[4]BDS, MDS (OMFS), Fellowship in Oral Oncology(Sharad Pawar Dental College, Sawangi), Consultant Oral Surgeon, Bangalore, Karnataka, India
[5]Assistant Professor, Department of Oral and Maxillofacial Surgery, Tirumala Institute of Dental Sciences and Research Centre, Bardipur, Nizamabad, India
[6]MDS, Assistant Professor, Dept of Oral and Maxillofacial Surgery, Saveetha Dental College and Hospitals, Chennai, 77, Tamil Nadu, India
[7]OMFS, FOGS, (MHA), PhD Scholar, Dept of OMFS, Narsinhbhai Patel Dental College and Hospital, Sankalchand Patel University, Visnagar, Gujarat, India

Correspondence:
Dr. K Pratyusha
Assistant Professor, Department of Anaesthesia, Government General Hospital, Suryapet, Telangana, India
Email: pratyushakotari006@gmail.com

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ABSTRACT

Aim: The purpose of the present study was to assess the efficacy of fentanyl transdermal patch in case of impacted mandibular third molar surgery.

Methodology: 20 patients within the age group of 18–40 years with asymptomatic impacted mandibular third molars were equally divided into 2 groups as group A & group B which underwent surgery in Local Anaesthesia. In every patient one side belonged to group A and other side belonged to group B. 50 µg FTS was applied in group A while placebo patch was applied in group B.

Results: Patients in group A performed significantly better than group B in terms of mean pain intensity scores assessed by VAS and VRS along with minimum need of post-operative rescue analgesics.

Conclusion: It was found that FTS resulted in significantly better pain relief, longer pain-free intervals, and lesser post-operative analgesic consumption.

Keywords: Analgesia, fentanyl, transdermal administration, third molar surgery.

INTRODUCTION

Surgery results in damage to local tissue with consequent release of analgesic substances (prostaglandins, histamine, serotonin, bradykinin, 5- hydroxytryptamine, substance P) and generation of noxious stimuli that are transduced by nociceptors and transmission to the

neuraxis by A delta and C nerve fibers.[1] Post-operative good analgesia improves the quality of life , reduces the morbidity and provides greater comfort, allowing for rapid recovery and early return of patients to daily routine. This may be achieved by use of non-steroidal anti-inflammatory drugs (NSAIDS), opioids, or a combination.[2] Some patients present with bilaterally similar impacted third molars provides an opportunity to carry out two similar surgical procedures on separate occasions. So, it is not surprising that the impacted third molar model has been widely used in clinical pharmacology to evaluate a variety of therapeutic measures.[3] A relatively new phenomenon, an adhesive skin patch has been formulated that delivers drug systemically. In addition, the drug when applied topically in the form of a transdermal patch, penetrates the skin, subcutaneous fatty tissue, muscle and finally into the blood stream in amounts sufficient to exert therapeutic effects without reaching higher plasma drug concentrations when compared to parenteral or intramuscular route.[4,5] NSAIDS and Opioids administered through skin patches include Diclofenac, Ketoprofen and fentanyl transdermal patch. Ketoprofen is a propionic acid derivative which has analgesic and antipyretic effects. Ketoprofen used in IM/IV and oral preparations by several authors for postoperative analgesia for moderate to severe postoperative pain. Ketoprofen transdermal patches in various doses have been found to be more effective in traumatic and nontraumatic patients without additional side effects.[6] Fentanyl was patented for use in a transdermal patch since 1984, and it has proven to be extremely effective in the treatment of severe chronic pain [7] and, interestingly, in the treatment of some postoperative pains.[8] Fentanyl Transdermal System (FTS) is a rectangular transdermal patch containing a high concentration of fentanyl, a potent, short-acting Schedule II opiate.[9] FTS includes a drug reservoir that contains Fentanyl in gel matrix, a release membrane that allows time- and surface-limited absorption of the drug, and an adhesive backing, providing a continuous systemic delivery of Fentanyl for 72 hours. It offers a prolonged and uniform analgesic effect, as well as euphoria and dysphoria.[7] Patch dosage is 50 μg per hour. Because of its low molecular weight, high potency and lipid solubility, soon after application to intact skin, a Fentanyl depot concentrates in subcutaneous fat and it is then gradually released to the systemic circulation. Peek plasma concentration is reached between 24 and 72 hours of the treatment.[10]

AIM OF THE PRESENT STUDY

The purpose of the present study was to assess the efficacy of fentanyl transdermal patch in case of impacted mandibular third molar surgery.

METHODOLOGY

20 patients within the age group of 18–40 years with asymptomatic impacted mandibular third molars were equally divided into 2 groups as group A & group B which underwent surgery in Local Anaesthesia. Randomization was accomplished using envelope containingrandom number of tooth and postoperative paincontrol protocol. Both, the operator and patients wereblinded to the use of FTS. The lower third molars were evaluated on the panoramicradiographs in order to confirm symmetrical positionon both sides. In each patient, surgical extractions of bilateral impacted lower third molars were done in separate visits, the interval between surgeries being approximately two weeks. All the procedures were performed in local anesthesia using 2% lidocaine chloride with adrenaline 1:80.000. Postoperative pain control regimens were randomly divided into two groups (FTS and control group). After the first operation, as the FTS group, all the patients received a transdermal patch containing Fentanyl. In every patient one side belonged to group A and other side belonged to group B. 50 μg FTS was applied in group A while placebo patch was applied in group B. Patients were advised to take an additional analgesic tablet as soon as their pain reached a moderate level, recording the exact moment of taking additional analgesic, so that

we could count the elapsed time till the occurrence of pain. After each operation, patients were instructed to record the number of tablets used. Each patient was evaluated at the follow-up control 24 hours postoperatively. Postoperative pain was evaluated using a 100 mm long visual analogue scale (VAS) with verbal descriptors "no pain" at the left end of the scale and "extremely severe pain" at the right end. The same examiner who assessed the patients preoperatively performed clinical measurements during follow-up examinations. Trismus and facial edema, measured as stated previously, were recorded as the differences between preoperative (baseline) and postoperative (after 24 hours) values. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS for Windows, version 20.0; SPSS Inc., Chicago, IL, USA). The normality of the data was evaluated using Shapiro–Wilk test. Categorical variables were analyzed by $\chi 2$ test. Statistical differences between groups were accepted for *p*-values <0.05.

RESULTS

Data from 20 patients (13 females, 7 males) were included in the study, the mean age being 22.8 ± 4.2 years. There was no statistically significant difference between study groups with regard to duration of surgery in both sessions. (Table 1)

Table 1- Summary of duration of surgery, postoperative pain and the need for additional analgesics postoperatively.

Parameter	Fentanyl Transdermal System (Group A)		Control group (Group B)		*p*
Duration of surgery (min)	Mean ± SD		Mean ± SD		0.416
	22.9 ±7.3		25.3 ± 9.9		
Postoperative pain experience (Number of patients)	YES 4	NO 16	YES 14	NO 6	*p*<0.05
Need for additional analgesic (Number of patients)	YES 4	NO 16	YES 9	NO 11	*p*<0.05
Elapsed time to the pain perceived (h) - mean ± SD	4.0 ± 0.0		7.7± 4.3		-

Patients in group A performed significantly better than group B in terms of mean pain intensity scores assessed by VAS and VRS along with minimum need of post-operative rescue analgesics. A postoperative course was uneventful in all patients. However, when received a transdermal patch containing Fentanyl (FTS), patients experienced postoperative pain much more rarely than after surgery when received only a non-steroid anti-inflammatory drug. With respect to pain evaluation by the VAS, there was a statistically significant difference between the FTS and the control group after 24 hours. However, there was no statistically significant difference regarding postoperative facial swelling and trismus between the groups. (Table 2)

Table 2- Pain, swelling and trismus 24 hours after each surgery in the investigated patients.

Parameter	Fentanyl Transdermal System	Control group	*P*
Pain (VAS in mm)	0.9± 1.6	18.4 ±12.3	*p*<0.05
Swelling (mm)	6.9± 5.8	6.2 ±5.0	0.703
Trismus (mm)	11.2 ±9.1	11.9±7.9	0.623

DISCUSSION

The impact that postoperative pain, among other postoperative sequels, has on patient quality of life after lower third molar surgery is undoubted. Of all the symptoms associated with this procedure, postoperative pain is one that patients apprise as the most inconvenient. In the literature, there are many articles regarding control of postoperative pain using various analgesics over timeand comparing their efficacy. Theoretically, FTS couldbe an ideal drug for patients who are unable to eat due tosevere trismus, swelling and especially for patients withgastrointestinal problems such as ulcer.Although the efficacy of FTS has already been provenin the treatment of chronic cancer pain[11,12], there havebeen relatively few reports evaluating the effectivenessof FTS for the treatment of acute postoperative pain.According to the best of our knowledge, there is not anyreport in the literature on use of FTS for pain controlafter lower third molar surgery. However, there are few considerations that have to be discussed. Adverse events due to transdermal fentanyl use can be divided into three categories based largely on the intent of use: appropriate therapeutic use, inappropriate therapeutic use (misuse), and abuse. Abuse is defined as the intentional inappropriate use of the transdermal device, or its contents, for purposes other than those for which the transdermal device was intended or prescribed. This is typically done with euphoric intent, though it may occasionally be for suicidal reasons. Besides euphoric intent, other side effects such as skin irritation, nausea, fever, headache and clinically relevant respiratory depression are also described in the literature.[13] Case reports detail that elevation in skin or ambient temperatures from external sources, such as hot tubs or heating blankets, may lead to fentanyl overdose.[14] In our study, patients were distinctly informed about the procedure and possible side effects, thus monitoring of each patient was organized in agreement with family member. In very few cases, nausea was reported, especially when patients were moving, which was stopped at moment of siting. Other side effects were not reported. The recipient site on the skin that is most appropriate for application of FTS and its condition should also been discussed. The average skin thickness of the human body is 40 μm, but it ranges between 20 and 80 μm based on location, race, age, and gender, among other factors. In skin samples from 8 individuals, there was a >50% difference in the permeability of fentanyl.[15] Skin surface areas with similar stratum corneum thickness typically possess similar diffusion rates within an individual, explaining why the chest, extremities, and abdomen are acceptable sites for transdermal device application without the need for any dosage changes.[16,17] Also, following application of a transdermal fentanyl device to broken skin, blood fentanyl concentrations can rise 5-fold.[18] In our study, as a recipient site, skin of the upper arm was used, after meticulous inspection of the area. Recently, Fentanyl Iontophoretic Transdermal System (fentanyl ITS) was introduced as a system that has been approved especially for the management of acute, moderate- to-severe postoperative pain.[19] Fentanyl ITS is the first needle-free, self-contained, patient-activated system that delivers fentanyl directly through the skin by application of a low-intensity electrical field.[20] Future investigations should consider the use of Fentanyl ITS, as it allows patients to maintain an acceptable level of pain control following titration to comfort with a loading dose of opioid, while avoiding the first-pass effect and analgesic gaps associated with a delayed passive delivery using FTS patch.

CONCLUSION

FTS to be very effective in relieving postoperative pain after lower third molar surgery, with excellent tolerability. However, future clinical trials are necessary, with sufficient sample size and use of fentanyl ITS, regarding possible standard use of opioids for control of acute pain after oral surgery.

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