e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(1); 696-703

Original Research Article

To Study the Safety and Efficacy of Fentanyl TTS Patch in the Management of Multiple Rib Fracture: A Comparative Study

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Received: 30-10-2022 / Revised: 30-11-2022 / Accepted: 30-12-2022

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Conflict of interest: Nil

Abstract

Multiple fracture of ribs in blunt chest trauma, causes significant amount of pain, which can lead to hypoventilation, collection of secretions in the lungs, atelectesis and pneumonia. Adequate analgesia will decrease these complications. We studied the safety and effectiveness of Fentanyl Transdermal Therapeutic System (TTS) versus transdermal Diclofenac patch for analgesia in patients with multiple fracture of ribs.

Aim: To study the safety and efficacy of Transdermal fentanyl patch versus transdermal Diclofenac patch in case of multiple fracture ribs due to blunt chest trauma.

Methodology: It is a Prospective, Analytical, Hospital based study, in a Tertiary care Hospital in a Metropolitan City for a period of 18 months. Total 70 patients who had multiple rib fracture were studied. The study participants who fulfilled the inclusion criteria were enrolled in either group using method of random sampling. Group A was transdermal Fentanyl patch and Group B was transdermal Diclofenac patch group. Dosage of Fentanyl TTS- 50 μg, Diclofenac patch was 200mg. Each patch was given for a period of 72 hours. Patch was applied on the clean, intact skin over the chest wall. Clinical history, general, and Clinical examination findings were noted. Intensity of pain was noted using pain scale-1 to 10, ABG, respiratory rate for respiratory Depression and follow up secondary clinical examination were conducted on day 1, 2, 3, 4 and day 5. Patient's demographic details, examination findings, investigations findings like, CBC, Oxygen saturation, Chest X-ray and CT Scan of Chest were noted. Complications like, pneumothorax, hemothorax, pneumonia, requirement of ventilatory support were noted. All the findings were recorded in the standard, semi-structured, pre-validated case record proforma.

Results: We observed greater reduction and stabilization of the pulse rates in Fentanyl group (f-value: 246.81), as compared to Diclofenac group (f-value: 27.28). There was increase in Oxygen saturation in Fentanyl group (f-value: 28.1), as compared to Diclofenac group (f-value: 16.51). There was significant increase in Oxygen saturation in Fentanyl group (f-value: 28.1), as compared to Diclofenac group (f-value: 16.51).

Conclusion: Transdermal Fentanyl Patch is effective, non-invasive and safe, as an analgesic in treatment of Multiple rib fractures.

Keywords: Multiple Rib Fractures, Fentanyl TTS, Diclofenac Transdermal Patch, Blunt Chest Trauma.

Introduction

In, the management of patients with multiple rib fractures, effective pain treatment, pulmonary physiotherapy and respiratory care are essential components. [1,2] When treating the patient with multiple rib fractures, it is of particular importance to provide enough pain relief to allow for improvement of pulmonary mechanics, clearance of secretions, and patient mobility. A variety of approaches to pain management exist, which include systemic analgesia and regional techniques.[3]

The intention of our study, was not only to provide adequate analgesia for preventing the pain related sequelae, but also safe and non-invasive method of effective analgesia. We wanted to study, the use of transdermal Fentanyl Patch for management of fracture of ribs and to compare its safety and efficacy with transdermal Diclofenac patch.

Aims

To study the safety and efficacy of Transdermal Fentanyl TTS patch versus Transdermal Diclofenac patch in the management of pain in a case of multiple fracture ribs with Blunt chest trauma.

Materials and Method

It is a Prospective, Analytical, Hospital based study, conducted in a Trauma ward in a Tertiary care Hospital in a Metropolitan City, Lokmanya Tilak Municipal Medical College & Hospital, Mumbai. The study was done for a period of 18 months.

Sample size

1. Population size (for finite population correction factor or FPC) (N):>60.
2. Hypothesized % frequency of outcome factor in the population (p): 12.6%.
3. Confidence limits as % of 100(absolute +/- %) (d):+/- 5.
4. Design effect (for cluster surveys-DEFF): 5%.
5. After adding the 15% extra sample considering non-response = 60+ 10 = 70.

Therefore, the round figure of 70 decided to be the total sample size for the present study as follows: Fentanyl group: 35 patients and Diclofenac group: 35 patients. The study participants were enrolled in either group using method of random sampling.

Inclusion Criteria:

1. Both male and female patients with age group between 12 – 60 years
2. More than 3 multiple ribs fracture in a blunt chest trauma patient.
3. Blunt trauma to chest with pneumothorax or hemothorax with associated fracture of ribs.

Exclusion criteria:

1. Ribs fracture with major head injury (< 12 GC scale)
2. With long bone injury / spine injury
3. Traumatic amputation of limbs
4. Penetrating chest injury
5. Flail segment ribs fracture with ventilatory support.
6. Unconscious, intubated patient
7. Abdominal trauma patient which requiring surgery/ diaphragm injury
8. Pregnancy
9. History of chronic smoking / pulmonary tuberculosis
10. History of COPD

Methodology

Patients with history of trauma, fulfilling the inclusion criteria were enrolled in the present study after approval from the Institutional Ethics Committee. Written informed consent was obtained from the study participants. In the initial treatment, all patients were given Intravenous Pidimol-1000 mg,100 ml infusion for pain relief on receiving in the trauma ward as per our protocols.

The study participants were enrolled in either group using method of random sampling. Group A was transdermal Fentanyl patch and Group B was transdermal Diclofenac patch group. Dosage of Fentanyl TTS- 50 μg, Diclofenac patch was 200mg. Each patch was given for a period of 72 hours. Patch was applied on the clean, intact skin over the chest wall.

Study tools: Clinical history, General, and Clinical examination findings were noted. Intensity of pain was noted using pain scale-1 to 10. ABG, respiratory rate was noted for respiratory depression. Follow up, secondary clinical examination was conducted on day 1, 2, 3, 4 and day 5.

Patient's demographic details, examination findings, investigations findings like, CBC, Oxygen saturation, ABG, Chest X-ray and CT scan of Chest were noted. Complications like, pneumothorax, hemothorax, pneumonia, requirement of ventilatory support were noted. All the findings were recorded in the standard, semi-structured, pre-validated Case Record Proforma.

Statistical Analysis

The data was entered using MS excel software. The data was analyzed using SPSS version 20 software. The data was represented in the form of tables and graphs for frequency analysis. Repeated measures ANOVA test was used to analyze the significance in the difference between repeated measures of pain intensity, PaO2, and mean pulse rate in either study groups. The 'F' value in one way ANOVA is a tool to help you answer the question "Is the variance between the means of two populations significantly different. A large 'F' ratio means that the variation among group means is more than you'd expect to see by chance. Chi-square test was used to study the association between nominal or categorical variables. Observations with P values < 0.05 were considered to be statistically significant.

Results

The mean age of the patients in the first group was, 41.94 ± 13.11 years, while in the second group it was 39.37 ± 11.69 years. Maximum number of patients were in age between 26-45 years. The M:F ratio in the present study was 6:1 and 4.83:1 in group A and B, respectively.

Out of 35 patients, in group A-there were 3-5 rib fractures in 19(54.28%) patients and in 21 (60%) patients in group B. There were 6-10 ribs fracture in 16 (45.71%) patients in Group A and 14 (40%) patients in group B.

The X-Ray Chest and CT Scan of chest, findings showed, 16(45.71%) patients had pneumothorax, 4(11.42%) patients had hemothorax, 17(48.57%) had Contusions of lung in Group A. Whereas, 19(54.28%) patients had pneumothorax, 3(8.57%) had hemothorax and 15(42.85%) patients had contusion of lung in group B.

All the three findings were either in combinations or isolated. Intercostal Drainage tube were inserted for pneumothorax and hemothorax patients.

Repeated measures ANOVA test was used to analyze the significance in the difference between repeated measures of pain intensity, PaO2, and mean pulse rate in either of the study groups.

In the present study, we assessed the mean pulse rates among study patients in both

study groups, over follow up days-1 to 5. We observed greater reduction and stabilization in pulse rates in Fentanyl group (f-value: 246.81), as compared to Diclofenac group (f-value: 27.28) [Table I]

Table 1: Trends of Mean Pulse Rate

Mean Pulse rate	Fentanyl group	Diclofenac group
Day 1	106.22	110.05
Day 2	103.54	107.26
Day 3	96.97	106.2
Day 4	82	104.57
Day 5	69.02	103.25
Significance (F-value)	246.81 (p-value: <0.0001)	27.28 (p-value: <0.0001)

The mean Oxygen saturation among study patients in both study groups, over follow up days 1 to 5 were evaluated. We observed significant increase in Oxygen saturation in Fentanyl group (f-value: 28.1), as compared to Diclofenac group (f-value: 16.51) [Table II].

Table 2: Trends of Mean Oxygen Saturation

Mean Oxygen saturation	Fentanyl group	Diclofenac group
Day 1	94.82	95.7
Day 2	96.85	97.36
Day 3	97.84	97.72
Day 4	98.74	98.1
Day 5	98.91	98.28
Significance (F-value)	28.1 (p-value: <0.0001)	16.51 (p-value: <0.0001)

We assessed the mean pain scores in both study groups, over follow up days 1 to 5. We observed significant reduction in pain scores in Fentanyl group (f-value: 150.9), as compared to Diclofenac group (f-value: 26.53) [Table III].

Table 3: Trends of Mean Pain Score

Mean Pain score	Fentanyl group	Diclofenac group
Day 1	5.74	5.94
Day 2	4.74	5.48
Day 3	3.65	5.28
Day 4	2.28	4.94
Day 5	1.485	4.65
Significance (F-value)	150.9 (p-value: <0.0001)	26.53 (p-value: <0.0001)

We assessed the complications among the study patients in both the study groups. We evaluated for development of Pleural effusion (in patients whose initial radiological investigations did not show Hemothorax), Pneumonia and respiratory depression. We observed that in first group, 5.71% patients developed pleural effusion, while 2.86% developed pneumonia. While in the second

group, 11.43% patients developed PE and 11.43% patients developed pneumonia. However, we could not establish statistical significance. (The chi-square statistic is 0.2444. The p-value is .621014. Not significant at $p < .05$) [Table IV].

Table 4: Complications

Complications	Fentanyl group		Diclofenac group	
	Number	Percentage	Number	Percentage
Pleural Effusion	2	5.71	4	11.43
Pneumonia	1	2.86	4	11.43
Significance	The chi-square statistic is 0.2444. The p-value is 0.621014. Not significant at $p < .05$.			

Discussion

The associated pain with rib fracture is notoriously difficult to manage, but effective analgesia started promptly prevents hypoventilation, enables deep breathing, adequate coughing with clearance of pulmonary secretions, and compliance with chest physiotherapy. Overall, this reduces secondary pulmonary complications, including atelectasis, pneumonia, respiratory failure, and the need for respiratory support. However, pulmonary complications often only become evident 48–72 h after the injury. It is therefore imperative that effective analgesia is started promptly, preferably in the emergency department upon admission, not just for analgesia and patient comfort, but also to try and prevent the complications that ensue over the subsequent days.[4]

There are various ways in which analgesia can be provided. Regular simple analgesia, like paracetamol, a weak opioid, a non-steroidal anti-inflammatory drug (if not contraindicated), and a strong opioid for severe pain.[4] Regional anaesthetic techniques like, Thoracic epidural analgesia, Paravertebral Erector Spinae plane Blocks, Serratus anterior plane blocks can be given. These blocks are increasingly being used despite of a lack of evidence base.[5]

We conducted this study to check the effectiveness and safety of Fentanyl Transdermal Patch in in-patient of chest trauma with multiple fractures of ribs. We did not find many studies of Fentanyl transdermal patch for fracture ribs, though many studies are there for post-operative pain and for chronic pain in malignancy patients.

In our study, we observed that the mean age of the patients in group A, was 41.94 ± 13.11 years, while in the group B, it was 39.37 ± 11.69 years. Okan Solak *et al*, in their study observed a mean age of 49.7±13.5 years, while Kottareddygari *et al*, in their study observed a mean age of 46.3±11.7 years. [6,7]

We observed that majority of the study patients were males (85.71% and 82.86%) in both groups respectively. The M:F ratio in the present study was 6:1 and 4.83:1 in both groups respectively. Okan Solak *et al*. in their study observed male: female ratio of 1.5:1 among the study patients managed with trans-dermal opioids.[6]

We did literature study for Transdermal Diclofenac patch. Many of them used it for post-surgery Analgesia. Kottareddygari VS *et al*, found that, Transdermal NSAID administration is effective in analgesia for rib fracture cases. The analgesia effect with transdermal NSAID administration is slow in onset as evidenced by high VAS readings on day 1, whereas it is comparable with analgesia effect of intravenous NSAID administration in the long run as evidenced by VAS readings on day 3.[7]

Transdermal fentanyl provides continuous opioid delivery, without the need for special equipment. The. ability to maintain relatively stable plasma levels of fentanyl offers hope for fewer opioid related side effects than are experienced with the oral route of administration. [8,9] Thus, fentanyl in a transdermal preparation has been suggested as an alternative to oral opioids for the management of cancer pain.[10]

Fentanyl is a potent synthetic opioid, which, similar to morphine, produces analgesia but to a greater extent. This robust pharmacologic agent is typically 50 to 100 times more potent. Fentanyl is typically administered intravenously (IV), intramuscularly (IM), transdermally (TD) as skin patches, intranasally (IN) in the form of a volatile nasal spray, and intrathecally (IT). It is also available as a buccal soluble thin film, which can dissolve in the mouth, similar to the sublingual tablets.[11]

Its low molecular weight, high potency, and lipid solubility make it ideal for delivery via the transdermal route. After absorption and entrance into circulation, fentanyl can exert potent effects on areas of the brain that are highly responsible for analgesia.[12] Fentanyl's side effects are similar to those of heroin, which produce euphoria, confusion, respiratory depression (which, if extensive and untreated, may lead to arrest), drowsiness, nausea, visual disturbances, dyskinesia, hallucinations, delirium, a subset of the latter known as "narcotic delirium," analgesia, constipation, narcotic ileus, muscle rigidity, constipation, addiction, loss of consciousness, hypotension, coma, and even death.[13]

Matrix patches are designed to deliver fentanyl at a constant rate and are available in various doses: 12, 25, 50, 75, and 100 mcg/hour, requiring replacement every 72 hours. It may require 12 to 24 hours for plasma levels of fentanyl to stabilize after starting patch therapy or changing the dose.[12] Transdermal fentanyl has a 30% lower incidence of adverse effects such as constipation and sedation ($p<0.05$). Furthermore, randomized, controlled, open-label trials suggest that transdermal fentanyl is safe and as effective as sustained release oral morphine (SROM) in treating chronic cancer pain.[12] The most common adverse drug reactions of transdermal fentanyl are nausea (incidence of 10 to 90%), vomiting (incidence of 10 to 90%), and constipation.[14] Other less common adverse effects associated with chronic cancer pain include respiratory depression.[12]

Okan *et al*, conducted a Randomized Clinical Trial study, to check the Effectiveness of Transdermal Opioid in the management of multiple rib fractures. Their conclusion was that, in the analgesia of patients with multiple rib fractures, TTS (Transdermal Therapeutic System) administration with Intercostal Block (ICB), showed similar effectiveness with Intravenous patient controlled anaesthesia (IVPCA) administration with ICB. They suggested that in the management of pain due to multiple rib fractures, TTS administration is a safe, non-invasive and effective procedure.[6]

In our study, we compared the safety and efficacy of Fentanyl TTS with Diclofenac TTS. We assessed the mean pulse rates among study patients in both study groups, over follow up days 1 to 5. We observed greater reduction in pulse rates towards normalisation in Fentanyl group (f-value: 246.81), as compared to Diclofenac group (f-value: 27.28). Okan Solak *et al*, did not find any differences in one minute pulse between their 3 groups.[6]

We assessed the mean Oxygen saturation among our patients in both study groups, over follow up days 1 to 5. We observed greater increase in Oxygen saturation in Fentanyl group (f-value: 28.1), as compared to

Diclofenac group (f-value: 16.51). Okan Solak *et al*, in their study observed that on day 1, the mean oxygen saturation was 68.02%, while on day 5 it was 66.08%. They did not observed reduction or increase in oxygen saturation with respect to days of follow up. They observed no significant difference between the groups in respect to the mean PaO2 values measured in blood gas analysis before the treatment ($p>0.05$). The mean PaO2 values measured on the 1st, 2nd, 3rd, 4th and 5th days after the treatment were significantly higher in the Group IVPCA compared to the other groups ($p<0.05$).[6]

The mean pain scores in both our study groups, over follow up days 1 to 5, was 5.74 on day 1, while it reduced to 1.48 on day 5. We observed greater reduction in pain scores in Fentanyl group (f-value: 150.9), as compared to Diclofenac group (f-value: 26.53). Okan Solak *et al*, in their study observed similar findings. They observed that the mean pain score on day 1, was 5.3, while it reduced from day 1 to day 5. On day 5 it was 2.0.[6]

The most severe adverse effect of TTS is hypoventilation. The other adverse effects of TTS are nausea, vomiting, constipation, hypotension, bradycardia, dizziness, headache, confusion, hallucination, euphoria, itching, sweating and difficulty in urinating. Adverse effects related to the skin such as erythema and severe itching can be observed.

Those effects generally disappear within 24 hours after the transdermal plaster is re-moved.[6] It is reported that TTS adverse effects are observed at doses of 60 μg and over, for the management of acute pain. An effective and safe dose interval is reported to be between 40 and 60 μg. [14,15]

The complications in our patients in the group A were - 5.71% patients developed pleural effusion, while 2.86% developed pneumonia. While in group B, 11.43% patients developed pleural effusion and 11.43% patients developed pneumonia. We did not find deterioration in the saturation or ABG reports. No deterioration in the respiratory rate was seen in any of the patients in both the groups. Six patients in Fentanyl group and 3 patients in Diclofenac group developed constipation but on inquiring they had previous history of chronic constipation, so we were not able to co-relate this finding with our study in both the groups.

Three patients developed nausea on day two of fentanyl patch which was treated by, Tablet Ondansetron 4 mg once a day dose for two days after which, it was not required. None of the patients in either group developed allergic skin reaction or dermatitis on the site of application of the patch. Olak *et al*, have also used 50 μg fentanyl patch dosage, and they had an observation of only one patient developing nausea, and they concluded that TTS is a safe, non-invasive and effective method in the treatment of pain secondary to multiple rib fractures.[6]

Conclusion

We statistically proved that Fentanyl patches reported greater reduction in pain intensity as compared to the diclofenac patches, and Fentanyl patches were associated with significant increase in Oxygen saturation as compared to Diclofenac group. Pulse rates stabilized more significantly after application of Fentanyl patches as compared to Diclofenac patches.

No respiratory depression was seen in Fentanyl group. Transdermal Fentanyl Patch at dosage of 50 μg, is effective, non-invasive and safe, in treatment of multiple rib fractures. More Studies with larger number of participants are required to substantiate this finding.

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