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Research Paper

Efficacy of Transdermal Fentanyl Patches In Acute Post Operative Pain Relief: A Randomised Double Blinded Placebo Controlled Trial

Medical Science

KEYWORDS : PCA morphine, Fentanyl patch, TDDS

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ABSTRACT

The aim of this study was to assess the efficacy and safety of 25microg/hr transdermal fentanyl patch in acute postoperative pain relief by analysing the degree of sparing of rescue analgesic consumption and side effect profile. 60 ASA I & II patients between 20-60 years, undergoing major orthopaedic and gynaecological procedures were included. Patch was applied 3 hrs before the surgery. All patients were anaesthetised as per standard protocol and in the postoperative ward rescue analgesia was delivered via PCA morphine. A blinded observer visited the patient at multiple intervals and recorded the quality of analgesia, rescue analgesic consumption and complications till 48 hours and the patch was removed at the end of 72 patch hours. Average reduction of rescue analgesic consumption was about 20 % reached maximum of 27% and attained statistical significance at the end of 48 post operative hours. It was concluded that the 25 µg/hr fentanyl patch applied 3 hrs before the surgery helps to relieve acute post operative pain as part of multimodal analgesic regimen.

INTRODUCTION

Post-operative pain relief is a necessity; it is a basic human right. Post-operative analgesia has been a major concern in the past few decades and various conventional methods have been utilized to relieve post operative pain, such as oral, painful intramuscular, intravenous and other regional techniques. Unrelieved postoperative pain may cause various physiological derangements such as anxiety, sleep disturbances, demoralization and may interfere with mental activity and social interactions.1,2 The use of adhesive skin patches (Transdermal Drug Delivery Systems - TDDS) to deliver drugs systemically is a relatively new phenomenon and offers lots of pharmacological and non pharmacological advantages over the conventional enteral and parentral routes of administration. They are shown to provide a steady plasma concentration of the drug, improved patient acceptability because of no administrational discomfort; and once a day to once in three days application, increases the patient compliance to the therapy and is cost effective when compared to the other modes of continuous opioid administration.3, 4,5The efficacy of these Transdermal fentanyl patches have been established in chronic pain relief4, 5 but their efficacy in relieving acute post operative pain is varying. It is because of the relative dose administered to the surgical procedures and the initial time lag in achieving effective therapeutic plasma concentration in the early post operative period.6,7,8 50 and 75 microgram per hour patches provide more effective pain relief but are associated with increased incidence of complications like respiratory depression, nausea, vomiting etc.6,7 ,8 Hence we designed this study to determine the efficacy and safety profile of 25 microgram per hour transdermal fentanyl patches in acute postoperative pain relief.

Aims and Objectives:

To assess the efficacy and safety profile of 25 microgram per hour transdermal fentanyl patch in

acute postoperative pain relief in terms of

1. Degree of sparing of post operative rescue analgesic consumption (Primary outcome measure).
2. Side effect profile (Secondary outcome measure)

METHODOLOGY

The study was done in Mahatma Gandhi Medical College and Research Institute during the period from March 2013 to August 2014. Approval was obtained from the institutional ethical committee. 60 ASA I & II patients in the age group of 20-60 years, undergoing major orthopaedic and gynaecological procedures were included in the study. A detailed consent was taken from each patient. Those patients who were not willing to take part into the study, or unable to understand or utilize the Patient controlled analgesia pump, patients planned for continuous regional analgesia techniques, morbidly obese, patients having obstructed sleep apnoea syndrome and COPD were excluded from the study. After a through pre-operative examination the patients were educated about the functioning of PCA pump and were demonstrated how to utilize them in a proper manner. During the pre anaesthetic visit the day prior to the surgery, patients were randomized in to any one of the groups, F (fentanyl patch) or P (placebo patch) by selecting a numbered sealed envelope which contains a standard data collection sheet along with allocation card. In the surgical ward the staff nurse in charge applied either 25 mocrogram/hr fentanyl patch or the placebo patch on to the anterior chest wall just below the clavicle 3 hours prior to the proposed surgery according to the allocation card and applied an opaque white labelled plaster on top of the either patch which indicates only the time and the date of application after that she took no further part in to the study (Figure 1, 2).

All patients received a standard premedication containing Tab. Alprazolam and Tab.

Ranitidine on the previous day night and on the day of surgery. On the day of surgery

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before shifting in to the operating room, the level of sedation was assessed using Ramsay sedation score. In the operating rooms the attending anaesthesiologist with following guidelines decided the primary anaesthetic technique. In General anaesthesia, all patients were induced with Propofol, and maintained with Isoflurane, O2 and N2O. Morphine was used for intraoperative analgesia and titrated according to the primary anaesthesiologist. In case of regional, spinal anaesthesia would be administered using 0.5% heavy bupivacaine 3.2 ml without any adjuvant. In case of epidural, single dose would be administered with 15ml 0.25% bupivacaine without any adjuvant. All patients received a single dose of 1gm of Paracetamol and 75 mg of Diclofenac sodium IV infusion over a period of 20 minutes just before the skin closure as a part of multimodal analgesia. If any deviation from the above mentioned guidelines were needed for intra operative management, then those patients were excluded from the study. At the end of the

surgery; patients were shifted to the post anaesthesia recovery room where they were observed for complete recovery from anaesthesia. When the patients were conscious, oriented and comprehending; the base line analgesia was recorded on a 10 point numeric rating scale (NRS) and the PCA pump was connected to the intravenous line and a loading dose of 4 mg morphine was given and the demand button handed over to the patient and the time was noted as 0 postoperative hour. (Figure-3) The PCA was set to deliver 1 mg on demand with a lock out interval of 5 minutes and can deliver up to a maximum dose of 30 mg in any 4 hour period. Then the patients were shifted to the postoperative ward where the vital parameters such as heart rate (HR), respiratory rate (RR), oxygen saturation (SpO_2) and non-invasive blood pressure (NIBP) were monitored continuously for 48 postoperative hours. The quality of analgesia was recorded every 4th hourly for the first 24 post operative hours, then every 8th hourly till 48 post operative hours. After this the PCA pump was discontinued and the patients were shifted to general ward after confirming that they were alert, oriented, communicating with respiratory rate more than 12/min, room air saturation more than 96% and had stable haemodynamics. In the ward NRS scale was recorded every 12th hourly till 72 hours by a trained staff nurse and the patch was removed at 72 patch hours. Analgesic requirements after the 48th post operative hours were met with Tab. Diclofenac sodium 50 mg bd or Tab. Paracetamol 500 mg tds. During all these study intervals, the sedation score and other complications like nausea, vomiting, respiratory depression and pruritis were also noted. Patient controlled analgesia (PCA) is a pain management interactive technique that allows patients to take control over their pain by self administering a predetermined dose of opioids using a computerized pump.

In the post operative ward the vital parameters such as HR, RR, SPO2, BP and ECG were monitored continuously over a 48 hour period. An initial loading dose of 4 mg morphine was given after recording the NRS rating as the patient was conscious, oriented and comprehending pain following which a pre use check of PCA infusion pump was done, use of PCA pump explained again to the patient, drug dilution and labeling was done. The PCA was set to deliver 1 mg on demand (Figure 4) with a lock out interval of 5 minutes and can deliver up to a maximum dose of 30 mg in any 4 hour period. 30 mg of morphine was taken in a 60 ml syringe with a drug dilution of 1mg per 2 ml and a 100 cm pmo IV line extension was used to connect with the patients IV accesses and the PCA trigger switch was handed over to the patient. PCA was set in a manner that the patient received 1 mg of morphine with a press of the trigger button following which the machine would deliver another bolus dose after a period of 5 minutes only.

These were based on the standards and guidelines of the PCA morphine infusion criteria. The

PCA start time and ending time was recorded and satisfaction degree of operative analgesia was assessed using NRS rating. The data retrieved from the PCA pump at the end of the 48 hr postoperative period included the PCA start time, the demand doses of the patient, the hourly morphine consumption, total delivered dose of morphine and PCA stop time.

STATISTICAL METHODS

All data were recorded in Microsoft excel chart and statistical analysis was done by statistical package for social sciences (SPSS) software 16 version. Demographics were assessed using unpaired t test for parametric data and Chi square test for non parametric data. Cumulative morphine consumption and haemodynamics over the 48 hour postoperative period was analysed using repeated measures Anova to find statistical differences within and between the two groups.

RESULTS

The mean age in the fentanyl patch group was 45 ± 9 years and in Placebo group was 41 ± 8 years. Both the study groups were comparable with respect to the age distribution (P = 0.13). Gender distribution of male to female ratio was 5/25 in Fentanyl group and 4/26 in the Placebo group and it was comparable (P = 0.1). 60 patients undergoing major orthopedic (spine instrumentation) and gynecological procedures (TAH) were consented to take part in the study. On analysis we found that the distributions of surgical procedures were comparable between the groups (P = 0.192); Fentanyl patch group had 16 cases of spine instrumentation and 14 cases of abdominal hysterectomies. Placebo group had 10 cases of instrumentation and 20 cases of abdominal hysterectomies. The mean intra operative Morphine consumption in the Fentanyl group was 5.4 ± 4.5 mg and in the Placebo group was 4 ± 4.55 milligrams which was comparable between the groups with a p value (0.179).

The cumulative morphine consumption progressively increased in the postoperative period from

the 4th to the 48th hour (5 ± 3 to 59 ± 30 mg Vs 6 ± 3 to 81 ± 33 mg) respectively in the fentanyl and the Placebo group, but statistically significant difference was attained at the intervals of 40th (55 ± 29 Vs 70 ± 28; P = 0.04) and 48th (59 ± 30 Vs 81 ± 33; P = 0.01) post operative hours. (Graph1). The quality of the pain relief was assessed on a Numeric Rating Scale at post operative interval which indicates the pain relief was satisfactory (median NRS Score of < 3) at all the time intervals till 48hrs in both the groups which was not statistically significant. (Graph 2)

The percentage changes in the Heart rate and Mean arterial blood pressures were within 25% of the baseline between both the groups in all the postoperative intervals and was not statistically significant between the groups at any interval.

There was no statistically significant difference in the Respiratory rate (RR), percentage Saturation (SpO2) and Ramsay sedation scores (RSS) at any of the postoperative intervals till 48 hours. (Graph 3) 12 patients suffered Nausea and vomiting needing intervention in the placebo group whereas only 5 patients suffered in the Fentanyl patch group which was statistically significant (P = 0.047). These patients were treated with injection Ondansetron 4 mg IV. (Graph 4)

DISCUSSION

The cumulative morphine consumption progressively increased in the postoperative period from the 4th to the 48th hour (5 ± 3 to 59 ± 30 mg Vs 6 ± 3 to 81 ± 33 mg) respectively in the Fentanyl and the Placebo group, but the difference between the two study groups attained statistical significance at the intervals of 40th (55 ± 29 Vs 70 ± 28 mg; P = 0.04) and 48th (59 ±

30 Vs 81 ± 33 mg; P = 0.01) post operative hours which corresponds to a 21 and 27 percentage reduction of rescue analgesic consumption respectively in the fentanyl group. Considering the comparable intraoperative morphine consumption (5.4 ± 4.5 Vs 4 ± 4.55 mg; P = 0.179), comparably distributed regional anaesthetic cases (TAH cases 14 in F group Vs 20 cases in P group; P = 0.192) and no other systemic analgesics in the postoperative period, the transdermal delivery of fentanyl was attributed to the observation of 27 % reduction of rescue opioid consumption at the end of 48 postoperative hours in the fentanyl group. As anyone can expect the 50 µg/hr and 75 µg/hr fentanyl patches would provide more percentage reduction in the rescue analgesic consumption but at the expense of increased incidence of adverse effects. 6,7,9 Sandler et al6 demonstrated 36% and 40% reduction in rescue morphine consumption with 50 and 75 µg/hr fentanyl patches respectively over a period of 48 hrs in patients undergoing abdominal hysterectomies. But they observed, that the incidence of nausea vomiting was 57%, oxygen supplementation was required in (30 Vs 62%) and (8 Vs 15%) of patients were withdrawn from the study due to severe respiratory depression respectively in patients who received 50 and 75 µg/hr fentanyl patches. Hence they concluded that the Transdermal Fentanyl Patches should be used only under closed monitored conditions for acute post operative pain with resuscitation facilities close at hand. In our study we observed only nausea and vomiting in 16.67% of patients, none of the patients registered respiratory depression or increased sedation and pruritis. The respiratory depression was commonly associated with the fentanyl concentration more than 1.5 nanogram / ml but the expected maximum plasma concentration Cmax following 25 µg/hr patch is 0.3 to 1.2 nanogram / ml9. In our study the difference in the cumulative morphine consumption was not statistically significant in the first 24 postoperative hours. This observation could be because of two reasons one was either the expected maximal plasma concentration Cmax 0.3 to 1.2 nanograms / ml9 and the subsequent effect site concentration was not attained in the first 24 post operative hours or the attained maximal plasma concentration Cmax was not adequate enough to attenuate nociception and reduce rescue opioid consumption. Though this question can be definitely addressed with the serial plasma concentration studies, considering the time to maximal concentration tmax can vary from 26 to 78 hrs18 it may be possible to observe the statistical difference within 24 post operative hours if we would have applied the patch 10 -12 hours before the surgery. In our study we applied the patch 3 hours before the surgery, and the mean surgical duration was 2 ± 0.5 hours, given one hour allowance to complete recovery from anaesthesia, 24 post operative hours coincided with 30 patch hours which was close to the lower range of tmax (26 to 78 hrs). If the patches were applied 10 to 12 hrs before the surgery then the 24 post operative hours would have coincided with 40 to 42 patch hours which was well within the range of tmax. Significant reduction in the rescue analgesic consumption was demonstrated within 24 post operative hours when 50 µg/hr fentanyl patch was applied 10 hours before the surgery8. The median NRS scale at multiple post operative intervals was less than 3, indicating the effective usage of rescue analgesics that is PCA morphine. The hemodynamic fluctuations were within 25% of the base line and correlates to the effective analgesia. The limitation of the study was that we have not measured the serial plasma concentration of fentanyl to detect whether we attained the Cmax or not within the study period.

CONCLUSION

Average reduction of rescue analgesic consumption was about 20 % and 27% which was statistically significant at the 40th and 48th post operative hours. We conclude that the 25 µg/hr fentanyl patch applied 3 hrs before the surgery can be used effectively as part of multimodal analgesic regimen to relieve acute post operative pain in patients undergoing spine instrumentation and total abdominal hysterectomies. Considering the favourable side effect profile (nil respiratory depression and overt sedation) applying these patches 10 hours before surgery and combining with other non opioid analgesics like NSAIDs and Paracetamol at regular intervals in the post operative period, 25 µg/hr fentanyl patch may contribute to a significant reduction in the rescue opioid analgesics and acts as an effective multimodal analgesic regimen which needs further research.



Figure 1: Sealed Transdermal Fentanyl Patch



Figure 2: Durogesic Fentanyl 25µg/hr transdermal patch



Figure 3: Patient in postoperative ward using PCA pump with monitoring setup in place

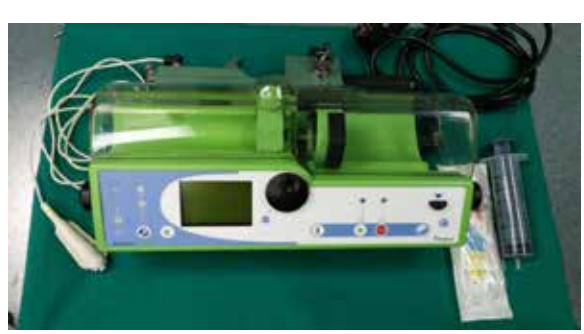

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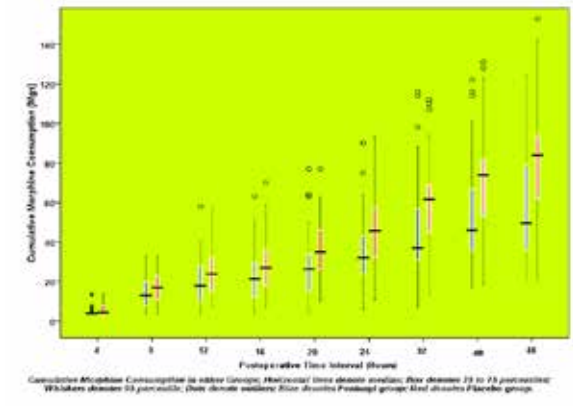
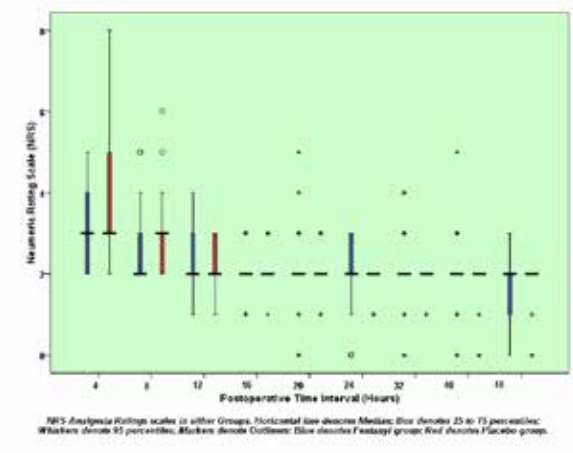
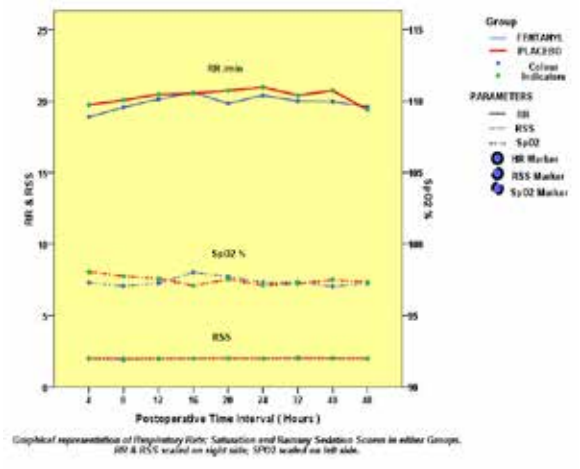
Figure 4: Master PCA Pump and Accessories Used



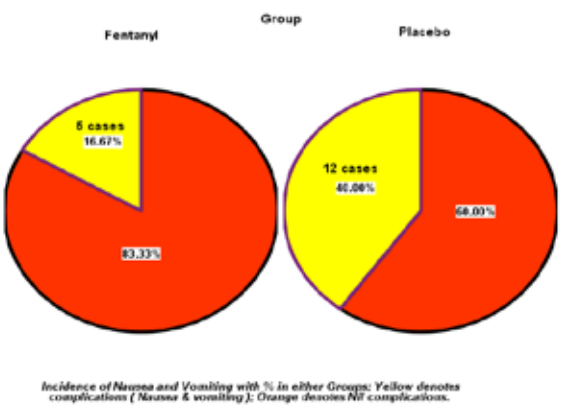
Graph-1: Mean Cumulative Morphine Consumption



Graph-2: Quality Of Analgesia



Graph-3: Respiratory Parameters



Graph-4: Complications

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