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Evaluation of Transdermal Fentanyl for Post-operative Pain Relief

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Abstract

Background: Overview of post-operative pain control strategies lacks high quality effectiveness of the commonly used analgesics. Restricted use of strong systemic analgesics borne out of the fear of respiratory depression and other opoids related complications like nausea, vomiting, constipation, urinary retention etc. that results in failure to provide continuous analgesia of good quality in post-operative period. Therapeutic transdermal fentanyl (TTF) is a unique & innovative way of administering strong analgesic fentanyl transcutenously. Pharmacokinetic studies provides sufficient evidences that with TTF plateau analgesic concentration of fentanyl are attained after *8–12 hours* and are maintained over prolonged period of *72 hours* or more as the drug remains in circulation even after removal of patch. Therefore, TTF is expected to provide continuous analgesia of superior quality in post,operative period. *Materials and Methods:* 25 patients included in the study underwent major surgeries under uniform method of general anesthesia with gas, oxygen, relaxant and analgesic technique with controlled ventilation on Bain circuit. On these patients fentanyl transdermal patch releasing *50 mcg/hour* fentanyl was applied to the hair free skin on lateral chest wall and secured in place just before induction of anesthesia. We assessed the quality, duration and intensity of pain; patient's comfort score, requirements of rescue analgesics, efficacy & safety in its use, patient's satisfaction. We vigilantly observed them for any adverse cardiovascular, respiratory and local complications. *Results:* 68% (17/25) patients did not demand rescue analgesic dose during entire post-operative period and mean VAS score was less than 1 after *12 hours* post-operatively till the observation period of *72 hours*. Only 32% (8/25) of the patients required supplement analgesic with one/two dose of *75 mg* diclofenac sodium by intramuscular route. All patients expressed satisfaction with the analgesia provided; some had local complications like erythema at patch application site. The patients under study neither showed incidences of severe respiratory depression nor acute changes in cardiovascular parameter (HR, ECG and SBP, DBP) measurement throughout study period. The changes observed in cardiovascular and respiratory parameter were in-significant and did not require specific treatment. *Conclusion:* Therapeutic Transdermal Fentanyl releasing *50 mcg/hr* fentanyl can be safely used to control post-operative pain and is effective after *8–12 hours* of application with fewer side effects at patch application site.

Keywords: Postop Pain; Transdermal; Cardiovascular.

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Introduction

Traditionally systemic administration of narcotic analgesics (morphine/pethidine) remained cornerstone for management of post-operative pain for decades. This practice exposed patients to opioid related complications like disorientation, depression of respiration, urinary retention, bladder and bowel disturbances, nausea, vomiting, pruritus etc. Reluctance in their prescription is because of fear of addiction, caused incidences of break through pain in post-operative period. Frequent administration of analgesics on demand poses work load on nursing/paramedical staff.[1,2] Series of synthetic analogue of morphine were researched and several narcotic analgesics were marketed as safer alternatives. Fentanyl citrate is one such potent narcotic analgesic synthesized in 1960 by Paul Johnson and is favored in clinical anesthesiology because of its excellent pharmacological and pharmacokinetic profile and intra-operative cardiovascular stability. 1975 onwards fentanyl was widely accepted as intravenous supplement to produce balanced anesthesia.[3] Although, fentanyl can be used by traditional systemic route of administration but, its pharmacokinetic properties prompted investigators to explore alternative methods of its administration in an attempt to enhance the quality of analgesia. Fentanyl was used as continuous intravenous infusion, by intra and extra thecal route and also with peripheral nerve blocks. Newer modalities of its administration like patient controlled analgesia system (PCA) came into existence. Fentanyl proved its effectiveness in all the routes of its administration. But all these require technical expertise and are costly methods.[2,4,5] Patch is a medicated tape, typically consists of one or multiple layers of medicated membrane, or a drug reservoir or a semisolid matrix of drug; for application to the skin. Patch application provides constant rate of drug delivery non-invasively and maintains uniform concentration of drug in blood for several hours. Novel methods to improve diffusion of drug through intact skin incorporates chemical enhancers, ionophorasis, micro needle, ultrasound etc. with patch.[3,5] Therapeutic transdermal fentanyl patch (TTF) was initially available for management of chronic pain. Since 1999, TTF have also been used for management of acute moderate to severe post-operative pain. USFDA has approved use of iontophoresis patch after Phase III clinical trials for post-operative pain control. TTF is an advanced pain management system that addresses many concern of safety and convenience of use.[4] We are presenting our experiences of using transdermal fentanyl administration in management of post-operative pain following surgeries of moderate to severe category. Study was aimed to assess the safety, efficacy and quality of analgesia provided by TTF.

Aim of the present study to determine quality and duration of Post-operative pain control offered by transdermal administration of fentanyl and association of side effects with transdermal route as seen with systemic administration fentanyl.

Materials and Methods

The present study was conducted between *June 2013* to *February 2015* in R D Gardi Medical College Ujjain. We calculated the sample size assuming that with TTF, 30% patients would need additional analgesic and an alpha error of 0.05% and 80% power of study. We needed 21 patients for the study and therefore, the Clinical observations were made on 25 adult patients of both genders of ASA physical status I/II undergoing various surgeries under general anesthesia. Pre-operatively all the patients were screened to rule out presence of pre-existing cardiovascular, respiratory, renal or hepatic diseases besides routine biochemical and hematological tests. Patients were assured for providing additional analgesia on demand.

Patch Application

Fentanyl patch was applied immediately before induction of general anesthesia on right side of chest wall on non-hairy skin without using antiseptic or spirit and secured in place. Time of patch application was counted as zero hour. Anesthesia technique: Uniform technique of balanced anesthesia was adopted for all the patients. Induction of anesthesia was done with injection propofol *2–3 mg/Kg*, followed by succinyl choline chloride *2 mg/Kg* (max. dose *100 mg*) to facilitate endotracheal intubation. Maintenance of anesthesia was achieved with injection pentazocine *30 mg* and atracurium. Patients were ventilated with Gas, Oxygen (50:50) and Isoflurane 0.6% to 1.2%. The dose of Isoflurane was adjusted to keep pulse rate and blood pressure within ± 20% of pre-operative values. Continuous monitoring of vital signs was done using multi-parameter. Heart Rate, Electrocardiogram, SpO_2, non-invasive blood pressure recorded at *30 minutes* till recovery from anesthesia. Duration of surgery was recorded in minutes. Residual neuromuscular block was reversed with neostigmine *2.5 mg* with glycopyrrolate *0.4 mg*. Post-operative monitoring:

Upon arrival in recovery room vital parameters were recorded and initial pain assessment was done using VAS (Visual Analogue Scale). Patients having initial pain score more than 5 were given injection diclofenac sodium *75 mg* by intramuscular route. After recovery from general anesthesia and in no discomfort condition, patients were shifted to post-operative surgery ward and monitored for pain intensity, changes in vital parameters, respiratory rate, SpO_2, comfort score every two hours for *24 hours* and every *six hours* for next *24 hours* and every *12 hours* till *72 hours*. Patients having pain score more than 5 were administered a dose of diclofenac sodium *75 mg* by intramuscular route. Although the patch was removed after *48 hours* after application; Patients were kept under observation for *72 hours* for occurrence of delayed respiratory depression. Application site was inspected for local tissue reaction. Patients received oxygen through face mask @ *4 lit/mt*. till *12 hours* post-operatively. After *48 hours* patients were asked to comment on quality of pain relief as - satisfactory or not satisfactory.

Results

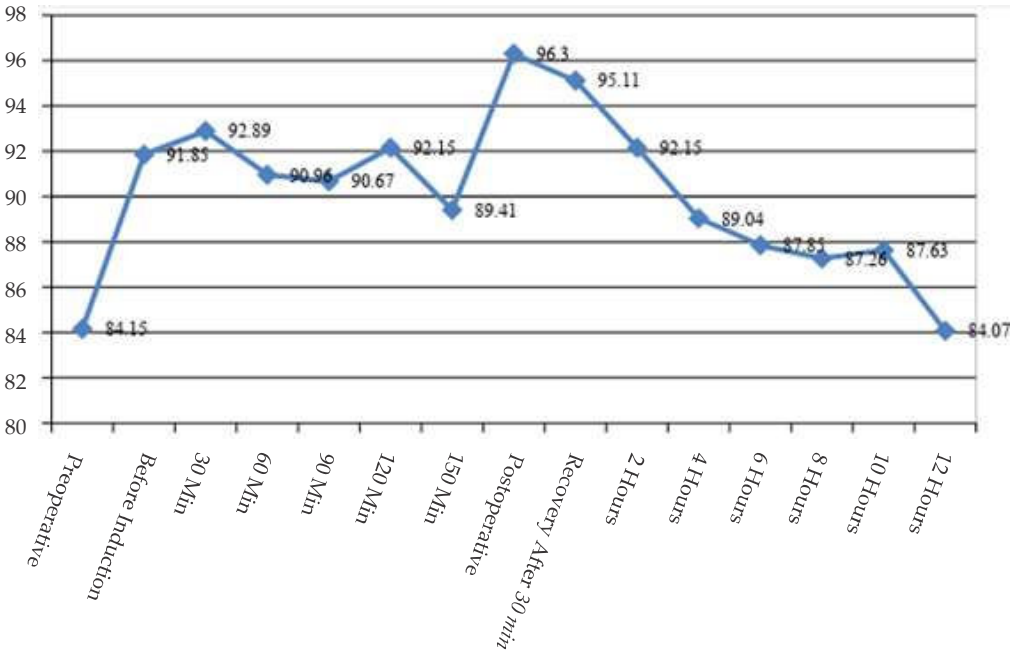
The demographic data of the patients, sex ratio and mean duration of surgery of patients under study shows in (**Table 1**).

The changes observed in mean Heart rate, systolic and diastolic pressure, ECG changes observed are displayed in (**Graphs 1–3**). After induction anesthesia and intubation an increase of *7.7 bpm* in HR, *5.41* and *5.0 mm* of *Hg* in systolic and diastolic pressure was observed. In remaining intra-operative period cardiovascular parameters remained within 20% of baseline value and did not needed treatment.

(Table 2) is showing the changes observed in mean heart rate, systolic and diastolic pressure

Table 1: Demographic details of Study Population

Parameter	Mean value	Range of observation
Age	*38.11 ± 11.69 years*	*20–60 years*
Height	*159.93 ± 9.58 cms*	*149–175 cms*
Weight	*60.56 ± 6.23 Kg*	*50–70 Kg*
Body Mass Index	24.00	
Male/Female	11:24	
Mean duration of surgery	*134.07 ± 27.49 minutes*	*100–200 minutes*



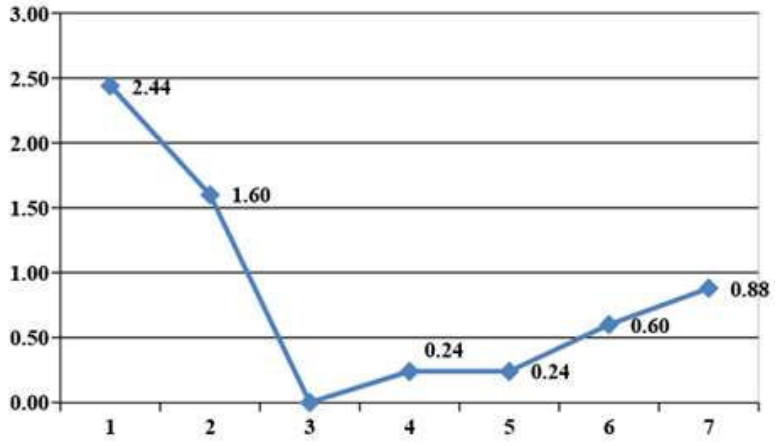
Graph 1: Mean Pulse rate in beats per minute

Table 2: Mean Heart rate, systolic and diastolic pressure during the first *12 hours* of TTF application

Time intervals	Mean value in *bpm* HR (Mean ± SD)	Mean value in *mmHg* SBP (Mean ± SD)	Mean value in *mmHg* DBP (Mean ± SD)
Post-operative on arrival in RR	96.30 ± 8.26	131.11 ± 13.28	86.07 ± 9.81
After 30 *min* in RR	95.11 ± 7.18	133.33 ± 8.66	87.93 ± 7.57
2 hours	92.15 ± 5.14	129.48 ± 8.22	81.56 ± 7.81
4 hours	89.04 ± 7.61	129.48 ± 8.69	82.89 ± 7.43
6 hours	87.85 ± 6.81	128.52 ± 10.12	82.96 ± 7.77
8 hours	87.26 ± 7.73	128.22 ± 9.30	81.56 ± 7.93
10 hours	87.63 ± 8.67	127.33 ± 10.05	80.81 ± 7.91
12 hours	84.07 ± 10.10	123.48 ± 11.38	77.33 ± 9.20

Table 3: Mean VAS score at different time intervals

Time intervals	VAS score mean value (Mean ± SD)
2 hours	2.37 ± 0.93
4 hours	1.89 ± 0.93
6 hours	1.96 ± 1.37
8 hours	2.00 ± 1.47
10 hours	1.63 ± 1.01
12 hours	1.67 ± 1.47
24 hours	0.00 ± 0.00
36 hours	0.24 ± 1.01
48 hours	0.24 ± 1.01
60 hours	0.60 ± 1.50
72 hours	0.88 ± 1.59



Graph 2: Mean comfort scale (post-operative to *72 hours*)

Table 4: Mean Pulse rate, systolic and diastolic blood pressure at post-op time intervals

Time intervals	Pulse rate in *bpm* (Mean ± SD)	Systolic blood pressure in *mmHg* (Mean ± SD)	Diastolic Blood Pressure in *mmHg* (Mean ± SD)
Post-operative (at *30 minutes* in RR)	96.72 ± 8.44	130.32 ± 13.42	85.52 ± 9.95
12 hour	84.16 ± 10.41	123.28 ± 11.76	77.04 ± 9.51
24 hours	70.32 ± 5.91	109.04 ± 10.63	68.40 ± 7.02
36 hours	71.44 ± 7.67	115.92 ± 11.28	74.00 ± 7.23
48 hours	72.32 ± 8.36	115.20 ± 9.95	73.12 ± 8.41
60 hours	77.60 ± 7.21	123.76 ± 10.45	78.24 ± 8.29
72 hours	77.68 ± 8.16	123.20 ± 9.35	78.56 ± 8.42

Table 5: Mean Value of comfort score at different time intervals

Time intervals	Mean value of comfort score (Mean ± SD)
2 hours	2.26 ± 0.53
4 hours	2.04 ± 0.44
6 hours	2.26 ± 0.71
8 hours	2.26 ± 0.66
10 hours	2.04 ± 0.44
12 hours	1.96 ± 0.71
24 hours	1.00 ± 0.00
36 hours	1.56 ± 0.65
48 hours	1.68 ± 0.63
60 hours	2.08 ± 0.40
72 hours	2.12 ± 0.33

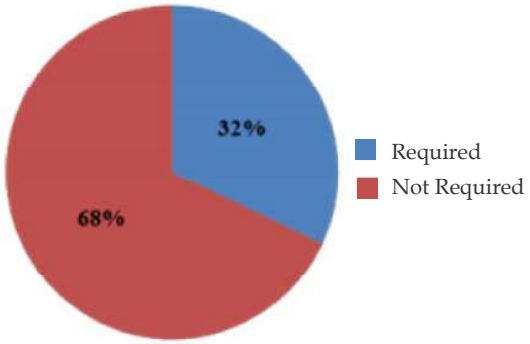
during the first *12 hours* of TTF application. We observed statistically and clinically insignificant fall in Heart rate, systolic and diastolic pressure. Patients were closely observed in remaining post-operative period upto *72 hours* and we observed insignificant changes in cardiovascular parameters did not found clinically significant changes. Mean value of oxygen saturation and respiratory rate were clinically and statistically insignificant. Patients were closely observed in remaining post-operative period up to *72 hours* and we observed in-significant changes in respiratory parameters did not found clinically significant changes. Patient was considered to have respiratory depression if RR was less than 10 and SpO_2 less than 90%. At *2 hours* of observation the mean VAS score was 2.37 ± 0.93. It decreased to *1.67 at 12 hours* post-operatively, indicating that some patients had mild post-operative pain after recovery from anesthesia. Patients who had VAS score equal to or more than 5 were given rescue analgesic dose by intramuscular route (injection diclofenac sodium *75 mg*). Patients were practically pain free between *12* and *72 hours*. **Table 3** shows the pain intensity measured on Visual Analogue Scale in early post-operative period (Pain Scale) (N = 25)

Table 4 shows that mean pulse rate, systolic and diastolic blood pressure remained close to pre and immediate post-operative mean and did not need corrective treatment. **Table 5** shows the mean comfort score majority of patients had a comfort score of 2–3 indicating that either patient had no pain or mild discomfort. Patient's comfort was monitored on 6 point scale used by Rafael and Miguel *et al.* (1995).

Table 6 shows the requirement of rescue analgesia *75 mg* diclofenac. Pain and analgesic requirement were lowest after *18–24 hours*. 68% (17/25) did not required where as only 32% patients demanded (14 doses) rescue dose of analgesic in majority in early post-operative period. In later period demand was reduced greatly.

Table 6: Requirement of rescue analgesia

Rescue analgesia	Number of patients and dose	% of patients
Required	8 (14)	32.0
Not required	17 (Zero)	68.0
Total	25	100.0



Graph 3: Requirement of rescue analgesia

Table 7 shows the patient's narration on quality of analgesia provided to them in post-operative period. All patients included in the study expressed satisfaction with the analgesia provided with or without need of rescue analgesia.

Table 7: Patient's satisfaction

Satisfied	25
Non-satisfied	00

Table 8 shows the complication rate of occurrence of side effect peculiar to systemic narcotic analgesic. No patient included in the study shown clinically significant fall in respiratory rate or oxygen saturation of hemoglobin requiring supplemental oxygen therapy after *12 hours* till the removal of patch at *48 hours* and thereafter till *72 hours*. No incidence of pruritus at the site of patch application or generalized itching was noted. 08 patients had erythema of surrounding skin of patch application site.

Table 8: Adverse drug reaction and local reaction to Patch

Parameter	Number of patients
Fall in respiratory rate	00
Low oxygen saturation (Less than 95%)	00
Urinary retention	00
Pruritus	00
Local erythema	08/25

Discussion

Pain management is an essential element of patient care and rehabilitation following surgery, as the results of clinical studies has shown that effective pain control can reduce patient's morbidity and associated healthcare cost in addition to minimization of patient's anxiety and physical discomfort.[6] Currently used Patient Controlled Analgesia (PCA) to treat post-operative pain introduces some potentially dangerous risk from invasive method, errors in manual programming of pump, needle related injuries, infection, limitation of mobility and high maintenance cost and availability for all patients.[6] Transdermal fentanyl is an advanced pain management system and addresses many concerns (issues) of safety and convenience of use. Transdermal Drug Delivery System (TDDS) needs more clinical evaluation across population divided according to body weight, age and time of surgery to evaluate potential impact of transdermal fentanyl[16] in clinical practice.

Dose Selection

Choice of transdermal delivery system of fentanyl with predicted delivery rate of *50 mcg/hr* was based on previous studies characterizing the relationship between serum concentration and analgesic effect in post-operative patients. We used matrix type of patch in the study.

Hug CC *et al.* (1984)[7] found that use of lower dose releasing fentanyl patch *25 mcg/hr* resulted in in-significant reduction in morphine consumption. Higher doses of *75 mcg/hr* placed the patients at risk of respiratory depression. IJ Broome *et al.* (1995)[8] have shown that peak analgesic concentration of *1.425 ng/ml* much below the dose (*3–4 ng/ml*) causing severe respiratory depression is achieved at *36 hours*. Higher rates of fentanyl delivery were associated lower VAS score and reduced morphine consumption as rescue analgesic. Concentration of fentanyl in plasma can be increased by administering intravenous loading dose at the start of surgery. Analgesic concentrations are maintained from *12 hours* to *48 hours*. Samy A *et al.* (2012)[9] found that reservoir and matrix type of patch are bioequivalent and delivered fentanyl at constant rate and shown liner kinetics. Authors found that using TDDS with predicted nominal rate *50 mcg/hr* achieve effective and safe analgesia in patients undergoing pelvi-abdominal cancer surgery. Severino *et al.* (1997)[10] questioned the utility of transdermal fentanyl in combination with intravenous morphine supplement considering multi factorial genesis of post-operative pain.

Time of Patch Application

We applied the fentanyl patch just before induction of anesthesia which did not take pharmacokinetic consideration of transdermal administration. Patients therefore, were expected to have plasma concentration lower than analgesic concentration in the window period and may demand rescue analgesic. For the above reasons in present study, we did not find adequate analgesia in all patients in first *12 hours* of patch application; 32% patients required rescue analgesia in immediate post-operative period. Similar to our findings Rawbotham *et al.* (1989),[11] Severino et al (1997),[12] Caplan *et al.* (1989),[13] Gourlay *et al.* (1990),[14] Alan N sandler *et al.* (1994),[15] did not consider pharmacokinetics and administered transdermal fentanyl before induction of anesthesia and reported in their studies that analgesic effect was commonly less apparent during first *12 hours* after application.

Pharmacokinetic profile suggests (IJ Broome *et al*. 1995)[8] that patch should be applied *8–12 hours* before anesthesia to achieve analgesia in early post-operative period. Those studies in which fentanyl patch applied *8–12 hours* before anesthesia provided adequate analgesia in early post-operative period.

Rescue Analgesia

In present study, *75 mg* of diclofenac sodium was administered by intramuscular route as rescue analgesic. We considered that post-operative pain is a complex phenomenon and involves multiple factors. Presence of inflammation in post-operative patients at the operative site is an important accompanying factor and hence, diclofenac was used.

In none of study, available anti-inflammatory drug was used as rescue analgesic. All reported studies employed morphine as supplemental analgesic either as bolos or PCA pump delivering pre-fixed dose of fentanyl intravenously.

Efficacy of Transdermal Fentanyl

Sixty-eight percent of the patients did not require additional rescue analgesic dose. Only 8 patients needed 14 doses of additional analgesia in majority in early post-operative period. Hug CC (1984)[7] reported that there is a interpersonal variability in serum concentration resulting from pharmacokinetic, pharmacodynamic and psychological factors. Sandler *et al.* (1994)[15] compared transdermal fentanyl in two different delivery rate

50 mcg/hr and *75 mcg/hr* with placebo for post-operative analgesia after abdominal hysterectomy. The patch was applied *two hours* before surgery and removed after *72 hours*. They found that there were significant reduction in pain intensity and rescue analgesic with delivery rate of *75 mcg/hr* when compared with placebo and there was significant reduction in rescue analgesic consumption with *50 mcg/hr* dose. Kilbride M *et al.* (1994)[16] reported a significant reduction in post-operative analgesic requirements after hemorroidectomy using *50 mcg/hr* fentanyl releasing patch. Severino *et al.* (1992)[10] compared two different delivery rate *25* and *50 mcg/hr* with placebo for post-operative analgesia after abdominal gynecological surgery. There were no differences in the pain intensity in both TDF group and no difference in rescue analgesia in TDF group with delivery rate of *25 mcg/hr* when compared with placebo group. There was only a significant reduction in the rescue analgesia in the TDF group with a delivery rate of *50 mcg/hr*.

Quality of analgesia

During entire observation period 68% patient felt no pain during entire observation period; Only in 8/25 patients experienced pain of intensity more than 5 on VAS in majority in early post-operative period for that 14 doses if rescue analgesic diclofenac sodium by intramuscular route were administered. Additional dose of diclofenac sodium reduced VAS at next observation.

Hug CC (1984)[7] reported that there is a interpersonal variability in serum concentration resulting from phramcokinetic and pharmacodinamic and psychological factors. And we decided to use diclofenac as multimodal approach. VAS score was 0–2 in all patients, after *12 hours* of patch application and was maintained till *48 hours* and started rising after wards. All patients expressed satisfaction with the analgesia provided with either transdermal fentanyl alone or with intramuscular diclofenac as rescue analgesia when they rated their pain intensity equal to or more than 5 and remained pain free throughout observation period. The safety and efficacy of transdermal fentanyl used as main post-operative analgesic in patients undergoing dorsal or lumbar spine fusion VAS score and rescue analgesic were lower in transdermal fentanyl group.

I power (2007)[6] reported that patients rated pain relief as good to excellent analgesia in post-operative period in ITF group in II and III *24 hour* period. Rafael M *et al.* (1995)[17] reported on patient's global satisfaction of analgesia in TDF groups in comparison to placebo. Difference between the two fentanyl group was not significant. Also reported that patient's comfort score significantly better compared with placebo group patients. We did not find significant lowering of pulse rate, blood pressure and ECG abnormality during post-operative observation period of *48 hours*. Cardiovascular parameters remained within ± 20% of their base line values. Similar to findings of our study Lauretti GR *et al.* (2009),[18] reported that all physiological parameters fluctuated within normal range. Philip WH *et al.* (1999)[19] in a review article shown that fentanyl at a plasma concentration of *3–4 ng/ml* alters carbon dioxide response of central respiratory control by 50%. These concentrations are not achieved with *50 mcg/ml* patch but cautions for continuous measurement of ventilation is preferable. Factors responsible for respiratory depression are type of surgical procedure, elderly patients, interaction with other central depressive drugs and individual variation in pharmacokinetics and pharmacodynamics.

Adverse drug reactions

The patients were observed for opioids like side effects after patch application. We did not notice significant fall in respiratory rate, fall in oxygen saturation below 95% requiring oxygen therapy, urinary retention and pruritus. Local complication like erythema occured at the patch application site in 32% cases which did not required any kind of treatment and resolved in *72 hours*. In contradiction to our findings Rafael M (1995)[17] reported that pruritus occurred in 10 patients who received *90–100 mcg/hr* than in patients and in 6 with *70–80 mcg/hr* group. Erythema was more common in *90–100 mcg* group. Possible reason for not confirming to our findings is employment of higher dose of transdermal fentanyl.

Conclusion

Transdermal fentanyl is superior, safe and effective method of managing post-operative pain over the traditional systemic opioid and can be a part of multimodal approach. It is free from side effects of intravenous administration. *50 mcg/hr* fentanyl releasing patch proved as safe and effective in patients of normal built.

Caution

It is important to observe patients for respiratory parameters closely for occurrence of respiratory

depression and oxygen supplement should be done as and when required. Medication (Injection Nalaxone) readily reverses the respiratory depression.

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