Asian Journal of Pharmaceutical and Health Sciences
www.ajphs.com

Comparative study between transdermal buprenorphine patch with intravenous tramadol for post-operative analgesia in laparotomy cases

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ARTICLE HISTORY

Received: 03.12.2016

Accepted: 04.02.2017

Available online: 30.03.2017

Keywords:

Laparotomy, transdermal buprenorphine, tramadol ,VAS score

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ABSTRACT

Post-operative pain is very common in laparotomy cases. It is one of the main concerns for the patient undergoing major surgery. Various techniques and drugs have been used for this purpose with variable success. Every technique and drugs has its own advantages and disadvantages. The present study compares transdermal buprenorphine patch and intra venous tramadol in relieving post-operative pain. Sixty patients aged 18 to 60 years scheduled for laparotomy under general anaesthesia in Poona Hospital and Research Centre, Pune between May 2014 and November 2015 were included in this prospective , randomised double-blind study. They were randomly divided into two groups. Group B patients received transdermal buprenorphine patch of 10 mg six hours prior to surgery whereas Group T patients received intravenous tramadol 1 mg per kg half hour prior to completion of surgery. Comparison of quantitative variables between the groups was done using unpaired student's "t" test, whereas comparison of qualitative variables was done by using chi-square test or Fisher's exact test. Visual analogue scale pain score at 0 hour, 8 hours, 10 hours, 12 hours and 24 hours was significantly higher in tramadol group compared to buprenorphine group. Incidence of post-operative nausea and vomiting was significantly higher in tramadol group compared to buprenorphine group. Majority of patients in buprenorphine group required rescue analgesia up to 6 hours and in tramadol group, majority of patients required rescue analgesia after six hours which was statistically significant. Buprenorphine is more effective than tramadol for post-operative analgesia in laparotomy cases

INTRODUCTION

The International association for the study of pain defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." This definition recognizes the interplay between the objective, physiological sensory aspects of pain and its subjective, emotional and psychological components.[1] Pain is conducted along three neuronal pathways that transmit noxious stimuli from the periphery to the cerebral cortex. Modulation of pain occurs peripherally at the nociceptor, in the spinal cord and in supraspinal structures.[1]

Post-operative pain is very common in laparotomy cases. It is one of the main concerns for the patient undergoing major surgery. These patients require adequate post-operative analgesia. By virtue of their efficacy, opioid analgesics have long been used for the treatment of both acute and chronic pain. Various techniques and drugs have been used for this purpose with variable success. Every technique and drugs has its own advantages and disadvantages.Transdermal drug delivery systems are simple, non-invasive and compliant method of delivery. They are designed to provide sustained drug release for prolonged period. They are available for analgesics like opioid (fentanyl and buprenorphine), non-steroid anti inflammatory drugs (NSAIDS) such as diclofenac, antihypertensive like nitro glycerine (NTG) ,hormones (estrogen, testosterone), anticholinergics (scopolamine), clonidine, rivastigmine,

monoamine oxidase inhibitor (MAOI) selegiline, methylphenidate, cyanocobalamine, nicotine etc.[2] Opioid are one of the most commonly used analgesics for postoperative pain and their transdermal patches provide sustained blood levels of the drug for sufficient period.

Buprenorphine is a semisynthetic opioid with a μ-agonistic and κ-antagonistic receptor-binding profile. Studies over the past two decades have shown buprenorphine to have a complex and unique pharmacological profile, which results in enhanced therapeutic benefits combined with a favourable safety profile. Having been underused before, the development of a new transdermal drug delivery system for buprenorphine has revived interest in this substance. Transdermal buprenorphine provides a non-invasive method of rate-controlled drug release ensuring constant and predictable serum buprenorphine levels over a prolonged period. This preparation has been shown to be advantageous for long-term treatment of chronic pain patients providing reliable pain control. The transdermal buprenorphine patch, Transtec®, was first launched in Switzerland and Germany in 2001 and is now marketed all over Europe. Using matrix technology, buprenorphine is homogenously incorporated in a solid polymer matrix patch which is applied to the skin. The adhesive buprenorphine patch is non invasive and slowly and continuously releases the drug into the systemic circulation.[3] Its side effects are itching, nausea, dizziness, headache, constipation.

Tramadol is a serotonin releaser, reuptake inhibitor of norepinephrine and a weak μ-opioid receptor agonist. Tramadol is metabolized to O-desmethyltramadol, a significantly more potent μ-opioid agonist. Tramadol and its major metabolite(s) are distinguished from other more potent opioid agonists by relative selectivity for μ-opioid receptor.[4, 5] Its side effects are nausea, dizziness, constipation. The present study compares transdermal buprenorphine patch and intra venous tramadol in relieving post-operative pain.

MATERIALS AND METHODS

This prospective , randomised double-blind study was conducted between May 2014 and November 2015. After scientific advisory committee and institutional ethics committee approval, written informed consent was obtained from all patients. Patients aged 18 to 60 years of either sex weighing between 40 kg and 80 kg scheduled for laparotomy under general anaesthesia ,and American society of anaesthesiologist (ASA) grade I and II were included in the study. Pregnant and lactating women, patients with severe hepatic or renal dysfunction, bleeding disorders, respiratory diseases such as chronic obstructive pulmonary disease, bronchial asthma, hypersensitivity to study drugs, were excluded from the study.

Sixty patients were randomly divided into two equal groups of 30 each, using computer generated randomization code. Group B patients received transdermal buprenorphine patch of 10 mg six hours prior to surgery whereas Group T patients received intravenous tramadol 1mg per kg half hour prior to completion of surgery. The randomization code was provided to operation theatre nurse who prepared the study medication. *Researcher and patients were blind as to group assignment.*

ANAESTHETIC MANAGEMENT

Written informed consent for surgery and for participation in the study was taken from all the patients. Detailed pre-anaesthetic check up was done for fitness for the surgery. Patients were asked to remain nil by mouth for six hours before surgery. During the pre-operative visit day before surgery, all patients were thoroughly explained the visual analogue scale (VAS) score of reporting pain, and were told that they would indicate pain using this method after surgery (Fig.1).

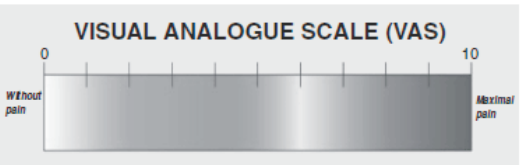

Figure 1. Visual Analogue Scale used to measure Pain.

The patients were asked to mark the line to indicate pain intensity in relation to 0 (no pain) to 10 (worst possible pain). The result was interpreted as distance in centimeter between 0 to the point marked by the patient.

Patients in buprenorphine group were applied transdermal buprenorphine patch 6 hours prior to surgery. Patients in tramadol group were given Inj. tramadol 1mg/kg half hour prior to completion of surgery.

In operation theatre , adequate intra-venous (IV) access was confirmed. Non-invasive blood pressure (NIBP), pulse-oximeter, electrocardiogram (ECG), end tidal CO_2 ($ETCO_2$) were monitored after intubation. Before induction of anaesthesia, all patients were given IV Inj. glycopyrolate (0.2 mg), Inj. ondensetron 4 mg, and Inj. ranitidine 50 mg.In all patients, anaesthesia was induced with Inj. fentanyl 2 μg / kg, Inj. propofol 2-2.5 mg / kg IV followed by Inj. atracurium 0.5 mg / kg IV.

Intubation was done with appropriate sized cuffed oral endo-tracheal tube (ETT). ETT placement was confirmed. Anaesthesia was maintained with Air:O2 50:50, sevoflurane 1.5- 2.5 % (adjusted according to clinical signs) with controlled ventilation.ET CO_2 was maintained between 30 and 35 mm of Hg. Supplemental doses of atracurium 0.1mg / kg. were given. After surgery was over *and spontaneous respiratory efforts appeared, residual* muscle relaxation *was* reversed with Inj. neostigmine 50 μg / kg and Inj. glycopyrolate 4 μg / kg. After confirming adequate reversal and return of consciousness patients were extubated and shifted to post anaesthesia care unit (PACU). Patients pain was assessed using VAS score on arrival in PACU when patient was awake and oriented (0 hour), thereafter, at 2,4,6,8,10,12 and 24 hours. At any time, if pain was more than 3 cm on VAS, rescue analgesia was given in the form of IV Inj. diclofenac 75 mg in 1 ml diluted with 100 ml normal saline.

On the basis of previously published study [6], assuming a VAS pain score of 4.5 cm in buprenorphine group and 3 cm in tramadol group with a difference of 1.5 cm in the pain scores between the two groups with a standard deviation of 2, setting alpha error at 0.05, and power at 80%, the required sample size was calculated by a formula [7] as 28 patients per group. We included 30 patients in each group for better validation of results.

Data collected were entered in the Excel 2007 and analysis of data was done using Statistical package for social sciences (SPSS) version 20. The comparison of quantitative variables between the groups such as mean age, mean weight, mean duration of surgery, mean VAS score was done using unpaired student's “t” test, whereas comparison of qualitative variables such as gender and ASA grade was done by using chi-square test or Fisher's exact test . The confidence limit for significance was fixed at 95% level with p-value < 0.05

RESULTS

Between May 2014 and November 2015, 30 patients in each group were recruited for the study.

As shown in table 1, the two groups were demographically comparable. There was no statistically significant difference with respect to age groups, mean age, gender distribution, mean weight and ASA grade distribution between the two groups. There was also no statistically difference between mean duration of surgery between the two groups.

As depicted in table 2 the average VAS pain score at 0 hour, 8 hours, 10 hours, 12 hours and 24 hours was significantly higher in tramadol group compared to buprenorphine group whereas average pain score at 2 hours, 4 hours and 6 hours did not differ significantly between buprenorphine and tramadol groups.

As shown in table 3, incidence of post-operative nausea and vomiting (PONV) was significantly higher in tramadol group compared to buprenorphine group whereas incidence of itching and respiratory distress did not differ significantly between the two groups.

As depicted in table 4, the majority of patients in buprenorphine group required rescue analgesia up to 6 hours and in tramadol group, majority of patients required rescue analgesia after six hours which was statistically significant.

DISCUSSION

The present study was undertaken to compare the post-operative analgesic effects of transdermal buprenorphine patch and intravenous tramadol in patients undergoing laparotomy. In the present study the average pain score at 0 hour, 8 hours, 10 hours, 12 hours and 24 hours was significantly higher in tramadol group compared to buprenorphine group .The average pain score at 2 hours, 4 hours and 6 hours did not differ significantly between buprenorphine and tramadol groups. Requirement of rescue analgesia was significantly higher after 6 hours in tramadol group as compared to buprenorphine group. The incidence of PONV

Table 1 : Characteristics of patients at baseline

Characteristics	Buprenorphine Group (N=30)	Tramadol Group (N=30)	p value
Age – no (%)			
<30.0	5(16.7)	7(23.3)	
31.0 – 40.0	10(33.3)	6(20.0)	0.556
41.0 – 50.0	5 (16.7)	8(26.7)	
51.0 – 60.0	10(33.3)	9(30.0)	
Mean age (SD)	42.5 ± 11.7	41.6 ± 12.1	0.639
Gender – no (%)			
Male	16(53.3)	17(56.7)	0.795
Female	14(46.7%)	13(43.3%)	
Body weight(kg) no- (%)			
< 50	3(10.0)	3(10.0)	0.736
50< 60	8(26.7)	10(33.3)	
60< 70	12(40.0)	8(26.7)	
= 70	7(23.3)	9(30.0)	
ASA Grade no- (%)			
Grade 1	16(53.3)	14(46.7)	0.606
Grade 2	14(46.7)	16(53.3)	
Mean duration of surgery in minutes (SD)	140.3(±26.8)	140.2(±23.6)	0.980

Table 2 : Comparison of VAS pain score at various time interval.

VAS pain score	Buprenorphine Group (N=30)	Tramadol Group (N=30)	p value
	Mean (SD)	Mean(SD)	
0 hour	4.03(0.37)	3.65(0.90)	0.034
2 hours	2.19(0.57)	2.38(0.55)	0.185
4 hours	2.43(0.53)	2.24(0.77)	0.262
6 hours	2.34(0.52)	2.14(0.43)	0.111
8 hours	2.24(0.61)	2.67(0.76)	0.019
10 hours	2.18(0.50)	2.95(0.36)	0.001
12 hours	2.47(0.46)	3.06(0.58)	0.001
24 hours	1.96(0.48)	3.51(0.54)	0.001

Table 3 : Comparison of incidence of side effects

Side effects		Buprenorphine Group (N=30)	Tramadol Group (N=30)	p value
		N (%)	N (%)	
PONV	No	26 (86.7)	18 (60.0)	0.039
	Yes	4(13.3)	12(40.0)	
Itching	No	25(83.3)	30(100.0)	0.050
	Yes	5(16.7)	0(0.0)	
Respiratory Distress	No	30 (100.0)	30(100.0)	0.999
	Yes	0(0.0)	0(0.0)	

Table 4 : Time of requirement of rescue analgesia

Time to rescue analgesia	Buprenorphine Group (N=30)	Tramadol Group (N=30)	p value
	N (%)	N (%)	
Up to 6 hours	30(100.0)	7(23.3)	0.001
6 to 24 hours	0(0.0)	23(76.7)	
Total	30(100.0)	30(100.0)	

was significantly more with tramadol compared to buprenorphine group.

Alon E et al reported that analgesic effects as well as side effects, circulatory and respiratory parameters of 50 mg tramadol were compared with 0.3 mg buprenorphine in a double blind, randomized study for the relief of postoperative pain. Buprenorphine produced a more potent and longer acting analgesic effect compared to tramadol, although slightly delayed. There were only few and slight side effects and no influence on the circulation and respiration. In the search for a new long-acting and strong analgesic tramadol proved to be unable to replace buprenorphine in the control of postoperative pain.[8] Alon E et al studied buprenorphine, tramadol and nicomorphine for control of post-operative pain. They conducted a double-blind, randomized study for the relief of post-operative pain. They concluded that buprenorphine produced an equally potent, but longer acting analgesic effect, although with slightly delayed onset, in comparison with nicomorphine. Nicomorphine produced a more potent analgesic effect with quicker onset compared with tramadol. There were only few and slight side effects and no influence on circulation or respiration. In the search for a new

long-acting and strong analgesic, buprenorphine in this study proved to be superior to tramadol and to nicomorphine in the control of postoperative pain.[9] The present research substantiates the findings of these studies. The duration of study was only 24 hours and all side effects of both drugs were not recorded and compared were some of the limitations of the present research.

CONCLUSIONS

Buprenorphine is more effective than tramadol in late post-operative hours i.e. 6 to 24 hours. Incidence of PONV was more with tramadol.

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