VOLUME - 12, ISSUE - 01, JANUARY - 2023 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Neurosurgery

COMPARISON BETWEEN SAFETY AND EFFICACY OF TRANSDERMAL BUPRENORPHINE AND FENTANYL PATCHES FOR THE MANAGEMENT OF POST-OPERATIVE PAIN FOLLOWING LUMBAR SPINAL INSTRUMENTATION.

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ABSTRACT

Introduction: Pain is a complex sensory perception. Post-operative pain management is multimodal. We compared transdermal fentanyl and buprenorphine patches for management of post-operative pain following lumbar spinal instrumentation. **Material & Methods:** A sample size of 60 patients were included equally divided into 2 groups. Group B: Receiving transdermal buprenorphine at 10mcg/hr and Group F: Receiving transdermal fentanyl at 25mcg/hr. Transdermal patches were applied 6 hours before proposed surgery. Statistical analysis was done by SPSS version 25.0, In,Chicago II ,USA and Graph pad Prism version 5. **Results & Analysis:** Analysis of different data vs group was not statistically significant. **Conclusion:** Buprenorphine transdermal patch (TDP) is better as it has less adverse events than fentanyl TDP which is a better analgesic .

KEYWORDS :

INTRODUCTION:

In 1979 the International Association for Study of Pain (IASP) defined pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage and described in terms of such damage". Postoperative pain is one of the main concerns for the patients undergoing major surgery. Buprenorphine, a derivative of the morphine alkaloid thebaine, has strong analgesic with marked narcotic antagonist activity. Fentanyl is a potent short acting narcotic analgesic. Most of the parenteral opioids cause sedation, respiratory depression,nausea,vomiting and pruritus. The transdermal delivery system (TDS) can overcome the adverse effect of oral and parenteral opioids. Pain is perceived by stimulation of nociceptors which are of 2 groups.1.High threshold mechanoceptor: Respond to natural stimuli.The impulses are carried by 'A delta' fibres.2 Polymodal nociceptors: They respond to mechanical, thermal and chemical injuries. The impulses are carried by 'C fibres'. The neurotransmitter released from nerve endings are substance P,histamine,bradykinin and leukotrienes.After entry into spinal cord, the nociceptor signal is relayed to the projection cells in the spinal cord.The projection cells are of two types .One is wide dynamic range cells (WDR) which are abundant in laminaII and receive mainly fibres from 'A Delta fibres'.Other is nociceptive specific cells (NS) which are abundant in lamina I.The fast pain is due to the activity of A delta fibres and slow pain is due to the activity of C fibres.The first order neurons ends here about 2-3 segments above the point of entry. The second order neuron from here cross the midline and ascend as spinothalamic tract or tract of Lissaur that ends in the nucleus ventroposterolateralis in thalamus.The third order neuron project to the cerebral cortex. Pain inhibition occurs by excitation of periaqueductal grey matter by the noxious impulse that travel along spinomesenkephalic tract, excite the serotonergic nerves, which in turn excite the opioid receptors in the spinal cord in the region of inhibitory neurons.They liberate enkephalins which produce antanalgesia. Melzack and Walls also proposed gate control theory of pain.

In the endogenous inhibitory system, the neurotransmitters are serotonin,nor -adrenalin, acetylcholine, somatostatin, GABA and neurotensin. The exogenously administered opiates also act on μ & receptors.

Adverse sequelae of surgical trauma and pain includes:

1. Cardiovascular stress
2. Autonomic hyperactivity
3. Tissue breakdown and catabolic state
4. Increased metabolic rate
5. Pulmonary dysfunction
6. Hyper-coagulability
7. Fluid retention
8. Immune dysfunction
9. Delayed return of bowel function
10. Development of chronic pain syndrome

The Common methods adopted for postoperative pain relief are:

1. By increasing pain threshold Pharmacological means
a. Centrally acting analgesics
b. Peripherally acting analgesics

Non – Pharmacological means

a. Counselling
b. Hypnosis

2. By modulating pain pathways
a. Transcutaneous electrical nerve stimulation(TENS)
b. Acupuncture
c. Cryotherapy
d. Heat therapy
e. Narcotics

3. By interrupting the nociceptor pathway
a. Nerve block, neurolysis
b. Surgical ablasion- cryoanalgesia

The centrally acting analgesics are traditionally opiate analgesics. Commonly available are Morphine, Pethidine, pentazocine,Buprenorphine and tramadol.

Opioid analgesics can be given by various means

a. Oral
b. Intramuscular
c. Intravenous
d. Neuraxial
e. Transdermal

There are various methods of pain measurement

1. Introspective method: Patient or trained attender assess pain
2. Behaviourist method: By measuring the alterations in pulse rate, respiratory rate.
3. Visual analogue scale (VAS): It is used commonly.First described by Aitken in 1966.The subject makes mark on a 10 cm line ,one end of which is "No pain" and other end is "The worst pain one can imagine".
4. Numeric Rating scale (NRS):

0 No pain
1-3 Mild pain
4-6 Moderate pain
7-10 Severe pain

Other methods of pain measurement are:
Mc Gill's pain Questionnaire
TOTPAR (Total pain relief and analgesics)
SPID (Sum of pain intensity differences)

Opiate receptors:

Receptor	Location	Effect
Mu	Mammarybodies, Mesolimbic area striatum,amygdala,Peria queductal grey matter, median raphe	Miosis,analgesia,brady cardia,euphoria, respiratory depression, hypotension
kappa	Spinal cord layer VI of cerebral cortex	Spinal analgesia, sedation
Delta	Spinal cord, olfactory area, motor integration.	Spinal analgesia, psychomimetic action
Sigma	Spinal cord, Limbic system	Mydriasis, dysphoria, hypertonia, tachycardia, tachypnea

Endogenous opiates are endorphins, enkephalins and dynorphins. Their actions are revered by naloxone.Regulation of pain perception is a likely role for enkephalins. Enkephalins activate the descending inhibitory pathway through periaqueductal grey matter, nucleus magnus raphe,medial thalamus and substantia gelatinosa in the spinal cord. The endogenous opioids and morphine suppress the substance P.

Buprenorphine is an agonist- antagonist opioid derived from opium alkaloid thebaine. 0.3 mg IM Buprenorphine is equivalent to 10 mg morphine.After IM administration ,effect occurs in 30 minutes, action lasts for 8 hours.After IM administration it is metabolized in the liver .2/3rd of the drug appears unchanged in the bile and the remainder is excreted in urine.

Side effects are drowsiness, nauseas, vomiting, respiratory depression, pulmonary edema,dependence.It can be used sublingually, IM/IV injection, transdermal patch or an implant.

Fentanyl is a phenypiperidine derivative.It is 75 to 125 times more potent than morphine.It has rapid onset of action, effects lasts less than an hour or two.It is available in a number of forms like intravenous, intrathecal, transdermal patch, intranasal, sublingual, lozenges.

It has agonistic action to opioid receptors. It is lipophilic and can easily penetrate CNS. Common side effects are nausea, constipation, sleepiness, confusion, respiratory depression, serotonin syndrome, low blood pressure and addiction.

MATERIAL AND METHODS

The clinical study was conducted at Neurosurgery and orthopaedic department of our tertiary care hospital over a period of 1 year and 6 months.Ethical committee permission was taken.Total number of patients were 60, randomly divided into 2 groups.

Group B: Patients receiving transdermal buprenorphine 10 mcg/hr

Group F: Patients receiving transdermal fentanyl 25mcg/hr

The patient population was ASA 1 & 2, age between 25-60 years, either sex and undergoing lumbar spinal instrumentation at our hospital.

Exclusion criteria was:

a) Patients' refusal
b) Known history of allergy to the drugs under study
c) ASA physical status 3 or more
d) Patients on anticoagulant
e) Patients having sepsis and or local site infection
f) Patients with known CVS disease
g) Hepatic/Renal impairment, obese,myasthenia gravis, delirium tremens, dermatitis at patch site.

Thorough Pre-anaesthetic check up and routine laboratory Biochemical investigations including complete haemogram, Blood sugar, urea, creatinine, ECG and Chest X-ray were done.

Parameters which were monitored are: NIBP, SPO2, ECG, ETCO2, Temperature, respiratory rate,pain score.

Drug patches were applied to patients 6 hours before proposed surgery in both groups after noting baseline haemodynamic parameters.Patients were premedicated with inj Midazolam 1mg IV, inj Fentanyl 2 mcg/kg IV and inj ondensetron 4mg iv, inj Glycopyrrolate 0.2 mgIV and inj Ranitidine 5omg IV.Patients were induced with Propofol 2mg/kg and intubated with inj Atracurium 0.5mg/kg. Anaesthesia was maintained with N2O & O2 (66:33), Isoflurane (1 MAC) and muscle relaxation was maintained with atracurium and IPPV.Patients were extubated after reversing neuromuscular blockade with glycopyrrolate and neostigmine (0.01 mg/kg and 0.05 mg/kg respectively).

Analgesia was assessed using VAS and NRSafter regaining consciousness, 6 hourly for the first day and 8 hourly for next 2 days.Inj Diclofenac (75mg) IM was used as rescue analgesia. Side effects like giddiness, drowsiness, PONV, constipation respiratory distress and patch site redness was noted.

Statistical analysis was done by SPSS (version 25.0; SPSS In., Chicago,IL,USA) and Graph pad prism version 5.Unpaired proportions were compared by Chi-square test or Fishers exact test as appropriate.Once a t value is determined, a P value was found using a table of values from Students t-distribution. P value ≤ 0.05 was considered as statistically significant.

RESULTS & ANALYSIS:

Distribution of mean age,mean height ,mean weight, mean systolic BP, main diastolic BP,meanSpO2, mean ETCO2, mean temperature ,mean respiratory rate, mean VAS post extubation, mean NRS,sex, ASA,adverse effect VS group was not statistically significant.

DISCUSSION

Wolff RF et al (2012) found that in comparison with morphine , transdermal buprenorphine had a higher decrease of pain intensity, while morphine causes more adverse effects like constipation,drowsiness,respiratory depression [1]. Transdermal buprenorphine and fentanyl have comparable effects for pain with fewer adverse events with transdermal buprenorphine. Our study showed that among transdermal fentanyl and buprenorphine, fentanyl is a slightly better analgesia but with higher side effects.

Leppert W et al (2018) found that transdermal and topical routes, relieve local pain with minimal systemic adverse effects, provide long period of analgesia especially for patients who are unable to take drug orally, and has lower risks of addiction[2].

Canneti A et al (2013) found both fentanyl and buprenorphine patches showed significant reductions in neuropathic pain and allodynia, significant improvement in karnofsky

performance status , and neither of them affected CD4+ or CD8+ levels.[3]

Synder CJ et al (2009) found that on the first postoperative day transdermal buprenorphine was more effective than oral tramadol but not on subsequent days.

Pergolizzi Jr Jv et al(2015) found that transdermal buprenorphine provide effective pain relief and less scope of non-medical use. [4]

Yadav M et al (2019) found none of the patient required rescue analgesia in the first 2 hours,20% at the 4th hour,32% demanded rescue analgesia at 8th hour and 10% at 12th hour. [5] In our study we are applying the patches 6 hours before and hence most of the patients required rescue analgesia in the first postoperative hour. We have to consider applying the patches at least 12 hours before.

Arshad Z et al (2015) concluded that fentanyl is better than buprenorphine patch which is similar to our study (but there was no statistical significance)[6].

Patel M et al (2013) found that buprenorphine appeared to have a greater effect on bone associated pain and fentanyl on cold pressure induced pain with similar side effects(like our study).[7]

Kadapamannil D et al (2018)found transdermal buprenorphine patch applied 72 hours preoperatively provided better analgesic than applied 48 hours before surgery.We concluded that the patches should be applied more than 6 hours before.[8]

Read K et al (2019) found transdermal fentanyl is advantageous than oral tramadol[9].

Niyogi S et al (2017) found transdermal buprenorphine patches were better than oral tramadol[10].

Golcic M et al (2018) analyzed differences between the transdermal fentanyl and buprenorphine group by analyzing patient characteristic and evaluating the differences in survival in **hospice** patients over the age of 65, from 2013 to 2017.A total of 292 patients(75.8%) used fentanyl patch and 93(24.1%) were on buprenorphine patch[11]. Patients had virtually the same characteristics in both groups.There was no difference in survival between the two groups.

Patel M et al (2013) compared transdermal buprenorphine and fentanyl in the treatment of moderate to severe pain. Low dose patches provided significant analgesic effect compared to placebo.Buprenorphine appeared to have a greater effect on bone associated pain and fentanyl on cold pressure induced pain.Adverse effects were similar in both groups.However human experimental pain models were performed in healthy subjects and may not accurately represent response in chronic pain patients.

Wolff RF et al (2012), found transdermal buprenorphine and transdermal fentanyl have similar analgesic properties, with fewer adverse events caused by transdermal buprenorphine.

Canneti A et al (2013) enrolled 40 advanced AIDS patients(28 male and 12 female) with chronic peripheral neuropathic pain.Both buprenorphine and fentanyl groups showed statistically significant reduction in neuropathic pain and significant improvement in Karnofsky Performance status.Neither group affected CD4+ or CD8+ levels but buprenorphine group resulted in more stable CD4+ concentration.

Arshad Z et al (2015) compared (groupA) transdermal buprenorphine(10mcg/hr) with (group B)transdermal fentanyl (25 mcg/hr) in 60 patients undergoing major abdominal surgery under GA.The mean level of VAS was significantly lower in group B compared to group A.The mean level of sedation score was significantly lower in group B than group A .Hemodynamic variables were comparable in both groups.The difference is rescue analgesic requirement is not statistically significant. 20% in fentanyl group and 16.7% in buprenorphine experienced some adverse effects.

Limitations of our study was:

1. Small sample size (n=60)
2. Single centre study
3. Our hospital being a tertiary care hospital, referral bias cannot be ruled out.
4. Dosages should have been chosen according to body weight.

CONCLUSION

In our study VAS was less with fentanyl transdermal patch than buprenorphine patch but this was not statistically significant.NRS was less with fentanyl patch than buprenorphine patch but this was not statistically significant.Rescue analgesia was required in both groups post extubation.So the patches should be applied more than 6 hours before operation.

Adverse effects like pruritus ,nausea ,light headedness was common in fentanyl group, nausea was common in buprenorphine group.However it was not statistically significant.

Buprenorphine patch is cheap ,easily available and can be used for long duration of 7 days.Fentanyl patches are difficult to obtain ,last for 3 days and have higher side effects as well as abuse potential.

Therefore we come to the conclusion that buprenorphine patch is better than fentanyl patch, though the latter is a better analgesic.

REFERENCES

1. Wolff RF, Aune D, Truyers C, Hernandez AV, Misso K, Riemsma R, Kleijnen J. Systematic review of efficacy and safety of buprenorphine versus fentanyl or morphine in patients with chronic moderate to severe pain. Current medical research and opinion. 2012 May 1;28(5):833-45.
2. Leppert W, Malec–Milewska M, Zajaczkowska R, Wordliczek J. Transdermal and topical drug administration in the treatment of pain. Molecules. 2018 Mar 17;23(3):681.
3. Canneti A, Luzi M, Di PM, Cannata F, Pasqualitto F, Spinoglio A, Reale C. Safety and efficacy of transdermal buprenorphine and transdermal fentanyl in the treatment of neuropathic pain in AIDS patients. Minerva anestesiologica. 2013 Aug;79(8):871-83.
4. Pergolizzi Jr JV, Scholten W, Smith KJ, Leighton-Scott J, Willis JC, Henningfield JE. The unique role of transdermal buprenorphine in the global chronic pain epidemic. Acta Anaesthesiologica Taiwanica. 2015 Jun 1;53(2):71-6.
5. Yadav M, Mohan CL, Srikanth I, Raj ER, Gopinath R, Chandrasekhar P. Effect of preoperative application of buprenorphine transdermal patch on analgesic requirement in postoperative period in hip and knee replacement surgeries. Journal of anaesthesiology, clinical pharmacology. 2019 Jan;35(1):124.
6. Arshad Z, Prakash R, Gautam S, Kumar S. Comparison between transdermal buprenorphine and transdermal fentanyl for postoperative pain relief after major abdominal surgeries. Journal of Clinical and Diagnostic Research: JCDR. 2015 Dec;9(12):UC01.
7. Patel M, Kerstman E. Transdermal fentanyl compared to transdermal buprenorphine on descending pain modulation in human experimental models. The Journal of Pain. 2013 Apr 1;14(4):S75.
8. Kadapamannil D, Rajan S, Tosh P, Kumar L. Comparison of efficacy and safety of transdermal buprenorphine patch applied 48 versus 72 hours preoperatively in providing adequate postoperative analgesia following major abdominal surgeries. Indian Journal of Pain. 2018 Jan 1;32(1):46.
9. Read K, Khatun M, Murphy H. Comparison of transdermal fentanyl and oral tramadol for lateral thoracotomy in dogs: cardiovascular and behavioural data. Veterinary anaesthesia and analgesia. 2019 Jan 1;46(1):116-25.
10. Niyogi S, Bhunia P, Nayak J, Santra S, Acharjee A, Chakraborty I. Efficacy of transdermal buprenorphine patch on post-operative pain relief after elective spinal instrumentation surgery. Indian journal of anaesthesia. 2017 Nov;61(11):923.
11. Golčić M, Dobrila-Dintinjana R, Golčić G, Gović-Golčić L. Differences between Transdermal Fentanyl and Buprenorphine in the Elderly Hospice Patients. Pain research and treatment. 2018;2018.