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Original Research Article

Use of Transdermal Buprenorphine Patch of Strength 5mg and 10mg in Grade I and II Osteoarthritis Knee Patients for Pain Relief- A Prospective, Double-Blind, Randomised Study

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Conflict of interest: Nil

Abstract:

Objectives: To compare the analgesic efficacy of buprenorphine transdermal patches of strength 5mg and 10mg in grade I and II osteoarthritis knee patients with respect to improvement in pain score and physical function while taking into account of its adverse effects and effects on hemodynamic parameters.

Methods: Hundred patients of age of 40-65 years, of either sex, American Society of Anaesthesiology (ASA) physical status I and II were randomly allocated into two equal groups and received 5mg and 10mg patches on day 1, day 7 and day 14. Primary endpoints were Numeric Rating Scale for pain score and Western Ontario and McMaster Universities Arthritis Index (WOMAC) for improvement in quality of lifestyle. Secondary outcomes included hemodynamic variables, requirement of rescue analgesia and adverse effects.

Results: The mean NRS and WOMAC scores were reduced more in group B than in group A on day 7 and day 14 across different time points [NRS: F value-413.72, WOMAC: F value-395.02] and types of treatment received combined [NRS: F value-306.72, WOMAC: F value-350.48] with p values<0.05 in both the cases. Subjects in group A needed to take more rescue analgesia. Other variables were comparable in the two groups.

Discussion: Thus transdermal buprenorphine patch can be used as an alternative route providing constant level of analgesia with minimum adverse effects, the patch of 10mg strength showing higher analgesic efficacy and improved life-style in grade I and II osteoarthritis knee patients with comparable hemodynamic parameters and adverse effects to that of 5mg strength.

Keywords: Buprenorphine, Transdermal patch, Osteoarthritis, Analgesia.

Introduction

Pain is a complex, perspective and subjective phenomenon with several dimensions like intensity, quality, time course and impact in lifestyle. Osteoarthritis, the chronic degenerative joint-disease, affecting over 60% of elderly population[1] presents mainly with pain and limited joint function. It can lead to immobility, obesity and subsequently becomes associated with other comorbidities like diabetes, hypertension, dyslipidemia and heart disease. Thus, it is crucial to make prompt diagnosis and begin the management which includes both pharmacological and nonpharmacological treatments. Pharmacological management often includes analgesics, corticosteroids, counterirritant and viscosupplementary [2]chondroprotective agents which are often given in oral or injectable forms.

Transdermal buprenorphine patch is the preferred alternative mode of therapy. Buprenorphine, a centrally acting opioid, has a partial μ receptor agonistic action and κ and δ receptor antagonist with ceiling effect to its respiratory depressive effects [3] providing sustained analgesia with minimum physical dependence and psychomimetic effects. It avoids requirement of dose adjustment in elderly and renal impaired patients with minimum gastrointestinal or cardiovascular risks. Transdermal delivery bypasses first pass metabolism improving bioavailability, provides constant delivery of buprenorphine [4] with sustained level of analgesia, lower peak concentration thus minimizing adverse effects and allowing its long-term use in chronic disease.

With this background, in order to find the optimum dose, transdermal buprenorphine patch of strength

5mg and 10mg were used to assess and compare their analgesic efficacy in osteoarthritis knee patient of grade I and II. The rate of uptake of 5mg and 10mg patch are 5mcg/hr and 10mcg/hr for 7 days.

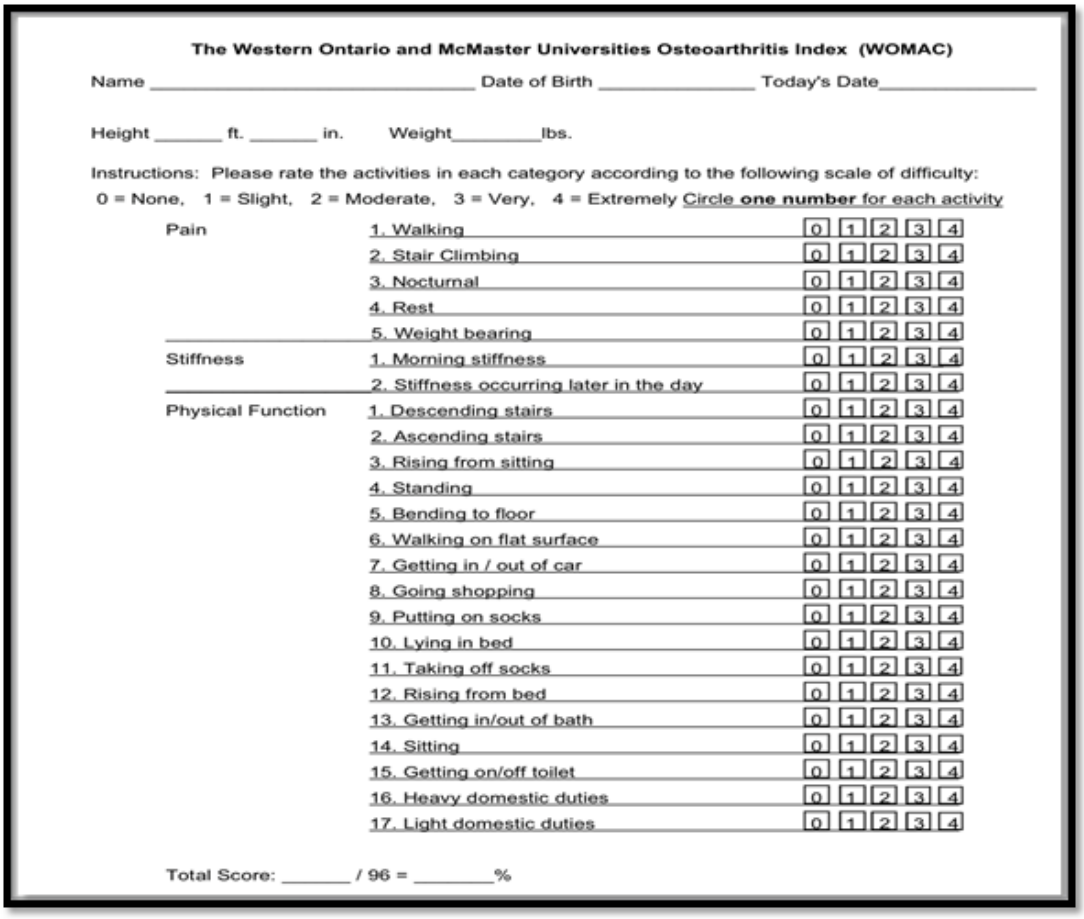
Methods:

The study was conducted at the Pain Clinic and Physical Medicine and Rehabilitation (PMR) outdoor in Calcutta National Medical College and Hospital from February 2020 to August 2020, after taking institutional Ethics Committee clearance and informed consent from each patient.

It was a prospective randomized double-blind clinical study. After ethical committee clearance, 100 patients belonging to ASA I and II, age of 40-65 years and of either sex who visited Pain Clinic and PMR outdoor with osteoarthritis knee of grade I and II were randomly selected using computer generated randomization table. Patients with known allergy to the study drug, uncontrolled hypertension, cardiovascular, renal or liver disease, opioid dependence, pregnancy and impaired respiratory function were excluded. All patients were subjected to detailed clinical history and examination. After checking required investigations (Routine blood investigation of Hemoglobin, total WBC count, Differential count, Platelet count, ESR, C- Reactive Protein, Fasting blood sugar, Urea, Creatinine and X-RAY of knee-AP and lateral views) and explaining the procedure to the patients, they were randomly divided into two groups of A and B of 50 subjects in each group. An independent assistant not involved in the study applied transdermal buprenorphine patch of 5mg and 10mg strength in group A and group B subjects respectively on a dry, non- hairy, non-irritated area of skin on upper body. The replacement patch was applied twice with one week interval to a different area of skin on patient's upper body. Haemodynamic parameters like Mean Arterial Pressure (MAP), Pulse Rate (PR) and oxygen saturation ($SP0_2$) were monitored pre-procedure, 1 hour and 2 hours after the procedure. Numeric Rating Scale (NRS) (Figure 1) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (Figure 2) were assessed on day 1, day 7 and day 14. Patients were advised to take oral paracetamol (acetaminophen) tablets (500 mg) as rescue analgesia or breakthrough pain (they could take 1,000 mg every four to six hours up to a maximum daily dose of 4,000 mg per day). Each day, patients recorded the number of tablets they had taken and the times at which they took them. Patients and/ the accompanying person were explained about the side effects of the drug, were asked to note if any adverse effect occurred and to bring the patient to the clinic if required. Patients were asked to attend Pain Clinic or PMR outdoor after one week and two weeks or SOS.

SCORE	SEVERITY	DAY1	DAY7	DAY14
10	UNABLE TO MOVE			
9	SEVERE			
8	INTENSE			
7	UNMANAGE - ABLE			
6	DISTRESSING			
5	DISTRACTING			
4	MODERATE			
3	UNCOMFORTA BLE			
2	MILD			
1	MINIMAL			
0	NO PAIN			

Figure 1:Numeric Rating Scale (NRS) Score



The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

Name _____ Date of Birth _____ Today's Date_____

Height _____ ft. _____ in. Weight_____lbs.

Instructions: Please rate the activities in each category according to the following scale of difficulty:
0 = None, 1 = Slight, 2 = Moderate, 3 = Very, 4 = Extremely Circle **one number** for each activity

Pain	1. Walking	0 1 2 3 4
	2. Stair Climbing	0 1 2 3 4
	3. Nocturnal	0 1 2 3 4
	4. Rest	0 1 2 3 4
	5. Weight bearing	0 1 2 3 4
Stiffness	1. Morning stiffness	0 1 2 3 4
	2. Stiffness occurring later in the day	0 1 2 3 4
Physical Function	1. Descending stairs	0 1 2 3 4
	2. Ascending stairs	0 1 2 3 4
	3. Rising from sitting	0 1 2 3 4
	4. Standing	0 1 2 3 4
	5. Bending to floor	0 1 2 3 4
	6. Walking on flat surface	0 1 2 3 4
	7. Getting in / out of car	0 1 2 3 4
	8. Going shopping	0 1 2 3 4
	9. Putting on socks	0 1 2 3 4
	10. Lying in bed	0 1 2 3 4
	11. Taking off socks	0 1 2 3 4
	12. Rising from bed	0 1 2 3 4
	13. Getting in/out of bath	0 1 2 3 4
	14. Sitting	0 1 2 3 4
	15. Getting on/off toilet	0 1 2 3 4
	16. Heavy domestic duties	0 1 2 3 4
	17. Light domestic duties	0 1 2 3 4

Total Score: _____ / 96 = _____%

Figure 2: The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

Sample size was calculated while assuming P value <0.05 to be significant and considering effect to be two sided and we got Z_α =1.96; assuming power of study to be 90% we got $Z_{1-\beta}$ = 1.28;

z_α (the Value of the standard normal variate at 5% error) =1.96

$z_{1-\beta}$ (the Value of the standard normal variate at 90% power) =1.28

Mean Pain Score 1 week after applying the patch Group 1 = 5.32

Mean Pain Score 1 week after applying the patch Group 2 = 3.40

d=Effect Size = (5.32-3.40) = 1.92

Considering an effect size (Difference in Pain Score 1 week after Applying the patch) of 1.92 to be statistically significant we got $n > 2(Z_\alpha + Z_{1-\beta})^2 \times SD^2/d^2$ we got n = 31. Hence minimum 31 patients were needed in each group. However, based on available data we had taken 50 patients in each group and the total sample size was 100. Two subjects in each group were lost to follow up after day 1, so 48 subjects were analyzed and results were calculated. Data was entered in MS Excel and analysed using SPSS (Statistical Package for Social Scientist, Version 25.0 for windows, Chicago, IL, USA), statistical tests used were Student's independent unpaired sample t test, Anova test and Pearson Chi-square test. Analgesic effect and effect on physical function were compared by using Anovatest, comparisons of demographical and hemodynamic parameters were done by student's independent unpaired sample t test. The proportion of side effects and need of rescue analgesia were compared using the Chi-square test. P value<0.05 was taken to be significant.

Results:

In our study, 100 patients were selected randomly and assigned to two groups A and B. When comparing NRS score, WOMAC score and requirement of rescue analgesia between the two groups, Group B produced statistically significant difference compared to Group A with the following results:

1. NRS score: Median scores were 5 and 4 for groups A and B on day 7 and 5 and 3 for groups A and B on day 14 respectively. (Table 1) The main effect of the difference in NRS scores among the days (Day1, Day7 and Day 14) was statistically significant (F= 413.01, p-value <0.05). Also, the combined interaction effect of days and the treatment received was statistically significant (F= 306.72, p-value <0.05). The test of between subjects' effects

suggested that there was also a statistically significant difference in the NRS scores among the two treatment groups (F = 25.93, p-value < 0.05). (Table 2)

2. WOMAC score: Median scores were 43.22 and 37.75 for groups A and B on day 7 and 43.22 and 32.75 for groups A and B in day 14 respectively (Table 3). The main effect of the difference in WOMAC scores among the days (Day1, Day7 and Day 14) was statistically significant (F= 395.02, p-value <0.05). Also, the combined interaction effect of days and the treatment received was statistically significant (F= 350.48, p-value <0.05). The test of between subjects' effects suggested that there was also a statistically significant difference in the NRS scores among the two treatment groups (F = 30.91, p-value < 0.05). (Table 4)
3. Intake of rescue analgesia: On day 14, 22.91% and 6.25% of subjects in groups A and B required to take rescue analgesia. P=0.021 (Figure 3)

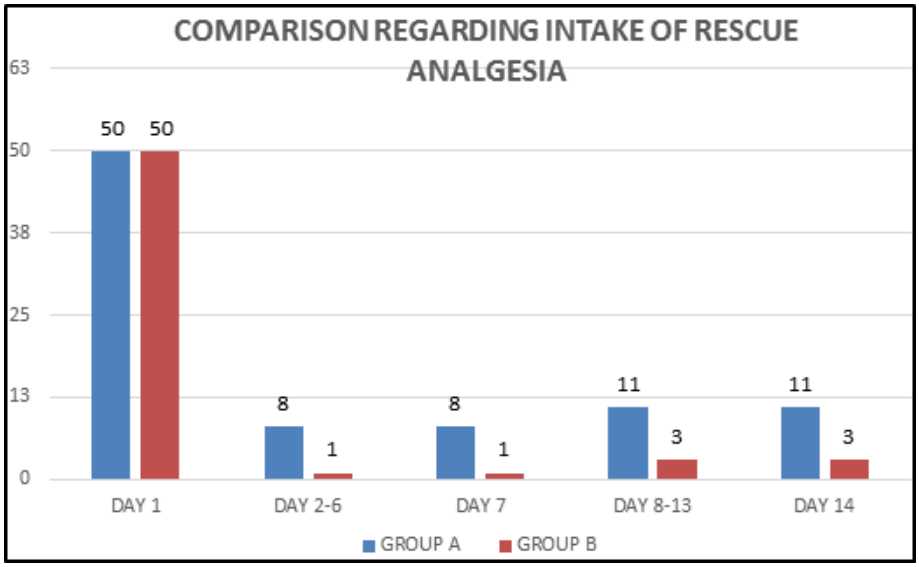


Figure 3 -Comparison regarding intake of rescue analgesia between the two groups(via Pearson Chi square test)

There was no statistically significant difference in their demographic profile, P value being 0.564 for age, 0.434 for weight, 0.422 for sex and 0.545 for ASA (Table 5). The haemodynamic parameters (Mean arterial pressure, Pulse Rate, Pulse Oximetry) noted before procedure and 1 hour and 2 hours after procedure did not show any statistically significant difference. (Table 6, Figure 4, Figure 5 respectively). There was also no statistical association regarding incidence of adverse effects during the study period between the two groups. (Table 7).

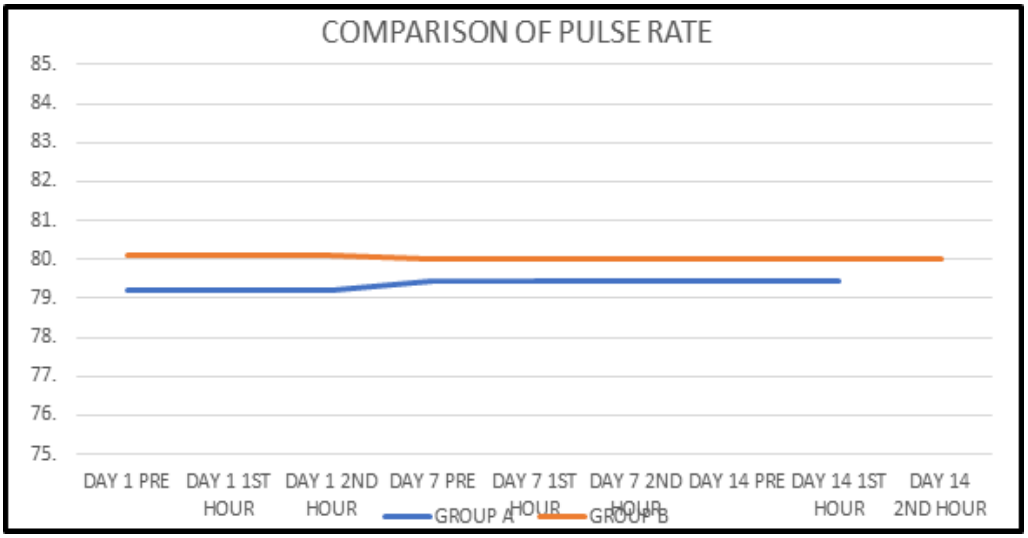


Figure 4 - Comparison of Pulse Rate of patients between the two groups, at three phases

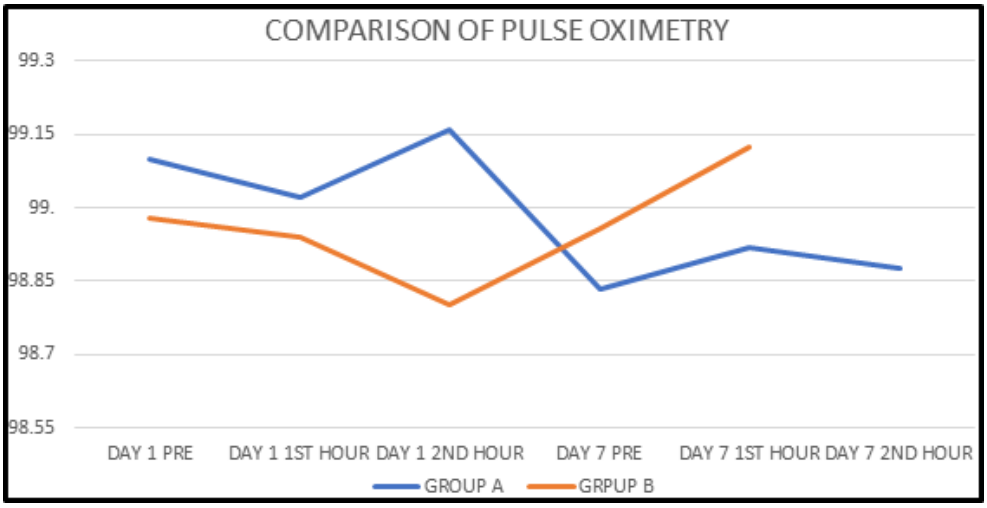


Figure 5: Comparison of PULSE OXIMETRY of patients between the two groups, at three phases

Table 1: NRS score of the two groups in terms of median and IQR:

Score	Treatment	Median	1st quartile	3rd quartile	IQR
Day1 NRS	5mg	5.00	4.00	6.00	2.00
	10 mg	5.00	4.00	6.00	2.00
D7 NRS	5mg	5.00	4.00	5.00	1.00
	10 mg	4.00	3.00	5.00	2.00
D14 NRS	5mg	5.00	4.00	5.00	1.00
	10 mg	3.00	2.00	4.00	2.00

IQR= Interquartile range

Table 2: Anova test of NRS Score

Type of comparison	F value	p-value
Tests of within subjects' contrasts		
Comparison of NRS Scores based on Days (Main Effect)	413.01	<0.05
Comparison of NRS Scores based on Days and Type of treatment (Interaction Effect)	306.72	<0.05
Tests of between subjects' contrasts		
Comparison of NRS scores among Treatment groups	25.93	<0.05

Table 3: WOMAC scores of two groups in terms of median and IQR.

Score	Treatment	Median	1st quartile	3rd quartile	IQR
Day1 WOMAC	5mg	43.75	39.58	45.83	6.25
	10 mg	43.22	40.62	46.87	6.25
D7 WOMAC	5mg	43.22	38.80	45.83	7.03
	10 mg	37.75	34.62	40.87	6.25
D14 WOMAC	5mg	43.22	38.80	45.83	7.03
	10 mg	32.75	29.62	36.65	7.03

Table 4: Anova test of WOMAC SCORE

Type of comparison	F value	p-value
Tests of within subjects contrasts		
Comparison of WOMAC Scores based on Days (Main Effect)	395.02	<0.05
Comparison of WOMAC Scores based on Days and Type of treatment (Interaction Effect)	350.48	<0.05
Tests of between subjects contrasts		
Comparison of WOMAC scores among Treatment groups	30.91	<0.05

Table 5: Comparison of demographic parameters (age, weight and sex) and ASA physical status between study groups

Catagory		Group A	Group B	p value	Significance
AGE (year)		52.98±7.89	52.16±6.15	0.56	Not significant
WEIGHT (kg)		60.18±3.17	59.68±3.19	0.43	Not significant
SEX	MALE	25	21	0.42	Not significant
	FEMALE	25	29		
ASA	I	27	30	0.54	Not significant
	II	23	20		

Data entered as Mean±Standard deviation, Sex and ASA expressed as count, P<0.05 considered statistically significant
(student's independent unpaired sample t test)

Table 6: Comparison of Mean Arterial Pressure of patients between the two groups

Time Point		Group A Mean±SD	Group B Mean±SD	t-value	p- value	Significance
DAY 1	PRE	84.98±2.85	84.86±2.79	0.21	0.83	Not significant
	1ST HOUR	84.98±2.85	84.86±2.79	0.21	0.83	Not significant
	2ND HOUR	84.980±2.85	84.86±2.79	0.21	0.83	Not significant
DAY 7	PRE	85.042±2.80	84.75±2.79	0.51	0.17	Not significant
	1ST HOUR	85.04±2.80	84.75±2.79	0.51	0.17	Not significant
	2ND HOUR	85.04±2.80	84.75±2.79	0.51	0.17	Not significant
DAY 14	PRE	85.04±2.80	84.75±2.79	0.51	0.61	Not significant
	1ST HOUR	85.04±2.80	84.75±2.79	0.51	0.61	Not significant
	2ND HOUR	85.04±2.80	84.75±2.79	0.51	0.61	Not significant

(student's independent sample t test, P<0.05 considered statistically significant)

Table 7: Comparison between the two groups regarding incidence of adverse effects

Adverse Effects		Group A	Group B	P value	Significance
DAY 1	YES	0	0	--	Not significant
	NO	50	50		
DAY 2-6	YES	23	25	0.68	Not significant
	NO	25	23		
DAY 7	YES	0	0	--	Not significant
	NO	48	48		
DAY 8-13	YES	13	17	0.37	Not significant
	NO	35	31		
DAY 14	YES	13	17	0.37	Not significant
	NO	35	31		

(Pearson chi-square test, P<0.05 considered statistically significant)

Discussion:

Osteoarthritis is a combination of degradative and reparative processes in the articular cartilage and subchondral bone, associated with osteophyte formation and low-grade inflammation[5] with the main goals of management being control of pain and improvement in joint function by pharmacological and/ nonpharmacological methods. Transdermal buprenorphine patches have been popular for chronic pain management because of non-invasive dosing, longer duration of action and minimal side effects.[6] Buprenorphine patch is available in strengths of 5mg, 7.5mg, 10mg, 15mg and 20mg in the market. We used 5mg and 10mg patches to see whether a low dose(5mg) of the drug can achieve same result of pain relief and improvement of lifestyle in order to decrease the probable side effects associated with the drug since we were using this drug in outpatient basis where 24 hours monitoring is a limitation. In this study, transdermal buprenorphine patches were used in osteoarthritis knee patients of grade 1 and 2. Numeric Rating Scale (NRS)[7] for pain score, Western Ontario and McMaster Universities Arthritis Index (WOMAC) to assess improvement in quality of lifestyle and hemodynamic parameters after application of patch were compared between the two groups. Adverse effects and requirement of rescue analgesia were also compared between them.

With respect to pain control, in our study, it was found that there was more reduction of pain score in patients to whom strength of 10mg buprenorphine patch was applied. The main effect of the difference in NRS scores among the days (Day1, Day7 and Day 14) was statistically significant (F= 413.01, p-value <0.05). This suggested that there was a significant difference in the overall NRS scores across the different time points. Also, the combined interaction effect of days and the treatment received was statistically significant (F= 306.72, p-value <0.05). This suggested that there was a significant difference in the overall NRS scores across the different time points and the type of treatment received combined.

The test of between subjects' effects suggested that there was also a statistically significant difference in the NRS scores among the two treatment groups. (F = 25.93, p-value < 0.05)

RajmalaJaiswal et al in 2017 did a prospective randomized single blind study comparing the efficacy of transdermal patches of buprenorphine and diclofenac to combat pain in osteoarthritis knee patients and concluded that both the patches were effective, well tolerated and safe. It was observed that pain scores were less in the group receiving diclofenac patch.[8] Do Heum Yoon et al in 2017 did a prospective study in Asian patients with moderate to severe musculoskeletal pain, and concluded that transdermal buprenorphine patch provides effective pain relief with an acceptable tolerability profile over the treatment period of 11 weeks.[9]

The main effect of the difference in WOMAC scores among the days (Day1, Day7 and Day 14) was statistically significant (F= 395.02, p-value <0.05). Also, the combined interaction effect of days and the treatment received was statistically significant (F= 350.48, p-value <0.05). This suggested that there was a significant difference in the overall WOMAC scores across the different time points and the type of treatment received combined.

The test of between subjects' effects suggested that there was also a statistically significant difference in the WOMAC scores among the two treatment groups. (F = 30.91, p-value < 0.05).

Thus, it was observed that quality of life was better improved in patients receiving 10mg buprenorphine patch. K Wahlee et al in 2013 did post-marketing surveillance study on patients receiving transdermal buprenorphine patch with 7 days interval and came into conclusion that quality of lifestyle , social activities as well as self-reliance improved significantly and compliances and tolerability were assessed as very good or good in > 90% of patients.[10]Breivik H et al in 2010 did 6 months randomised placebo-controlled evaluation of tolerability and efficacy of a low dose 7-day transdermal buprenorphine patch in osteoarthritis knee patient and it was seen that WOMAC Osteoarthritis score for functional abilities (P = 0.055) showed more effects from buprenorphine than placebo.[11]

Regarding rescue analgesia in our study, it was found that Group A needed to take more rescue analgesia that Group B. It was observed that 22.91% in group A and 6% in group B needed rescue analgesia on day 14. FarzanaMitra, Shahead-Chowdhury, Mike Shelley and Gary Williams in 2013 did a prospective, randomized, clinical study comparing effectiveness of transdermal buprenorphine patch vs fentanyl patch in chronic management of persistent non-cancer pain. It was observed that 31% of buprenorphine group and 57% of fentanyl users needed adjuvants for pain relief by the end of 3 months.[12]ReinhardSittl in 2006 did clinical and post-marketing surveillance studies where transdermal buprenorphine patch had been assessed as a therapy for chronic cancer and non-cancer pain. It was observed that out of 13,179 patients, 49.6% did not require any analgesic supplementary.[13]

In this study it was seen that in both groups nausea & vomiting, constipation, drowsiness and pruritis were noted [14]. There was no significant variation in adverse effect among the two groups. There was also not much difference in hemodynamic parameters among the two groups.

Thus, in our study, we observed that 5mg drug patch could not achieve the same efficacy level as 10mg drug patch, which showed much greater pain relief and improvement in lifestyle and also did not show much significant difference in adverse effects or hemodynamic parameters (observed for 2 hours after patch application) between the two study groups. We avoided higher strengths since higher dosage limited its usage in outpatients. From various previous human studies [15], it was found that buprenorphine, being a partial KOP receptor antagonist, it showed ceiling effect on respiratory depression at doses >0.1mg per 70kg. In another study [16], when data analysis was performed on the absolute respiratory and pain tolerance values, and on the values relative to baseline (change in minute ventilation and change in pain tolerance), buprenorphine displayed a plateau for respiratory depression over a dose range of 0.05-0.6mg without causing any ceiling in analgesic effect.

It is possible that difference in MOP receptor density (more in CNS pathways concerned with nociception than at the respiratory centers in brain stem and pons) may be the cause of differential buprenorphine effect.

According to some authors, with difference in the agonist/ MOR/ G-protein /Beta arrestin complex in pain and respiratory centers, it is suggested that I gal transduction attributable to buprenorphine

activation of MOP receptor in respiratory neurons is via beta arrestin mediation causing diminished responses of respiratory depression.[16]

In our study, we excluded patients with lung disease, liver disease, children, pregnant patient or others who are more prone to the adverse effect of the drug. We also explained the patient and the accompanying person about all probable side effects and asked them to note these and immediately contact or visit us or the nearest hospital without any delay.

Limitation in this study was, we dealt with the outdoor patients and observed them for two hours for any hemodynamic instability. Thus, we were unable to keep them under continuous monitoring. 4 patients could not be followed up since they did not show up in their second visit in the outdoor. Moreover, there might be inconsistent absorption of the drugs from the transdermal patch, which was not possible to measure, but might affect the expected outcome. Assessment of scoring system was also difficult since it needed patient's cooperation.

Conclusion

Based on the results and analysis of the present study, it can be concluded that transdermal buprenorphine patch of 10mg strength causes more relief of pain and improvement in quality of lifestyle in osteoarthritis knee patients of grade I and II with less requirement of rescue analgesia and comparable hemodynamic parameters or adverse effects to the buprenorphine patch of 5mg strength.

Declaration of patient consent: The authors certify that all appropriate patient consent forms have been obtained. In the form the patient(s) has/have given his/her/their consent for his/her/their clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity.

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