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A STUDY TO COMPARE ANALGESIC EFFECT OF BUPRENORPHINE PATCH AND ORAL TAPENTADOL IN KNEE OSTEOARTHRITIS RELATED CHRONIC PAIN

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ABSTRACT

Osteoarthritis is a common chronic degenerative condition of joints in adult population, commonly affecting the hip and knee joints. It is a common cause of pain and difficulty in walking and has heavy impact on day to day life style and represents an ever-increasing burden on health care. Osteoarthritis is a slowly evolving articular disease characterized by a gradual development of joint pain, stiffness, and loss of full range of motion.. The main goals in management of OA are pain control and improvement in joint function and health-related quality of life. The approaches recommended for the management of knee OA are surgical and non surgical. Pharmacological treatment includes administration of non-steroidal anti-inflammatory drugs (NSAIDS) oral or topical, glucosamine, chondroitinsulphate and opioids (oral or patches),etc. We carried out a study over 50 patients divided in two groups (25 each) over a period of 4 weeks to compare analgesic effects of Buprenorphine patch (group B) and Tab Tapentadol (group T) . Low-dose 7 days buprenorphine transdermal patch and tab. Tapentadol were good treatment modality in OA knee for management of symptomatic osteoarthritis knee. Both the two drug provided good pain relief and improvement in physical disability to the patients in terms of improvement in pain score, physical status, quality of life and patient satisfaction. However decrease in pain score and improvement in WOMAC Index was significant in all the two groups with slightly better results in group B.

KEYWORDS :

Osteoarthritis (OA), which is also known as osteoarthrosis or degenerative joint disease (DJD), is a progressive disorder of the joints caused by gradual loss of cartilage and resulting in the development of bony spurs and cysts at the margins of the joints. It is a common chronic degenerative condition of joints in adult population, commonly affecting the hip and knee joints. It is a common cause of pain and difficulty in walking and has heavy impact on day to day life style and represents an ever-increasing burden on health care. OA has a multi-factorial etiology and can be considered the product of an interplay between systemic and local factors Its incidence as well as prevelance is on the rise due to the aging of the population and the obesity epidemic. Between the ages of 30 and 65 years, the general incidence and prevalence of knee OA has been reported to increase by as much as 10 times that of younger age groups. [1,2,3]

The main goals in management of OA are pain control and improvement in joint function and health-related quality of life. The approaches recommended for the management of knee OA are surgical and non surgical. Non surgical management includes pharmacological modalities and non pharmacological therapy. Among non- pharmacological measures, weight reduction is one of the first and unproblematic measures that can be taken to reduce knee OA. [4,5]

Buprenorphine is a derivative of the opium alkaloid thebaine and belongs to the 6,14-endo-ethano-tetrahydro-oripavine class of compounds. It is a semi-synthetic, centrally acting opioid analgesic and its clinical efficacy is due to its activity at opioid receptor [partial agonist at μ-receptor and antagonist at the κ and δ –receptor]. It was first used clinically as parenteral analgesic in 1978, sublingually in 1981 and as a transdermal formulation in the late 1990s. Opioid buprenorphine patch is known to provide sustained analgesia and has been shown to be well tolerated and effective for treating moderate to severe pain in a wide range of acute and chronic pain states. OA is mainly a disease in elderly population, and buprenorphine has several potential therapeutic advantages in this age group over other opioids, nonsteroidal anti- inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) selective inhibitors. Respiratory depression is rare in patients receiving buprenorphine for pain relief. Binding to and dissociation from the receptor is low giving sustained analgesia and a low level of physical dependence it is less likely to cause adverse psycho-mimetic effects (e.g dysphoria and hallucinations). [6,7,8]

Tapentadol (3-dimethylamino-1-ethyl-2-2methyl-propyl phenol hydrochloride) is a novel drug that is agonist at mu-opoid receptor and inhibits the reuptake of noradrenaline. It has 50 times less affinity to mu opioid receptors than morphine but is only 2-3 times less potent as an analgesic. This suggests that noradrenaline re-uptake inhibiting property of tapentadol plays a significant role in its analgesic effect. The μ-opioid agonist activity of tapentadol may be more effective at controlling the nociceptive pain arising from cartilage degradation, while the noradrenaline reuptake inhibitor activity of tapentadol may be more effective for reestablishing descending inhibitory pain pathways. Tapentadol tablet may cause side effects such as nausea, vomiting, constipation, headache, drowsiness. [9,10]

Overall, the safety profile was superior to that of other NSAIDS and opiods in regards to incidence and severity of side effects. The reduction in incidence and severity of gastrointestinal side effects correlated with a higher compliance rate. Therfore Tapentadol is a viable alternative to conventional strong opioids for chronic pain management .

AIMS AND OBJECTIVES

To compare the efficacy of transdermal patch of buprenorphine and tablet tapentadol in relation to:

1. Pain relief
2. Quality of life improvemen
3. Side effects if any

MATERIAL AND METHODS

The present prospective, randomized single blind study was conducted in the Department of Anaesthesiology and Critical care, Pt. B. D. Sharma PGIMS, Rohtak. A total of 50 patients of either sex and between age (40 years and above) attending Pain Clinic were enrolled for study for a period of 28 days. However, all the patients were followed further.

Inclusion Criterias

Patients fulfilling any of the following criteria were included in the study.

1. History of pain in the knee/ knees
2. Consistent pain to hampering the routine activity and
3. X-rays finding suggestive of OA grade (1-11)

i. OA grade I=Doubtful narrowing of joint space, possible osteophyte development;

ii. OA grade II=Definitive osteophytes, absent or questionable narrowing of joint space;

Exclusion Factors

Patients with following conditions:

1. Patients with known hypersensitivity to either study drug
2. Patients with myasthenia gravis, delirium tremens
3. Pregnancy
4. Opioid dependence, narcotic withdrawal and conditions in which the respiratory centre and its function are severely impaired or may become so.
5. X-rays finding suggestive of OA grade (III-IV)Were not included in study.

Clinical Examination

All patients were subjected to detailed clinical history and examination in the pain clinic. The imaging studies (X-ray knee; weight bearing view, AP and lateral) were performed. History of hypertension, cardiovascular, renal or liver disease, if any was noted. Routine blood investigations as required were done. Informed and written consent will be obtained from all the patients after explaining the procedure in detail.

Numeric Rating Scale (NRS, 0-10; 0 for no pain and 10 for severe pain) for the assessment of pain was explained to each patient before starting the study.

Technique

After a written informed consent for participation in the study, the patients were randomly divided in 2 groups (B and T) of 25 each by using color coded envelope picked up by fellow colleague, who also will put the patch.

Group B (Buprenorphine group) = Buprenorphine patch (10µghr-1) was applied once a week for four weeks.

Group T (Tapentadol group) = Tapentadol 50 mg bd, patient received per day for 28 days

Method of patch application and administration of oral tapentadol
Rescue analgesia

The dose of an analgesic required for the relief of breakthrough pain is called rescue dose. Patient received tablet Paracetamol 500mg orally on his/her demand as rescue analgesia. The dose of paracetamol can be increased by the requirement of the patient throughout the study period (0.5g to 2g) but it did not exceed more than 2gday-1.

Observations:

1. Assessment of Pain (Pain Score):

Pain was assessed using numeric rating scale (NRS, 0-10). Patients were asked to sit on a chair, stand and walk before rating their pain. The NRS was measured and recorded at following time intervals.

1. Before start of the study
2. 1st,2nd and 4th week after start of study.

2. Assessment for quality of life:

The Western Ontario and McMaster Universities (WOMAC) index of osteoarthritis The WOMAC index was used to assess patient with osteoarthritis of knee using 24 parameters. It was used to determine the effectiveness of the treatment. The patient answerd a set of question by choosing the best answer that describes the response or improvement in pain, stiffness and physical function. After the patient finished the test, his points were added, that number was divided by number of parameters answered (maximum 24), and multiplied by 100 to get his/her percent disability. The WOMAC index was calculated before applying the patch, one week, two week, four weeks after starting the study on a four point scale.

3. Consumption of rescue analgesia:

At the end of study, total dose of rescue analgesia was noted.

4. Side effects:

(I) Tapentadol tablet may cause side effects such as nausea, vomiting, constipation, headache, drowsiness.

(ii) Buprenorphine patch may cause nausea, constipation and dizziness, skin irritation at the application site, predominantly due to the adhesives used or to the drug itself.

Side effects were noted and managed accordingly. Usually these side effects were mild and self-limiting.

5. Patient Satisfaction:

Patient satisfaction was assessed one week, two weeks, four weeks after starting the study on a four point scale:

1. Excellent: when the pain was completely resolved or diminished by 75% or more.
2. Good: when diminution of pain was by 50% to 74%.
3. Fair: when diminution of pain was by 25% to 49%.
4. Poor: when diminution of pain was less than 25% or there occurs an increase in pain.

Statistical Methods

Statistical testing was conducted with the statistical package for the social science system version SPSS 17.0. Continuous variables were presented as mean±SD or median if the data was unevenly distributed. Categorical variables were expressed as frequencies and percentages. The comparison of normally distributed continuous variables between the groups was performed using Student's t test. Nominal categorical data between the groups was compared using Chi-squared test or Fisher's exact test as appropriate. Continuous variables over time within the groups were analyzed using repeated measures analysis of variance (ANOVA). For all statistical tests, p value less than 0.05 will be taken to indicate a significant difference.

RESULTS AND OBSERVATIONS

Table 1. Pain score (Numerical rating score 0-10)

Pain Score (Numerical rating score 0-10)	Group B Mean ± SD	Group T Mean ± SD	P Value
Before the study	7.68 ± 0.95	7.76 ± 0.72	0.738
1 week after the study	5.20 ± 1.08	3.88 ± 1.13	<0.001
2 week after the study	3.88 ± 0.97	2.80 ± 0.76	<0.001
4 week after the study	2.76 ± 0.93	3.16 ± 2.27	0.418

Pain Score (Numeric Rating Scale)

Pain was assessed using Numeric Rating Scale (NRS, 0-10). Patients were asked to sit on a chair, stand and walk before rating their pain. NRS was measured and recorded at following time intervals: before the study, one week after the study, two weeks after the study and 4 weeks after the study.

In group-T, mean pain score (NRS score) before the study was 7.68 ± 0.95which decreased to 5.20 ± 1.08after one week. Pain Score was 3.88 ± 0.97, 2.76 ± 0.93, at two weeks, 4 weeks after the study, respectively. The variation in pain score at different time intervals when compared to pain score before the study was **clinically and statistically significant (p<0.01).**

In group-B, mean pain score (NRS score) before the study was 7.76 ± 0.72which decreased to 3.88 ± 1.13after one week. Pain Score was 2.80 ± 0.76, 3.16 ± 2.27, at two weeks, 4 weeks after the study, respectively. The variation in pain score at different time intervals when compared to pain score before the study **was clinically and**

statistically significant (p<0.01).

When pain scores were compared amongst the two groups they were clinically less in group B as compared to group T at all time intervals of the study period. However, they were statistically significant amongst the two groups at one week and two weeks study intervals only (p<0.001) with lesser NRS in group B as compared to group T.

Table-2: Total WOMAC Index

Total WOMAC Index	Group T	Group B	P Value
	Mean ± SD	Mean ± SD	
Before the study	59.66 ± 4.95	62.02 ± 3.54	0.058
1 week after the study	36.78 ± 2.95	32.62 ± 6.58	0.006
2 week after the study	27.28 ± 2.12	21.45 ± 7.52	0.001
4 weeks after the study	25.74 ± 2.58	23.69 ± 4.11	0.040

The Western Ontario McMaster Universities Index of Osteoarthritis (WOMAC)

The Western Ontario McMaster Universities Index of Osteoarthritis (WOMAC) (as detailed in appendices) was calculated before the study and one week, two weeks, 4 weeks after the study.

In group T mean WOMAC index before applying the patch was 59.66 ± 4.95which decreased to 36.78 ± 2.95, 27.28 ± 2.12, 25.74 ± 2.58, one week, two weeks and 4 weeks after the study. The variation in WOMAC index at different time intervals when compared to WOMAC index before the study was not clinically and **statistically significant(p<0.001).**

In group B, mean WOMAC index before applying the study was 62.02 ± 3.54 which decreased to 32.62 ± 6.58, 21.45 ± 7.52, 23.69 ± 4.11 at one week, two weeks and 4 weeks after applying the patch. The variation in WOMAC index at different time intervals when compared to WOMAC index before the study was clinically and **statistically significant(p<0.001).**

When WOMAC index was compared amongst the two groups, it was **statistically significant** at all time intervals (1st week, 2nd week and 4th week) throughout the study period (p<0.05). The WOMAC index was better in group B than group T at all time intervals throughout the study period.

Table-3: Procedural complications

Procedural complications	Group T		Group B		P Value
	Frequency	%	Frequency	%	
Nil	25	100.0%	25	100.0%	-
Total	25	100%	25	100%	

The table and chart above shows the comparison of distribution of patients according to procedural complications between the two groups. It was observed that there were nil complications in the patients in both the groups.

Table-4: Side effects

Side effects	Group T		Group B		P Value
	Frequency	%	Frequency	%	
Nil	19	76.0%	18	72.0%	0.372
Nausea	4	16.0%	2	8.0%	
Vomiting	2	8.0%	5	20.0%	
Total	25	100%	25	100%	

The table and chart above shows the comparison of distribution of patients according to side effects between the two groups. It was observed that under the group T, 76% of the patients had no side effects while 16% patients had nausea and 8% had vomiting. Under the group B, 72% of the patients had no side effects while 8% patients had nausea and 20% had vomiting.

Further, it was observed that there was no significant difference in distribution of the patients according to side effects between the two groups (p value = 0.372).

Table-5: Patients satisfaction

Patients satisfaction		Group T		Group B		P Value
		Frequency	%	Frequency	%	
1 week after the study	Excellent	0	0.0%	6	24.0%	0.008
	Good	2	8.0%	6	24.0%	
	Fair	21	84.0%	13	52.0%	
	Poor	2	8.0%	0	0.0%	
	Total	25	100%	25	100%	
2 week after the study	Excellent	1	4.0%	9	36.0%	0.009
	Fair	0	0.0%	1	4.0%	
	Good	24	96.0%	15	60.0%	
	Total	25	100%	25	100%	
4 week after the study	Excellent	13	52.0%	13	52.0%	0.480
	Fair	1	4.0%	3	12.0%	
	Good	11	44.0%	8	32.0%	
	Poor	0	0.0%	1	4.0%	
	Total	25	100%	25	100%	

Patient Satisfaction

Patient satisfaction was assessed on a four point scale:

1. Excellent: when the pain was completely resolved or diminished by 75% or more.
2. Good: when diminution of pain was by 50% to 74%.
3. Fair: when diminution of pain was by 25% to 49%.
4. Poor: when diminution of pain was less than 25% or there was an increase in pain.

The results show clinically better patient satisfaction in group B as compared to group T, however it was statistically significant at one and two week time intervals of the study period.

Results obtained were **statically comparable** in both groups B and group T regarding Pain score (NRS), Change in pain score, Change in total pain score, Change in average pain score, WOMAC index, Total WOMAC score, WOMAC average, Stiffness subscale average of WOMAC, Stiffness subscale score of WOMAC, Physical activity subscale Total score WOMAC, Physical activity subscale average WOMAC, Patient satisfaction were **statically comparable** in both groups. But results were clinically better in group B as compare to group T.

The side effects noted were minimal in both groups B and group D and easily manageable **statically comparable** in both groups B and group D.

DISCUSSION

Pain Score (NRS score)

Both the drugs i.e. low-dose 7 days buprenorphine transdermal patch and tab tapentadol were effective and provided good pain relief to the patients with symptomatic osteoarthritis knee.

In present study group-T, mean pain score (NRS score) before applying the patch was 7.68 ± 0.95 which decreased to 2.76 ± 0.93, 4 weeks after applying the patch, respectively. In group-B, mean pain score (NRS score) before applying the patch was 7.76 ± 0.72 which decreased to 3.16 ± 2.27 at 4 weeks after the study, respectively. There was a statistically and clinically significant improvement in pain score after applying the patch and taking tablets in all the two groups at all time intervals during the study period.

When pain scores were compared amongst the two groups they were clinically less in group B as compared to group T at all time intervals of the study period. However, they were **statistically significant** amongst the two groups at one week and two weeks study intervals only (p<0.05) with lesser NRS in group B as compared to group T.

In study by Karlsson and Berggren (2009)[6] comparison of pain score (Numeric Rating Scale, NRS:0-10) from baseline to end of study was 6.16 ± 1.35 to 3.92 ± 2.07

In study by Breivik et al (2010) [11] comparison of pain score (Numeric Rating Scale, NRS:0-10) from baseline to end of study was 4.70 ± 1.50 to 3.60 ± 1.70.

In study by James and O'Brien (2010) [12] comparison of pain score (Numeric Rating Scale, NRS:0-10) from baseline to end of study was 6.30 ± 1.50 to 3.30 ± 2.00 Pain scores of present study are comparable to Karlsson and Berggren[6] (2009) Breivik et al[11](2010), James and O' Brien[12](2010) and Robert et al.

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

The two drugs i.e. low-dose 7 days of buprenorphine patch and tab tapentadol were effective as shown by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and resulted in improved quality of life of patients.

In present study; in group T mean WOMAC index before applying the patch was 59.66 ± 4.95 which decreased to 25.74 ± 2.58 , 4 weeks after the study. The variation in WOMAC index at different time intervals when compared to WOMAC index before the study was clinically and **statistically significant(p<0.001).** In group B, mean WOMAC index before applying the study was 62.02 ± 3.54 which decreased to 23.69 ± 4.11 at 4 weeks after applying the patch. The variation in WOMAC index at different time intervals when compared to WOMAC index before the study was clinically and **statistically significant(p<0.001).**

When WOMAC index was compared amongst the two groups, it was **statistically significant** at all time intervals (1st week, 2nd week and 4th week) throughout the study period (p<0.05). The WOMAC index was better in group B than group T at all time intervals throughout the study period.

In study done by Breivik[12] et al (2010), total WOMAC index reduced from 51.8 ±12.3 to 37.5 ±15.9

In study done by James and O' Brien[12] , WOMAC index reduced from 54.9 ±12.8 at the start of study to 37.4 (16.2) at the end of study i.e. 28 days.

Therefore the results were comparable and slightly better in present study. This might be possible because of the fact their large sample size and it included patients with both, low grade as well as high grade OA.

Rescue analgesia

In group T, out of 25 patients 19 (76%) had taken rescue medications for two weeks while 6 (24%) did not take medications and in group B, 14 patients(56%) had taken rescue medications for two weeks while 11 patients (44%) did not take medications.

The two groups were comparable and there was no statistically significant difference (p>0.136).

Patient safety

In present study the other common side effects observed in were nausea, vomiting, constipation and headache. These side effects were minor and easily treated with oral antacid. None of the patients had severe nausea and vomiting. No procedural complications were observed in any of the patient in the two groups.

In group B, 3 patients (12%) complained nausea and 2 patients (8%) complained vomiting; rest 20 had no complains .

In group T 3 patients (12%) complained nausea and 3 patients (12%) complained vomiting, remaining 19 had no complains. Side effects were comparable in both groups and **statically not significant (p>0.05).**

These side effects were managed by cap omeprazole 20 mg od for 7 days, patients responded well to the treatment .

Patient satisfaction

In present study , patient satisfaction was assessed at 1 week , 2 week and 4 weeks after the start of study . When patient satisfaction was compared amongst the two groups, it was clinically and statistically significant at one week and two week after the study. The results show clinically better patient satisfaction in group B as compared to group T, however it was statistically significant at one and two week time intervals of the study period.

As result shows that patient satisfaction slightly better in group B as compare to group T. Although the reduction of pain score from baseline was comparable in both the groups but since buprenorphine patch was applied once a week; therefore better patient satisfaction can be attributed to better compliance in group B . For this reason most of the patient favor buprenorphine patch. Also incidence of nausea and vomiting was higher in group T (24 %) as compared to group B (20 %).

While long-term outcomes of these drug focus on requirement for surgery, return to work and financial considerations; short-term outcomes focus on patient relief, numerical pain score, stiffness and physical function. The short-term measures in our study were pain score and WOMAC Index. The decrease in pain score and improvement in WOMAC Index was significant in all the two groups with slightly better results in group B.

Low-dose 7 days buprenorphine transdermal patch and tab. Tapentadol were good treatment modality in OA knee for management of symptomatic osteoarthritis knee. Both the two drug provide good pain relief and improvement in physical disability to the patients in terms of improvement in pain score, physical status, quality of life and patient satisfaction.

SUMMARY AND CONCLUSIONS

We summarize that:

1. The dose 7 days buprenorphine transdermal patch and daily basis tab tapentadol 50 mg bd were effective and provided good pain relief and improved quality of life in the patients with symptomatic grade 1 and 2 osteoarthritis knee.
2. Majority of the patients in the two groups were in 40-65 years age group, mean age was around 51.28 kg and 60% of them were females. This could be attributed to the social milieu of our region also to the fact that incidence of OA increases with increasing age. The females are regularly engaged in domestic work, agricultural work, animal husbandry and labour activities, which involve squatting, sitting on floor and climbing stairs. There was a statistically and clinically significant improvement in pain score (NRS) after using drugs in both the two groups at all time intervals during the study period. When pain scores were compared amongst the two groups they were clinically less in group B as compared to group T at all time intervals of the study period. However, they were statistically significant amongst the two groups at one week and two weeks study intervals only (p<0.05). Both the drugs, after applying drug patches were effective in improving health status of patients as shown by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), WOMAC index was significantly lower in group B as compared to group T at all time intervals throughout the study period. Nocturnal pain, rest pain, morning stiffness and stiffness later in the day were significantly reduced after using both the drugs.
3. After using drugs, clinically better patient satisfaction was observed in group B as compared to group T however it was statistically significant at one week and two weeks time intervals of the study period.

4. No procedural complications were observed in any of the patient in the two groups.
5. Other side effects observed in our study were nausea, vomiting, constipation and headache which were minor and easily treated with cap omeprazole 20 mg for 7 days.

To conclude, low-dose 7 days buprenorphine transdermal patch and tab tapentadol were effective treatment modality for management of symptomatic osteoarthritis knee (grade 1 and 2). As compared to tab tapentadol, low dose buprenorphine patch modality provides better pain relief and improvement in physical disability to the patients in terms of improvement in pain score, quality of life and patient satisfaction with very few and easily manageable side effects.

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