A Study to Evaluate and Compare the Analgesic Efficacy of Transdermal Patch of Buprenorphine and Diclofenac in Osteoarthritis Knee

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ABSTRACT

Introduction: We studied the effects of transdermal patch of Buprenorphine and Diclofenac in patients of osteoarthritis(OA) knee.

Material and methods: The present prospective, randomized single blind study conducted in the Dept. of Anaesthesiology PGIMS, Rohtak. A total of 50 patients of either sex and age (40years and above) enrolled for 1 month.Ethical clearance taken prior to study. Written informed consent taken for study. Patients randomly divided in 2 groups (B and D) of 25 each. Group B: Buprenorphine patch, received per week 10μg^{-hr}Group D: Diclofenac sodium patch, received per day 200 mg Diclofenac. Patch applied on dry, non-hairy of skin after cleaning the skin with spirit swab. The replacement patch applied to a different area of skin.Buprenorphine patch replaced once a week and Diclofenac patch replaced on daily basis. Paracetamol 500mg orally as a rescue analgesia**.**

Results: Results obtained were statically comparable in both groups B and group D regarding Pain score (NRS), WOMAC index, Stiffness subscale score of WOMAC. Patient satisfaction were statistcally comparable in both groups. Results were clinically better in group D as compare to group B. 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.

Conclusion: This randomised,blind controlled study suggests that the Diclofenac and Buprenorphine patch is an effective and safe treatment modality for symptomatic OA of the knee and were well tolerated.This method is convenient and easy to use with no procedural complications. Diclofenac is slightly better tolerable and has better pain relief as compared to Buprenorphine.

Keywords: Buprenorphine, Diclofenac, Transdermal Patch, OA Knee

INTRODUCTION

Osteoarthritis (OA) is the most common chronic degenerative condition of joints especially in aging population. Over the age of 30, up to 6% of adults are symptomatic of knee arthritis and around 3% are symptomatic of hip arthritis. It is a common cause of difficulty in walking and has heavy impact on daily activity and day to day life style. The pain is main symptom that bring the patient to the doctors. Many people with pathological and radiological evidence of OA have no symptoms.[1]

The main goals in management of OA are pain control and improvement in joint function and health-related quality of life. Non surgical management includes pharmacological modalities and non pharmacological therapy. Non pharmacological treatment includes self management programs, strengthening exercises, modification in physical activity, weight loss and assistive devices etc. Pharmacological treatment includes administration of non-steroidal anti-inflammatory drugs (NSAIDS), opioids (oral or patches).[2]

Buprenorphine is a opium alkaloid thebaine and belongs to the 6,14-endo-ethano-tetrahydro-oripavine. Semi-synthetic, centrally acting opioid. Partial agonist: μ-receptor and antagonist: κ and δ –receptor. Plasma conc. after administration of transdermal buprenorphine 20μg^{-hr} reaches plateau ~300pg/ml at 48 hours and maintaining concentration until the patch is removed at 168 hours. After removal patch plasma conc. reduced by ~50% in first 12 hours.

Diclofenac sodium is an aryl-acetic acid derivative. It is an analgesic antipyretic-anti-inflammatory drug. It inhibits prostaglandin synthesis and is somewhat COX-2 selective inhibitor. It is well Buprenorphine is a opium alkaloid thebaine and belongs to the 6,14-endo-ethano-tetrahydro-oripavine. Semi-synthetic, centrally acting opioid. Partial agonist: μ-receptor and antagonist: κ and δ –receptor. Plasma conc. after administration of transdermal buprenorphine 20μg^{-hr} reaches plateau ~300pg/ml at 48 hours and maintaining concentration until the patch is removed at 168 hours. After removal patch plasma conc. reduced by ~50% in first 12 hours. The plasma half life ($t^{1/2}$) is ~2 hours.

We aimed to assess and compare the efficacy of transdermal patches of Buprenorphine and Diclofenac in relation to pain relief.

MATERIAL AND METHODS

A total of 50 patients of either sex and age (40years and above) attending the pain clinic were enrolled for the study.

Inclusion Criteria

Patients with history of pain in the knee, consistent pain to hampering the routine activity and X-rays finding suggestive of OA grade I&II.

1. OA grade I=Doubtful narrowing of joint space, possible osteophyte development;
2. OA grade II=Definitive osteophytes, absent or questionable narrowing of joint space;

These patients randomly divided in 2 groups (B and D) of 25 each by using color coded envelope picked up by fellow colleague,

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who also applied the study drug patch.Group B[Buprenorphine group] the patient received buprenorphine transdermal patch 10μg^{-hr} Per week. GroupD[Diclofenac sodium patch] the patient received Diclofenac sodium patch 200mg per day.

Exclusion Factor

Patients with known hypersensitivity to either drugs myasthenia gravis, delirium tremens, pregnancy, opioid dependence, narcotic withdrawal and conditions in which the respiratory centre and its function are severely impaired or may become so, OA grade III and IV on radiological image. X-rays finding suggestive of OA grade (III-IV).

OA grade III= Moderate osteophytes, definite narrowing, some sclerosis, possible joint deformity

OA grade IV=Large osteophytes, marked narrowing, severe sclerosis, definitive joint deformity.

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 ruled out. Routine blood investigations as required were collected. Informed and written consent was obtained from all the patients after explaining the procedure and numeric rating scale (NRS, 0-10; 0 for no pain and 10 for severe pain) for the assessment of pain.

Method of patch application

The patch was applied on a dry, non-irritated, non-hairy area of skin on patient's upper body (such as chest, upper back, or the outside of arms), after cleaning the skin with spirit swab The replacement patch was applied to a different area of skin on patient's upper body. Re-use of same area of skin where the previous patch was avoided for at least three weeks. Buprenorphine patch was replaced once a week, on the same day of the week. In case of Diclofenac patch, it was replaced on daily basis.

Rescue analgesia

The dose of an analgesic required for the relief of breakthrough pain is called rescue dose. Patient received tablet Paracetamol 500mg orally as rescue analgesia.

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 after applying the patch Table 1.

1. Before applying the patch.
2. At one week after applying patch.
3. At two weeks and 4 weeks after applying patch.

2. Assessment for quality of life

The Western Ontario and McMaster Universities (WOMAC) index of osteoarthritis was used to assess patient with osteoarthritis of knee using 24 parameters. It was used to determine the effectiveness of the treatment. The patient answered a set of question by choosing the best answer that describes the response or improvement in pain, stiffness and physical function. After the test, points were added, that number was divided by number of parameters answered (maximum 24), and multiplied by 100 to get his percent disability. The WOMAC index was calculated before applying the patch, one week, two week,4 weeks after applying the patch on a four point scale[3] Table 2.

3. Consumption of rescue analgesia

At the end of study, total dosage of rescue analgesia was noted (500 mg).

4. Side effects

(I) Diclofenac patch may cause side effects such as dryness, redness, itching, swelling, irritation or numbness at application site.[4]

(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.[5]

The side effects was noted and managed accordingly.

5. Patient Satisfaction

Patient satisfaction was assessed at one week, two weeks, after 4 week applying the patch on a four point scale: Table 3,4.

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.

At the end of the study, the data thus obtained was compiled and

Pain Score	Group B (n=25)		Group D (n=25)		p value
	Mean ± SD	Min - Max	Mean ± SD	Min - Max	
Before Applying the patch	6.84 ± 0.55	6 - 8	6.44 ± 1.08	5 - 9	0.217
1 week after Applying the patch	5.32 ± 0.95	3 - 6	3.40 ± 1.47	0 - 6	<0.001
2 weeks after Applying the patch	4.40 ± 0.82	2 - 5	2.44 ± 1.29	0 - 5	<0.001
4 weeks after Appling the patch	3.72 ± 2.09	1 - 3	3.28 ± 0.84	1 - 5	0.334

Table-1: Pain Score (Numeric Rating Scale) in the Two Groups at Different Time Intervals

Total WOMAC Index	Group B (n=25)		Group D (n=25)		p value
	Mean ± SD	Min - Max	Mean ± SD	Min - Max	
Before Applying the patch	58.47 ± 3.38	53.10 - 67.00	59.14 ± 3.17	56.30 - 67.70	0.106
1 week after Applying the patch	35.86 ± 2.91	31.50 - 41.30	29.59 ± 5.24	21.60 - 40.60	<0.001
2 weeks after Applying the patch	27.65 ± 1.85	23.90 - 30.40	19.81 ± 6.41	8.00 - 29.50	<0.001
4 weeks after Applying the patch	26.16 ± 2.11	21.70 - 29.30	25.21 ± 3.67	18.40 - 36.40	0.270

Table-2: WOMAC Index at Different Time Intervals in the Two Groups

Total Stiffness score	Group B (n=25)		Group D (n=25)		p value
	Mean ± SD	Min - Max	Mean ± SD	Min - Max	
Before Applying the patch	5.88 ± 0.44	4 – 6	6.16 ± 0.82	5 - 8	0.112
1 week after Applying the patch	3.92 ± 0.28	3 – 4	3.36 ± 0.81	2 - 4	0.002
2 weeks after Applying the patch	2.04 ± 0.46	1 – 3	2.00 ± 0.29	1 - 3	0.712
4 weeks after Applying the patch	2.00 ± 0.50	1 – 4	2.96 ± 1.24	1 - 6	0.001

Table-3: Stiffness Subscale Score of WOMAC at Different Time Intervals in the Two Groups

Patients satisfaction	Group B (n=25)		Group D (n=25)		p value
	Frequency	%	Frequency	%	
1 Weeks after Applying the patch					
Excellent	0	0.0%	12	48.0%	-
Fair	21	84.0%	5	20.0%	0.185
Good	3	12.0%	7	28.0%	0.153
Poor	1	4.0%	1	4.0%	1.000
2 Weeks after Applying the patch					
Excellent	2	8.0%	15	60.0%	<0.001
Fair	1	4.0%	1	4.0%	1.000
Good	1	4.0%	0	0.0%	1.000
Poor	21	84.0%	9	36.0%	<0.001
4 Weeks after Applying the patch					
Excellent	6	24.0%	4	16.0%	0.480
Fair	3	12.0%	2	8.0%	1.000
Good	15	60.0%	18	72.0%	0.371
Poor	1	4.0%	1	4.0%	1.000

Table-4: Patients satisfaction at Different Time Intervals in the Two Groups

analysed statistically using:

- Unpaired t-test for quantitative data.
- Chi-square test / Fisher's exact test for qualitative data.

The value of $p< 0.05$ was considered as statistically significant, $p< 0.01$ as highly significant and $p< 0.001$ as very highly significant for statistical analysis.

Observations

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.

RESULTS

Results obtained were **statically comparable** in both groups B and group D regarding patient profile like age, sex and weight distribution.

Results obtained were **statically comparable** in both groups B and group D regarding Pain score (NRS), Change in pain score, Change in total pain score, Change in average pain score, WOMAC index, 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 D as compare to group B.

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

In our study mean age of group B and Group D was 52 yrs (±8.47) and 49.96 yrs (±7.88) respectively. 60% of the patients in our study were male and 40 % were female patients.

In our study group-B, mean pain score (NRS score) before applying the patch was 6.84 ± 0.55 which decreased to 5.32± 0.95 after one week. Pain Score was 4.40 ± 0.82, 3.72 ± 2.09, at two weeks, 4 weeks after applying the patch, respectively. In group-D, mean pain score (NRS score) before applying the patch was 6.44 ± 1.08 which decreased to 3.40 ± 1.47 after one week applying the patch. Pain Score was 2.44 ± 1.29, 3.28 ± 0.84 at two weeks, 4 weeks after applying the patch, respectively. There was a statistically and clinically significant improvement in pain score after applying the patch 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 D as compared to group B 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 D as compared to group B. Our result was comparable to studies done by Karlsson and Berggren[6] (2009) Breivik et al[7] (2010) and James and O' Brien[8] (2010).

Mean WOMAC index of Group B, before applying the patch was 58.47 ± 3.38 which decreased to 35.86 ±2.91, 27.65 ± 1.85, 26.16± 2.11, 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 applying the patch was clinically and statistically significant ($p<0.001$).

Mean WOMAC index of Group D, before applying the patch was 59.14 ± 3.17 which decreased to 29.59 ±5.24, 19.81 ± 6.41,

25.21± 3.67, 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 applying the patch was clinically and statistically significant (p<0.001). When WOMAC index was compared amongst the two groups in of present study, in was statistically significant at all time intervals throughout the study period (p<0.05), except at 4 weeks. The WOMAC index was better in group D than group B at all time intervals throughout the study period. Present study compare to Breivik[7] (2010) both result 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.[7] Our result were comparable to studies done by Breivik (2010) but it were slightly better in our study. This might be possible because of the fact Breivik included patients with both, low grade as well as high grade OA.[7]

In group B, mean WOMAC score before applying the patch was 53.60 ± 2.94 which decreased to 32.88 ±2.85, 25.36 ± 1.98, 23.96± 2.19,one week, two weeks and 4 weeks after applying the patch. The variation in WOMAC score at different time intervals when compared to WOMAC score before applying the patch was clinically and statistically significant (p<0.001). In group D, mean WOMAC score before applying the patch was 54.64 ± 3.67 which decreased to 26.48 ±5.32, 17.80 ± 6.12, 22.56± 3.73,one week, two weeks and 4 weeks after applying the patch. The variation in WOMAC score at different time intervals when compared to WOMAC score before applying the patch was clinically and statistically significant (p<0.001). Our results were comparable to studies done by Breivik.

In group B, mean Stiffness Subscale Score of WOMAC before applying the patch was 5.88 ± 0.44 which decreased to 3.92 ±0.28, 2.04 ± 0.46, 2.00± 0.50,one week, two weeks and 4 weeks after applying the patch. The variation in Stiffness Subscale Score of WOMAC at different time intervals when compared to Stiffness Subscale Score of WOMAC before applying the patch was clinically and statistically significant (p<0.001). In group D, mean Stiffness Subscale Score of WOMAC before applying the patch was 6.16 ± 0.82 which decreased to 3.36 ±0.81, 2.00 ± 0.29, 2.96± 1.24, one week, two weeks and 4 weeks after applying the patch. The variation in Stiffness Subscale Score of WOMAC at different time intervals when compared to Stiffness Subscale Score of WOMAC before applying the patch was clinically and statistically significant (p<0.001). Our results were comparable to studies done by Breivik.

In group B, mean Physical Activity Subscale Score of WOMAC before applying the patch was 35.72 ± 2.54 which decreased to 21.76 ± 2.37, 17.32 ± 1.44 and 16.52 ± 1.69 one week, two weeks and 4 weeks after applying the patch respectively. The variation in Physical Activity Subscale Score of WOMAC at different time intervals when compared to score before applying the patch was clinically and statistically significant (p<0.001). In group D, mean Physical Activity Subscale Score of WOMAC before applying the patch was 35.80 ± 3.11 which decreased to 16.88 ± 4.41, 11.52 ± 4.59 and 14.76 ± 2.68 one week, two weeks and 4 weeks after applying the patch respectively. The variation in Physical Activity Subscale Score of WOMAC at different time intervals when compared to score before applying the patch was clinically and statistically significant (p<0.001). Our results were comparable to studies done by Breivik.

One week after applying the patch 12 in group D had excellent satisfaction; and 3 patients in group B, 7 patients in group D good satisfaction. When patient satisfaction was compared amongst the three groups, it was clinically and statistically comparable (p=<0.01). However, patient satisfaction was clinically better in group D. 21 patients in group B and 5 patients in group D had fair satisfaction. 1 patient in group B, 1 patient in group D had poor satisfaction.

Two weeks after applying patch 2 patients in group B, 15 patients in group D had excellent satisfaction; and 1patients in group B, reported good satisfaction. 1 patient in group B and 1patients in group D had fair satisfaction. 21patients in group B, 9patients in group D had poor satisfaction. When patient satisfaction was compared amongst the two groups, it was clinically and statistically comparable (p=0.01). 4 weeks after applying patch 6 patients in group B, 4 patients in group D had excellent satisfaction; and 15 patients in group B, 18 patients in group D reported good satisfaction. 3 patients in group B and 2 patients in group D had fair satisfaction. 1 patient in group B, 1 patient in group D had poor satisfaction. When patient satisfaction was compared amongst the two groups, it was clinically and statistically comparable (p=0.831).

The results show clinically better patient satisfaction in group D as compared to group B, 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 D as compare to group B But We observed clinically better patient satisfaction in group B as compared to group D because in group B patch was replace once a week as compare to group D patch was replace daily basis. For this reason most of the patient favor buprenorphine patch. No procedural complications were observed in any of the patient in the two groups. Only mild skin rashes develop that was managed easily in some patients. In studies done by Breivik[7], James and O' Brien[8], Karlsson and Berggren common side effects observed were nausea, vomiting, constipation and headache. In our study these side effects were minor and easily treated with oral antacid and there was no need of rescue analgesia.[9,10]

Conclusion:

After studying various factors we concluded that low-dose 7 days Buprenorphine transdermal patch and Diclofenac transdermal patch were effective treatment modality for management of symptomatic osteoarthritis knee. The drug patch modality provides good pain relief and improvement in physical disability to the patients in terms of improvement in pain score, quality of life and patient satisfaction. So we conclude that Transdermal Buprenorphin and Diclofenac are better alternative in symptomatic grade I and II OA knee.

REFERENCES

1. Felson DT, Lawrence RC, Dieppe PA. Osteoarthritis: new insights—part 1: the disease and its risk factors. Ann Intern Med. 2000;133:635-46.
2. Lawrence JS, Bremner JM, Bier F. Osteo-arthrosis: Prevalence in the population and relation between symptom and X-ray changes. Ann Rheum Dis.1996;25:1-24
3. Hawker GA, Mian S, Kendzerska T, French M. Measure of adult pain. Arthritis Care Res. 2011;63:240-52.
4. Pelletier JP, Yaron M, Haraoui B, Cohen P, Nahir MA,

Choquette D, et al. Efficacy and safety of diacerein in osteoarthritis of knee. Arthritis Rheum. 2000;43:2339-48.
5. Banning M.Topical diclofenac: clinical effectiveness and current uses in osteoarthritis of the knee and soft tissue injuries. Expert Opin Pharmacother. 2008;9:2921.
6. Karlsson M, Berggren AC. Efficacy and safety of low dose buprenorphine patch versus prolonged released tramadol tablets. Clin Ther. 2009;31:503-13.
7. Breivik Harald, Ljossa MT, Persson J. A randomized, placebo-controlled evaluation of efficacy and tolerability of low dose 7-day buprenorphine transdermal patch osteoarthritis patients. Scandinavian Journal of Pain. 2010; 1:122-41.
8. James IG.V, O'Brien CM, McDonald CJ. A randomized double blind, double dummy comparision of the efficacy and tolerability of low dose transdermal and sublingual buprenorphine in patient with OA knee. J Pain Symptom Manage. Aug 2010;40:266-78.
9. Conghan PG, O'Brien CM, Wilson M, Schofield JP. Transdermal buprenorphine plus oral paracetamol vs an oral codeine-paracetamol combination for osteoarthritis of hip and/or knee: A randomized trial. Osteoarthritis Cart. 2011;19:930-8.
10. Schutter U, Ritzorf R, Hecker B. Chronic osteoarthritis pain: Efficacy and safety of a 7-day patch with low dose buprenorphine. MMW Fortschr Med. 2008;150:96-103.

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