Original Article • Journal of Southeast Asian Orthopaedics Vol 48 No 1 (2024) 8-14

Journal of Southeast Asian Orthopaedics
ISSN 2821-9848 (Print)
ISSN 2821-9864 (Online)
https://doi.org/10.56929/jseaortho-2024-0192 https://jseaortho.org

Effect of Transdermal Microneedle Patch Plus Nonsteroidal Anti-Inflammatory Drug in Knee Osteoarthritis: A Randomized, Double-Blind Study

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Purpose: No recent clinical study has shown the efficacy of transdermal microneedle patch (TDM) plus nonsteroidal antiinflammatory drug (NSAID) in early knee osteoarthritis (OA). This study aimed to determine the effect of TDM plus NSAID on synovial hypertrophy, knee pain, and the Western Ontario and McMaster Universities Arthritis Index (WOMAC) score in osteoarthritic knees.

Methods: A randomized, controlled, double-blind trial was conducted. One hundred participants, aged 40–70 years, with painful knee OA and radiographic nonstructural changes were randomly assigned into two groups to undergo TDM plus NSAID (ketorolac 30 mg) or TDM (placebo) at the medial joint line of the knee twice (once weekly). The synovial thickness was measured using ultrasonography at pretreatment, weeks 1, 2, and 4. The visual analog scale (VAS) for pain, WOMAC score, and adverse events (AEs) were also recorded.

Results: The TDM plus NSAID group demonstrated a significant reduction in synovial thickness and VAS at weeks 2 and 4 compared with the placebo group ($P<0.05$). At week 4, the mean synovial thickness reduction was 1.1 and 0.3 mm, and the mean VAS reduction was 3.2 and 1.7 for the TDM plus NSAID and placebo groups, respectively. The mean WOMAC scores at week 4 were significantly reduced (5.7 and 0.9 for the TDM plus NSAID and placebo groups, respectively). No complication and treatment-related AEs occurred.

Conclusions: TDM plus NSAID significantly reduced synovitis and improved the pain score in knee OA after 2 weeks. The WOMAC score improved at week 4 without any AEs.

Thai Clinical Trials Registry (TCTR), TCTR identification number is TCTR20200613001.

Keywords: microneedle patch, knee osteoarthritis, synovitis, transdermal patch, NSAID

Article history:
Received: June 26, 2023 Revised: December 4, 2023
Accepted: January 7, 2024
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Osteoarthritis (OA) is a common chronic joint disease that causes joint pain and disability. OA has recently been described as a whole-joint disease involving articular cartilage degradation, subchondral bone thickening, ligament degeneration, joint capsule hypertrophy, and synovial inflammation[1].

In early-stage knee OA, pain is the most prominent symptom. Nonsteroidal antiinflamma-

tory drugs (NSAIDs) keep on the mainstay of pharmacological management. Their use is strongly recommended along with the standard guidelines to control pain and inflammation[2]. Ketolorac is one of the NSAIDs that can be given through intraarticular, -muscular, and -venous injections as well as transdermal routes[3,4].

Transdermal microneedle patch (TDM) is a noninvasive choice of drug administration. It gives a more stable drug plasma concentration than oral and sublingual routes.[5] Regarding the mechanism of action, TDM pierces the stratum corneum, usually reaching a depth of 50–900 μm below the skin surface. A substantial benefit of this approach is its penetration range does not reach blood vessels or nerve fibers within the skin. Hence, it is painless, does not cause bleeding, and is unlikely to allow communicable disease transmission. Another key benefit of using TDM compared to the oral route is its ability to bypass the gastrointestinal tract and, thus, eliminate the first-pass metabolism. In addition, TDM is easy to terminate if complications occur. The systemic efficacy of TDM has been proven and used for many purposes, such as vaccination and hormonal therapy. Local controlled TDM is also used for cosmetic purposes[5,6].

Kellgren and Lawrence have provided a guide to radiographic imaging and grading for clinical diagnosis and treatment monitoring of OA. However, radiographic evidence of OA is a potential late sign indicating irreversible joint damage has already occurred[7]. Ultrasonography can detect synovial hypertrophy, the pathological hallmark of early-stage knee OA. Ultrasonography has been widely studied in synovitis monitoring, although the reliability of ultrasonography is operator-dependent. In a previous study, Termtanun et al.[8] found that the more advanced the knee OA stage, the higher the synovial hypertrophy prevalence. As the disease progresses, the knee structure decays, and the symptoms worsen. Synovial thickness was observed with moderate to good interobserver reliability. The overall prevalence of synovial thickness with a 2 mm cut-off value correlated well with the Kellgren-Lawrence (KL) classification. The prevalence of synovial hypertrophy with a 2 mm cut-off value, correlated with KL grade 2, was 70.8% and was statistically significant. In this study, the cut-off value in early knee OA (<2 mm) was the considerable thickness of synovial hypertrophy, relieving synovitis after treatment.

This study aimed to compare the differences in pain relief, satisfaction, and synovial thickness between patients with knee OA receiving a TDM plus ketorolac and those receiving a placebo.

METHODS

This study was approved by the participants and hospital ethics committee (RTA IRB No. R220h/62). All participants provided informed consent. The study design was a double-blind, blocked, randomized controlled trial (RCT). A nurse randomly assigned medication envelopes to patients. Sequentially numbered sealed opaque envelopes were used to ensure allocation concealment. Patients aged 40–70 years with primary knee OA KL classification grade I–II were randomized into two groups. Group 1 included 50 participants receiving TDM plus ketorolac, and group 2 comprised 50 participants receiving TDM without medication (placebo group). Patients had to be able to identify a predominantly painful (index) knee, defined as a score of 4 on the Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire. Participants with inflammatory and septic arthritis, skin infection, liver and renal insufficiencies, and who underwent intraarticular hyaluronic acid and steroid injections within 6 and 3 months, respectively, were excluded from the study. Baseline radiography on the affected knee was done in standing AP and lateral views.

[Blinded for review] designed solid microneedles using the following parameters: needle height of 600 μm, fabricated in 15 × 15 needle arrays, and individually shaped as half-pyramids for ease of fabrication (Fig. 1). They were approved by the related government authority through a biological evaluation for medical devices.

The patients were arranged in a supine position on the examination table, with the knee flexed but relaxed at 90 degrees (Fig. 2). All patients were applied TDM patch at the midpoint between

the inferior pole patella and tibial tubercle, shifted to the medial about two fingerbreadths at the joint line level. Solid microneedles were applied with an insertion force of about 10 Newton until skin imprints occurred (Fig. 1). Ketorolac 30 mg/ml was dripped onto the pad and covered the imprint. The TDM patch was peeled off after 6 h and reapplied at 1-week intervals.

The patients were followed up at weeks 1, 2, and 4 and completed the VAS, modified WOMAC (Thai version), and ultrasonography to measure synovial thickness in every appointment.

The synovial thickness was measured using ultrasound (GE Healthcare model LOGIQ® e), with midline scanning technique, preset: musculoskeletal-knee in B-mode, and a 12L-RS wide band linear probe (12 MHz). The patients were set in a supine position on the examination table, with the knee kept flexed but relaxed at 30 degrees (Fig. 3). The midline scanning technique was done by vertically applying the linear probe just proximal to the superior pole of the patella.

Vital signs, body weight, and temperature were recorded at each visit. Adverse event (AE) was recorded throughout the study and for 30 days after study termination. AE intensity was rated by the investigator according to the Common Terminology Criteria for Adverse Events.

Statistical analysis

The Statistical Package for the Social Sciences software version 22.0 (SPSS, IBM Crop, Armonk, New York.) was used for analysis. Descriptive parameters were presented as mean ± standard deviation. The paired sample T-test and two-way repeated measurement were used for comparison between groups. Sample size calculation was based on demonstrating the superiority of TDM plus ketorolac to placebo in relation to the primary efficacy endpoint, using a one-sided superiority test with $\alpha = 0.05$ and $\beta = 0.2$. A P-value of <0.05 was considered significant. Adverse events were evaluated according to the chi-square method.

The primary endpoints were the change in VAS, WOMAC score, and synovial thickness in the 4th week.

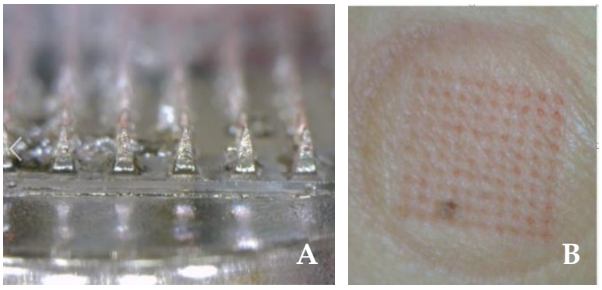

Fig. 1A Side view of solid microneedles and Fig. 1B skin after microneedle application.

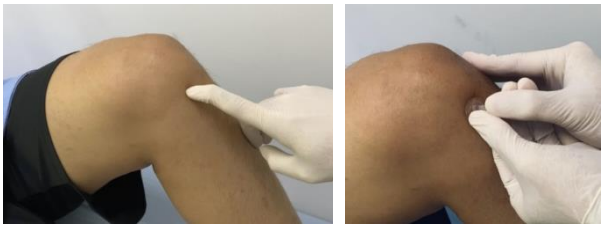

Fig. 2 Transdermal microneedle patch application at the medial joint line of the knee in 90-degree flexion.

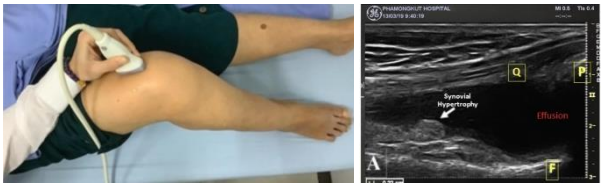

Fig. 3 Ultrasound measurement of synovial thickening. Q, quadriceps tendon; P, patellar bone; F, femoral condyle.

RESULTS

The mean age of patients in the TDM plus ketorolac group was 67.4 ± 7.4 years (40 women and 10 men). In the placebo group, the mean age of patients was 63.9 ± 8.4 years (35 women and 15 men). The prevalence of patients with body mass index >25 kg/m^2 was 56% and 60% in the TDM plus ketorolac and the placebo groups, respectively.

The mean VAS was 4.6 ± 1.4 in the TDM with ketorolac group and 3.8 ± 0.9 in the placebo group. The mean WOMAC score was 9.0 ± 5.3 in the TDM with ketorolac group and 6.6 ± 4.1 in the placebo group. The mean initial synovial thickness was 2.9 ± 1.1 mm in the TDM with ketorolac group and 2.9 ± 0.7 mm in the placebo group. Patient demographics and population baseline characteristics were balanced between groups (Table 1).

Table 1 Demographic data.

Parameter	TDM + ketorolac (N=50)	Placebo (N=50)	P-value
Age	67.4 ± 7.4	63.9 ± 8.4	0.225
Sex Female (N, %)	40 (80%)	35 (70%)	0.344
BMI < 25 (N, %)	22 (44%)	20 (40%)	0.317
BMI > 25 (N, %)	28 (56%)	30 (60%)	0.193
Synovial thickness (mm)	2.9 ± 1.1	2.9 ± 0.7	0.927
VAS (score)	4.6 ± 1.4	3.8 ± 0.9	0.099
WOMAC (score)	9.0	6.6	0.183

BMI, body mass index; VAS, visual analog score; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

Table 2 Comparison of mean synovial thickness, Western Ontario and McMaster Universities Arthritis Index score, and pain visual analog score between the transdermal microneedle patch plus ketorolac and the placebo groups.

Synovial thickness	TDM + ketorolac	Placebo	P-value
Pre-treatment	2.9	2.9	0.927
1st week	2.0	3.0	0.869
2nd week	1.8	2.7	0.014
4th week	1.8	2.6	0.004
WOMAC score	**TDM + ketorolac**	**Placebo**	**P-value**
Pre-treatment	9.0	6.6	0.183
1st week	5.6	6.0	0.713
2nd week	3.9	5.8	0.073
4th week	3.3	5.7	0.013
Pain VAS	**TDM + ketorolac**	**Placebo**	**P-value**
Pre-treatment	4.6	3.8	0.927
1st week	2.7	2.8	0.916
2nd week	1.9	2.6	0.014
4th week	1.4	2.1	0.037

The mean synovial thickness in the TDM plus ketorolac group was 2.9 mm at baseline and 2.0 mm, 1.8 mm, and 1.8 mm at 1st, 2nd, and 4th week, respectively. The mean synovial thickness in the placebo group was 2.9 mm at baseline and 3.0 mm, 2.7 mm, and 2.6 mm in the 1st, 2nd, and 4th weeks, respectively. The mean synovial thickening in the TDM plus ketorolac group showed a significant decrease in the 2nd and 4th weeks (P<0.05) (Table 2).

The mean synovial thickness reduction in the TDM plus ketorolac and placebo groups were 1.1 mm and 0.2 mm in 2nd week and 1.1 mm and 0.3 mm in 4th week, respectively (Fig. 4).

The mean WOMAC score in the TDM plus ketorolac group was 9.0 at baseline and 5.6, 3.9, and 3.3 in the 1st, 2nd, and 4th weeks, respectively. The mean WOMAC score in the placebo group was 6.6 at baseline and 6.0, 5.8, and 5.7 in the 1st, 2nd, and 4th weeks, respectively. The mean WOMAC score reduction in the TDM with ketorolac group significantly decreased in the 4th week (P<0.05) (Table 2). The mean WOMAC score reductions in the TDM plus ketorolac and placebo groups were 5.7 and 0.9 in the 4th week, respectively (Fig. 5).

The mean pain VAS in the TDM plus ketorolac group were 4.6 at baseline and 2.7, 1.9,

and 1.4 in the 1st, 2nd, and 4th weeks, respectively. The mean pain VAS in the placebo group were 3.8 at baseline and 2.8, 2.6, and 2.1 in the 1st, 2nd, and 4th weeks, respectively. The mean pain VAS in the TDM plus ketorolac group significantly decreased in the 2nd and 4th week compared with the placebo group (P<0.05) (Table 2). Mean pain VAS reduction in the TDM plus ketorolac and placebo groups were 2.7 and 1.2 in the 2nd week and 3.2 and 1.7 in the 4th week, respectively (Fig. 6).

During the four weeks, no complications and treatment-related adverse events were reported, such as skin irritation, injection site pain, and superficial skin infection.

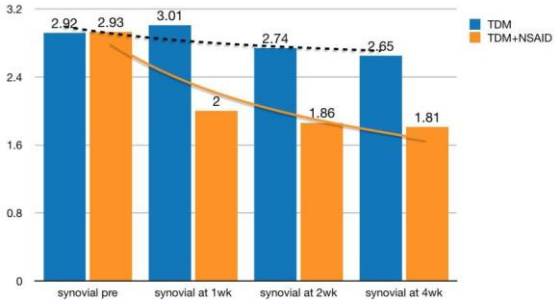

Fig. 4 Mean synovial thickness in TDM plus ketorolac and placebo groups at baseline, 1st, 2nd, and 4th week. TDM, transdermal microneedle patch; TDM+NSAID, transdermal microneedle patch plus nonsteroidal anti-inflammatory drug.

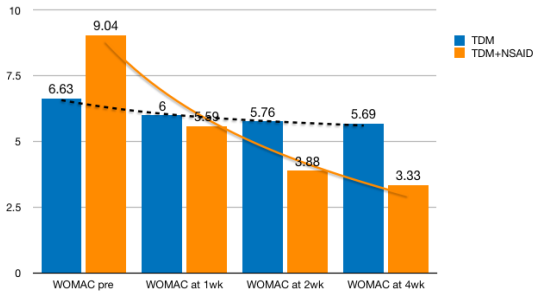

Fig. 5 Mean WOMAC score in TDM plus ketorolac and placebo groups at baseline, 1st, 2nd, and 4th week. WOMAC, Western Ontario and McMaster Universities Arthritis Index; TDM, transdermal microneedle patch; TDM+NSAID, transdermal microneedle patch plus nonsteroidal anti-inflammatory drug.

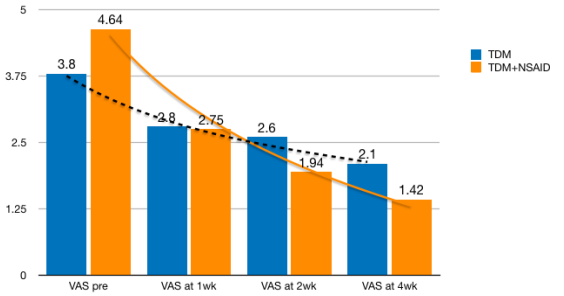

Fig. 6 Mean VAS in TDM plus ketorolac and placebo groups at baseline, 1st, 2nd, and 4th week. VAS; Visual analog score; TDM, transdermal microneedle patch; TDM+NSAID, transdermal microneedle patch plus nonsteroidal anti-inflammatory drug.

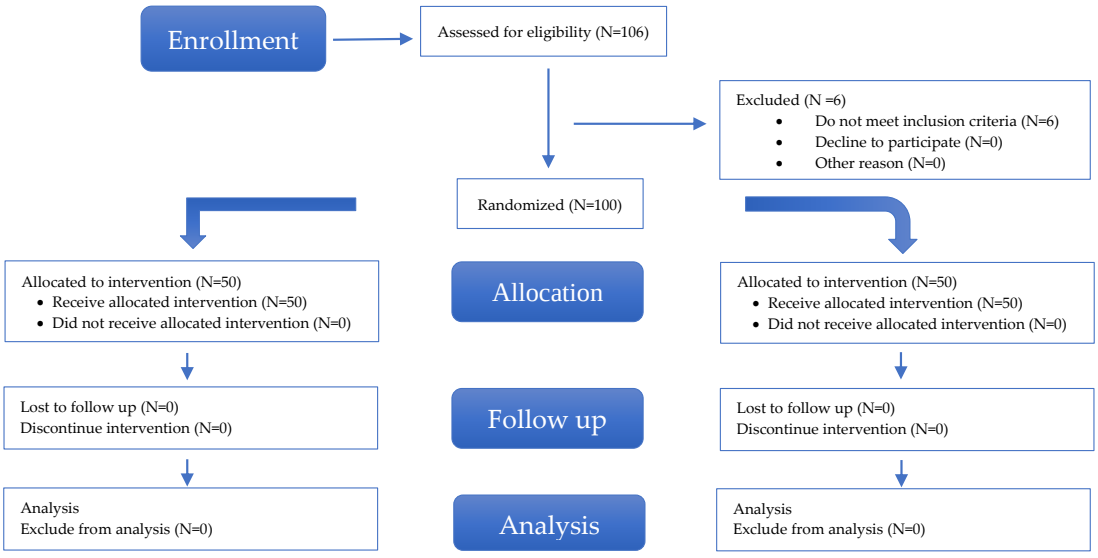

Fig. 7 Consolidated Standards of Reporting Trials 2010 flow diagram.

DISCUSSION

The patients in the TDM plus ketorolac group had a significant clinical improvement from the 2nd week to the last follow-up. No patients were lost to follow-up. The efficacy of TDM plus ketorolac 30 mg was statistically superior to the placebo in the 2nd and 4th week ($P<0.05$) in relieving knee OA pain and synovial thickness. Physical function and joint stiffness improvements throughout the 4-week study were better in the TDM plus ketorolac group than in the placebo group. No serious complications were found in both groups.

The metaanalysis by Lin *et al*. included 13 RCTs comparing the effects of topical NSAIDs with those of placebo or oral NSAIDs in 1983 patients with OA, mainly of the knee or hand, treated for up to 4 weeks[9]. The effects were calculated based on the pain, function, and stiffness. Topical NSAIDs were found to be significantly superior to placebo in terms of pain relief and functional improvement in the first 2 weeks of treatment. The global recognition of the critical role of topical NSAIDs in managing osteoarthritic pain is reflected in the increasing number of international societies and clinical practice guideline committees recommending them as an early treatment option[10-14].

This study showed that TDM plus ketorolac significantly reduced 1.1 mm of mean synovial thickness and led to a 40% reduction in VAS after the 2nd week. The mean decrease in the WOMAC score was 63% from baseline, statistically significant at 4 weeks.

There were some limitations in our study. First, the initial VAS and WOMAC scores were lower in the placebo group than in the TDM plus ketorolac group, although they were not statistically significant. Second, the ultrasonography of synovial thickness used to evaluate the antiinflammatory effect was an indirect method instead of measuring the intraarticular inflammatory cytokines, interleukin (IL)-1 or IL-6, and C-reactive protein. Third, the follow-up period was only 4 weeks. The short follow-up period reflected the efficacy of the single treatment and avoided the influence of other procedures. However, it did not provide information on the possible long-term effects of TDM. Finally, the intraarticular drug level after injection was unknown.

Given the advantages of minimal invasion and easy operation, microneedle therapy represents a promising alternative strategy for treating early knee OA, potentially improving pain and physical function.

CONCLUSIONS

This study showed that TDM plus Ketorolac improved pain, satisfactory score, and inflammation in patients with early knee OA (KL classification I–II). TDM plus ketorolac can be used for noninvasive treatment in knee OA. Further prospective controlled trials are necessary for confirm a longterm efficacy.

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