Research Square

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Effect of Transdermal Microneedle Patch with NSAID in Osteoarthritic Knee: A Randomized Controlled Trial

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Abstract

Background: In early osteoarthritis (OA) knee without structural damage, synovial hypertrophy is a good biomarker to monitor disease progression and response to any treatments. NSAID has been proved to reduce inflammation or synovitis effectively. Transdermal microneedle is a non-invasive device to deliver medication by transdermal route. However, no recent study shows the effectiveness of transdermal NSAID via microneedle.

Objective: To determine the effect of transdermal microneedle patch (TDM) with NSAID in synovial hypertrophy, knee pain and WOMAC score of osteoarthritic knees.

Methods: Two-group, randomized, double-blinded, controlled trial was done. 100 participants, age 40-70 years, with painful knee OA and non-structural change on radiography will be randomly allocated to underwent either TDM (placebo) or TDM with NSAID (ketorolac 30 mg) at medial joint line of the knee once weekly for 2 times. Synovial thickness was measured by ultrasonography at pre-treatment, 1, 2, and 4 weeks. Pain score (VAS), WOMAC score and adverse events (AEs) were also recorded.

Results: One hundred patients were enrolled into 2 groups. Comparing to TDM with NSAID and Placebo group demonstrated significant reduction of synovial thickness and VAS at 2, 4 weeks ($P<0.05$). Mean synovial thickness reduction were 1.12 and 0.27 mm. at 4 weeks and mean VAS reduction were 3.22 and 1.7 at 4 weeks (TDM with NSAID and placebo, respectively), but mean WOMAC score reduction statistically significant difference between groups at 4^{th} weeks. Mean WOMAC score reductions were 5.71 and 0.96 at 4 weeks (TDM with NSAID and placebo, respectively). Treatment related adverse events in total 4 weeks, i.e. skin irritation, injection site pain, superficial skin infection were similar in all groups and no report of any complication

Conclusion: Transdermal microneedle patch with NSAID significantly decreased synovitis and improved pain score in OA knee after 2 weeks and improve WOMAC score over 4^{th} week without any adverse events.

Trial registration: We enroll 100 the primary OA knee patients for their willingness to participate in this study. This research was enrolled on 22 April 2020, Research Ethic committee approved on 21 April 2020. During October, 22 2020 research were completed.

Background

Osteoarthritis (OA) is a common chronic joint disease that effect to joint pain and disability, recently OA has been described as a whole joint disease that involves the degradation of the articular cartilage, thickening of subchondral bone, degeneration of ligament and hypertrophy of the joint capsule and synovial inflammation.[1]

In early-stage OA knee, pain is the most presented symptom. Oral NSAID keep on the mainstay of the pharmacological management, their used is strongly recommended along the standard guideline to stop pain and inflammation.[2] However clinical consideration to use oral NSAID such as monitoring for potential adverse Gastrointestinal and renal side effect are also concerned.

Transdermal microneedle patch (TDM) is a noninvasive choice of drug administration, more steadier drug plasma concentration compares to oral and sublingual route.[3] TDM is easy to disconnected if there is any complication. The systemic efficacy of TDM is proved and used in many purposes, vaccination, hormonal therapy, in local controlled TDM is used for cosmetic. [4]

Kellgren and Lawrence provided radiographic guideline and grading for clinical diagnosis and treatment monitoring but radiographic evidenced of OA is a potential late sign that irreversible joint damage may have already occurred.[5] By used ultrasonography (US) to detected synovial hypertrophy, which is the pathological characteristic of early stage of OA knee. The US had been widely investigated in monitoring synovitis, although the reliability of US in detecting structural abnormality was operator dependence.[6]

The goal of this study was to evaluate the efficacy of NSAID via TDM to treat pain, improved satisfactory score and reduced synovial thickness detected by US compare to placebo.

Method

After the approval of patients and hospital ethics committee, RTA IRB No R220h/62 patients at the ages between 40 and 70 years with primary osteoarthritic knee Kellgren-Lawrence classification I-II have been enrolled in the double blinded blocked randomized controlled trial study, divided into 2 groups, group 1 were 50 participants with TDM + NSIAD (ketorolac) and group 2 were 50 participants with TDM without medication (Placebo group). Participants with inflammatory arthritis, septic arthritis, skin infection, liver and renal insufficiency, patients who underwent intra-articular hyaluronic acid within 6 months and steroid injection within 3months were excluded from the study. Baseline radiography on affected knee standing AP, lateral views were done.

Nanoneedle Research Team, National Nanotechnology Center (NANOTEC), NSTDA designed an array of solid polymer microneedles 365 needles, in the area of approximately 0.86 cm^2. The microneedle pyramid shape was 625 μm in height, 180 μm in width at the base, a tip-to-tip spacing of 700 μm for vertical and horizontal, and tip-to-tip spacing of 495 μm for diagonal. (Fig. 1, 2). Department of Medical Science, Ministry of Public Health, Thailand approved with biological evaluation for medical device.

Before application of TDM + NSAID and placebo arranged the patient in supine position on the examination table, kept knee flexed but relaxed at 90 degree. (Fig. 3, 4, 5) All patients were applied TDM patch at the midpoint between inferior pole patella and tibial tubercle, shift to medial 2FB at joint line level. Solid micro-needles were applied with insertion force about 10 Newton until skin imprint occur (the skin imprint as picture 2). Ketorolac 30 mg/1ml. was drop onto the Adhesive dressing with pad to covered

the imprint. The TDM patch was peeled off after 6hr. The patients were followed up at 1, 2 and 4 weeks but re-applying TDM only at 1st week, measured pain Visual analogue score (VAS), Modified WOMAC (Western Ontario and McMaster University) Thai version VAS, WOMAC score and synovial thickness by US in all patients every appointment.

Synovial thickness was measured by US with midline scanning technique Ultrasonogram machine (GE Healthcare model LOGIQ® e) preset musculoskeletal-knee in B mode, 12L-RS wide band linear probe (12-MHz) were used. Set the patient in supine position on the examination table, kept knee flexed but relaxed at 30 degrees. (Fig. 6, 7) Midline scanning technique was done by vertically apply of linear probe at just proximal to superior pole of the patella. the synovial which is the homogeneous echoic layer tissue overlying the fat pad. The thickness of synovial was measured in millimeters with 1 decimal.

All of the patients were recorded pain visual analogue score (VAS), Modified WOMAC (Western Ontario and McMaster University) Thai version before apply TDM patch and measure synovial thickness by US at suprapatellar pouch at baseline and 1st week follow up. For the 2nd and 4th week patients were evaluated only pain VAS, modified WOMAC score and measure synovial thickness by US without apply TDMpatch.

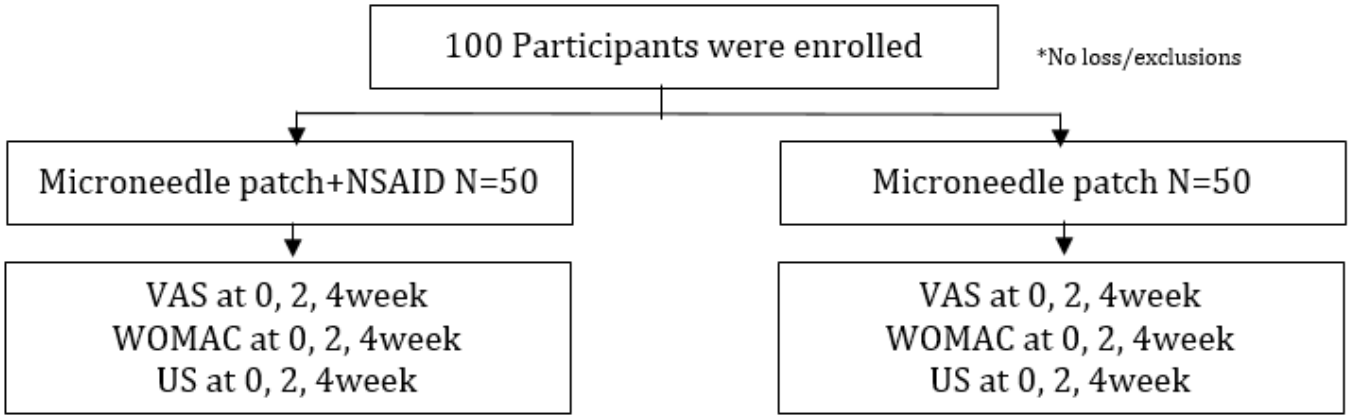
Statistical analysis

The SPSS software statistical package version 20.0(SPSS Inc., Chicago, Illinois) was used for analysis. Descriptive parameters were presented as mean+-standard deviation. The pair sample T-test and 2-way repeated measurement has been used for comparison between the groups. Adverse event was evaluated according to chi square method. A p-value of < 0.05 was considered as significant.

Results

The mean age of fifty patients in TDM with NSAID group was 67.4±7.4 years, there were 40 female and 10 male VS 63.9±8.4 years in Placebo group there were 35 female and 15 males. The Body Mass Index more than 25 kg/m2 in TDM with NSAID group was 56 % VS 60 % in Placebo group. There were no significant differences found between the groups in terms of demographical data. (Table 1)

The participant flow:



Significant decreases were detected in pain VAS score and WOMAC score (pain, physical activity, knee stiffness) and the synovial thickness compared between pre-treatment and post-treatment in TDM with NSAID over 4 weeks ($P<0.05$) by pair t-test sample correlation but there were no significant differences found in placebo group.

The mean Visual analogue score was 4.6±1.4 in TDM with NSAID group and 3.8±0.9 in Placebo group. The mean WOMAC score was 9.0±5.3 in TDM with NSAID group and 6.6±4.11 in Placebo group. The mean initial synovial thickening was 2.92±1.1 mm. in TDM with NSAID group and 2.93±0.7 mm. in Placebo group. There were no significant differences found between the groups in terms of baseline characteristic data.

The mean of pain VAS in TDM + NSAID group were 4.64 at baseline and 2.75, 1.94 and 1.42 at 1^{st}, 2^{nd} and 4^{th} respectively and in placebo group were 3.8 at baseline and 2.8, 2.6, and 2.1 at 1^{st}, 2^{nd} and 4^{th} respectively. The mean of pain VAS reduction in TDM + NSAID group compare with placebo group showed significantly decrease at 2^{nd} and 4^{th} week ($P<0.05$) (Table 3). Mean pain VAS reduction in TDM + NSAID group compare with placebo group were 2.7 and 1.2 at 2^{nd} week and 3.22 and 1.7 at 4^{th} week respectively.

The mean of WOMAC score in TDM + NSAID group were 9.04 at baseline and 5.59, 3.88 and 3.33 at 1^{st}, 2^{nd} and 4^{th} respectively and in placebo group were 6.63 at baseline and 6.01, 5.76, and 5.69 at 1^{st}, 2^{nd} and 4^{th} respectively. The mean of WOMAC score reduction in TDM + NSAID group compare with placebo group showed significantly decrease at 4^{th} week ($P<0.05$) (Table 3). Mean WOMAC score in TDM + NSAID group compare with placebo group reduction were 5.71 and 0.96 at 4^{th} week.

The mean of synovial thickness in TDM + NSIAD group were 2.93 mm. at baseline and 2.0 mm, 1.86 mm and 1.81 mm at 1^{st}, 2^{nd} and 4^{th} respectively and in placebo group were 2.92 mm. at baseline and 3.01 mm, 2.74 mm and 2.65 mm at 1^{st}, 2^{nd} and 4^{th} respectively. The mean of synovial thickening reduction in TDM + NSAID group compare with placebo group showed significantly decrease at 2^{nd} and 4^{th} week

(P<0.05) (Table 3). Mean synovial thickness reduction in TDM + NSAID group compare with placebo group were 1.07 mm. and 0.18 mm. at 2nd week and 1.12 and 0.27 mm. at 4th week

There was no report of any complication and treatment related adverse events in total 4 week, i.e., skin irritation, injection site pain, superficial skin infection.

Discussion

In new emerging evidence suggested that osteoarthritis is not a primarily disease of cartilage. But OA was the disease of the whole joint. The disease progression was increasingly activated innate and adaptive immune system. Nowadays there are no drugs therapy exists to effectively halt the progression of OA.

From several studies, mainstay treatments of osteoarthritic knee were started at the end stage of disease in which supportive treatment or joint replacement. Actually, conservative treatment of primary OA knee with should be aiming to prevent structural damage of the cartilage by controlling process of inflammation. From previous study, According to Termtanun C et al.[6] found that, the more advanced stage of OA knee became with the higher prevalence of synovial hypertrophy. As the disease progress, the knee structure decay and the symptom worsen. Synovial thickness was observed with moderate to good inter-observer reliability and overall prevalence of synovial thickness with 2 mm. cut-off level was well correlated with Kellgren-Lawrence (KL) classification. The prevalence of synovial hypertrophy with 2 mm cut-off level correlated with KL2 is 70.8% also statistically significant. In this study used less than 2 mm cut off level in early OA knee was the significant thickness of synovial hypertrophy, which relieve from synovitis after treatment.

In this study, focus on the effectiveness of transdermal micro-needle patch with or without NSAID in early osteoarthritic knee patients, and the correlation with ultrasonography changes, pain and WOMAC score improved. Adding Ketorolac resulted in a significant reduction in synovial thickening, Visual analogue score in the 2nd week. WOMAC score is significant reduction in the 4th week, although non-significantly difference in baseline VAS and WOMAC score during the group, but the values were quite low in placebo group. However locally drug level is questionable.

This study had potential limitation. First, this study had limited evidence of efficacy of intra-articular NSAID injection therefore further studies are needed. Second, the initial VAS score and WOMAC score in placebo group were lower than TDM plus NSAID group although the study did successfully randomize and there was no statistic significant. Finally, this study measured synovial thickening to evaluated anti-inflammatory effect of NSAID, which was the indirect method instead of measuring the intra-articular inflammatory cytokine, IL-1 or IL-6, CRP, which is more invasive technique than ultrasonography.

Conclusions

The current study shows that TDM combination of Ketorolac leads to improved osteoarthritis pain, satisfactory score and inflammation in osteoarthritic knee patients without adverse reaction, but further

clinical trial are necessary to allow to be standard treatment recommendations.

List Of Abbreviations

OA: osteoarthritis

NSAID: Non-steroidal anti-inflammatory drug

TDM: transdermal microneedle patch

WOMAC: Western Ontario McMaster Universities OA Index f

VAS: Visual analog scale

AEs: adverse events

US: ultrasonography

NANOTEC: Nanoneedle Research Team, National Nanotechnology Center

KL: Kellgren-Lawrence classification

Declarations

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Contributions:

All authors were involved in drafting the manuscript or revising it critically for important intellectual content and all the authors gave their approval of the final version of the manuscript to be published.

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Analysis and interpretation of data: Mongkon Pisuttanawat, and Saradej Khuangsirikul.

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Availability of data and materials: The datasets generated during and/or analyzed during the current study are available from corresponding author on reasonable request

Ethics approval and consent to participate: The human study was approved by the Institutional Review Board of Royal Thai Army Medical department (IRBRTA No. 523/2563). The study was performed in accordance with the Declaration of Helsinki. (Approval No. R220h/62).

Consent for publication: Not applicable.

Competing interests: The authors declare that they have no competing interests.

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Tables

Table 1 Demographic data

Parameter	TDM + NSAID (N=50)	Placebo (N=50)	P value
Age (years)	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

Table 3: The mean of pain VAS and WOMAC score synovial thickness comparison between pre-treatment, 1st week, 2nd week and 4th week in TDM plus NSAID and Placebo

Pain VAS	TDM + NSAID	Placebo	P-value
Pre-treatment	4.64	3.8	0.927
1st week	2.75	2.8	0.916
2nd week	1.94	2.6	0.014 (P<0.05)
4th week	1.42	2.1	0.037 (P<0.05)
WOMAC score	TDM + NSAID	Placebo	P-value
Pre-treatment	9.04	6.63	0.183
1st week	5.59	6.01	0.713
2nd week	3.88	5.76	0.073
4th week	3.33	5.69	0.013 (P< 0.05)
Synovial thickness	TDM + NSAID	Placebo	P-value
Pre-treatment	2.93	2.92	0.927
1st week	2	3.01	0.869
2nd week	1.86	2.74	0.014 (P< 0.05)
4th week	1.81	2.65	0.004 (P<0.05)

Figures

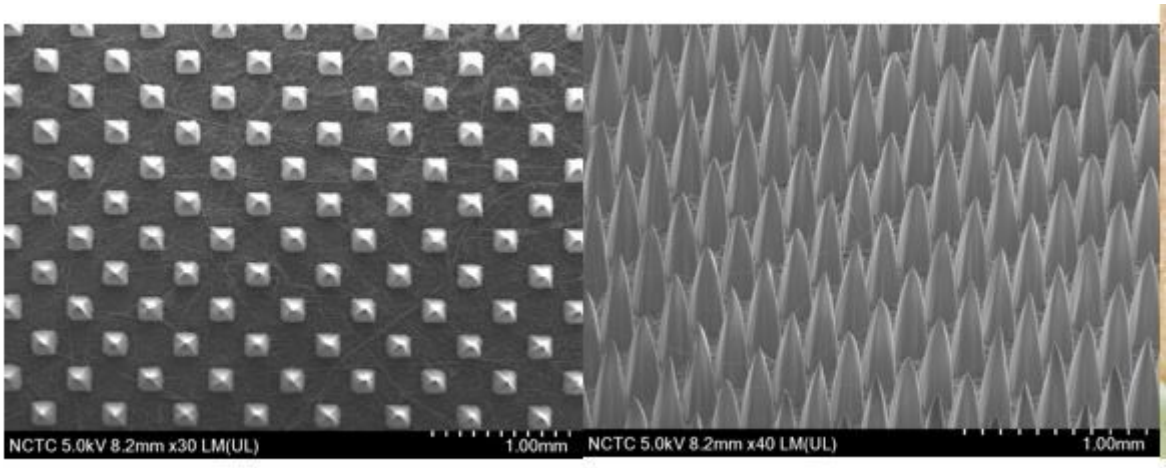

Figure 1

Top view and side of olid microneedle, and skin after apply microneedle

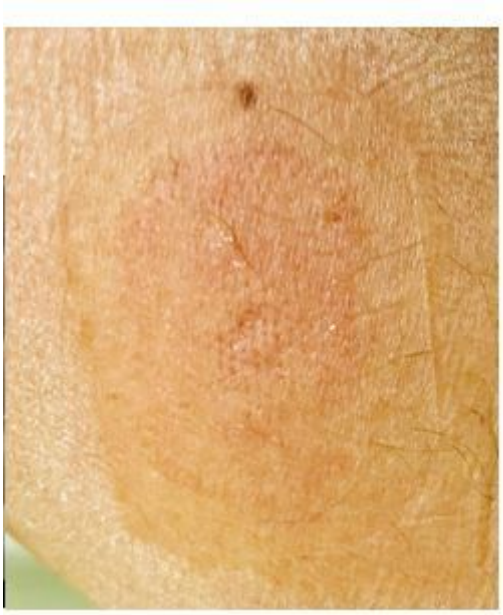

Figure 2

Top view and side of olid microneedle, and skin after apply microneedle

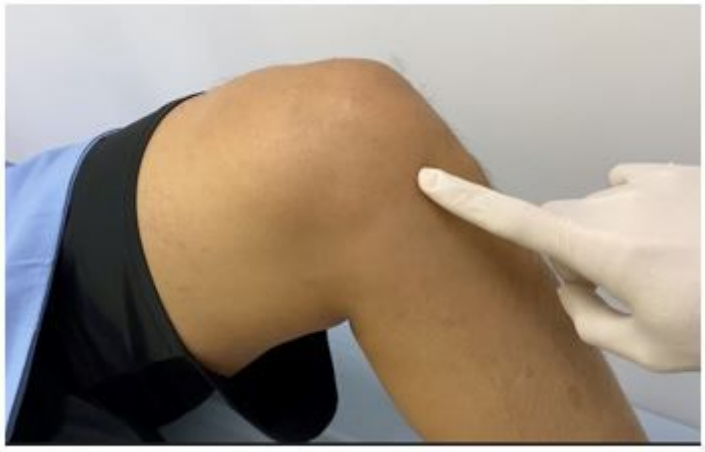

Figure 3

TDM underwent at medial joint line of the knee in 90 degrees flexion

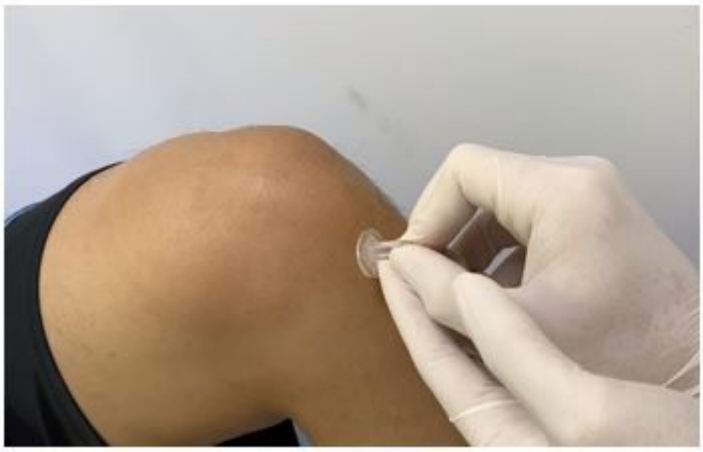

Figure 4

TDM underwent at medial joint line of the knee in 90 degrees flexion

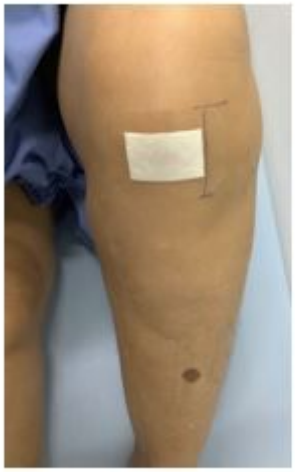

Figure 5

TDM underwent at medial joint line of the knee in 90 degrees flexion

Figure 6

US measurement of synovial thickening

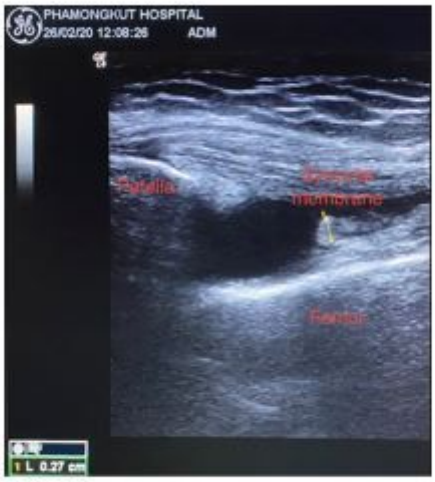

Figure 7

US measurement of synovial thickening

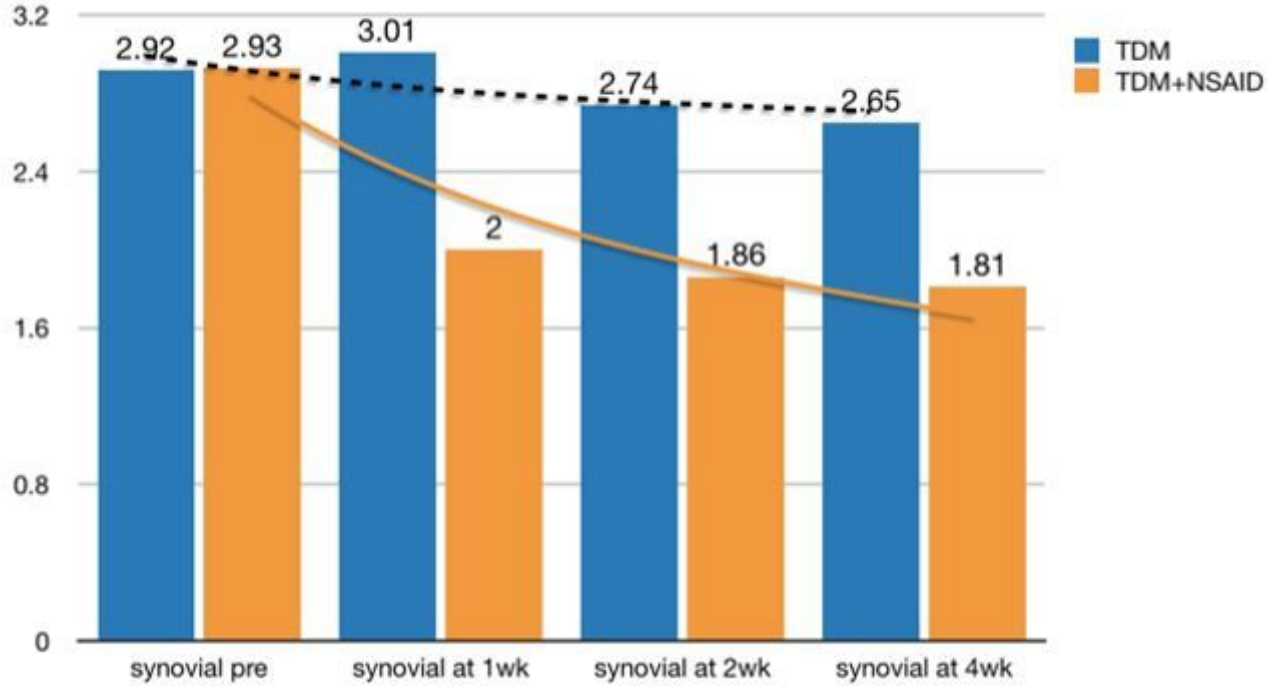

Figure 8

Mean synovial thickening after transdermal microneedle patch (TDM) compare to transdermal microneedle patch with NSAID (TDM+NSAID)

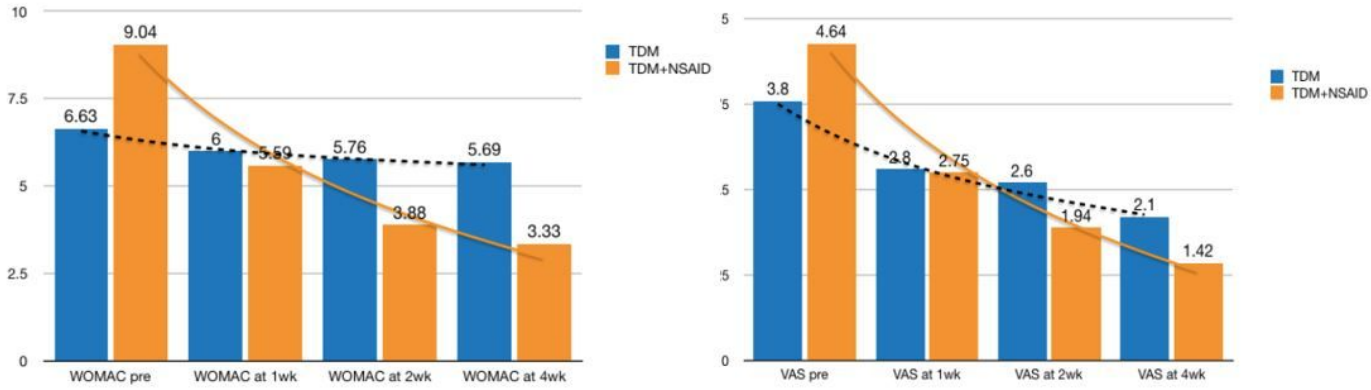

Figure 9

Mean WOMAC and VAS score after transdermal microneedle patch (TDM) compare to transdermal microneedle patch with NSAID (TDM+NSAID)