


A Randomized Placebo-Controlled Trial of Efficacy and Safety: Drug-Free Gel Containing Ultra-Deformable Phospholipid Vesicles (TDT 064) in Osteoarthritic Knees

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ABSTRACT

BACKGROUND: There are a number of topical agents that are used for treatment of knee osteoarthritis. Drug-free gels, containing ultra-deformable phospholipid vesicles (TDT 064) are one such topical therapy, which have been stated to act as a bio lubricant. However, the evidence of TDT 064 in treatment of knee osteoarthritis is limited. Hence, the aim of this study was to evaluate the efficacy of pain control as a primary outcome and safety of TDT 064 compared with a topical placebo.

METHODS: Sixty-four patients with primary osteoarthritis, with radiographic showing Kellgren and Lawrence classification grade II to III, were randomized into 2 groups. In the first group of 32 patients TDT 064 was used as topical agent, whilst in the second group of 32 patients a placebo identical in appearance was used instead. The verbal numerical rating scale (VNRS) was used for recording pain levels, Self-reported Knee Injury and Osteoarthritis Outcome Scores (KOOS) as well as amounts of rescue medication were also recorded. The data were recorded at the start of the study, and then at follow-up appointments of 14 days, 6 weeks, and 3 months.

RESULTS: The mean VNRS for pain in both groups were significantly improved, when compared to the start of treatment ($P < .0001$); however, there were no differences between groups at any follow up visit. KOOS in all subscales were not significantly different between both groups at baseline and at the end of treatment. However, the average amount of NSAIDs in the TDT 064 group was 26.39 ± 22.11 tabs, which was significantly lower than the control group; which used an average 37.03 ± 19.22 tabs in 3 months ($P = .047$).

CONCLUSIONS: There were no differences in the VNRS for pain and KOOS scores between the active and placebo groups. Although, TDT 064 could decrease usage of rescue medication the difference with use of a placebo was minimal. Further, larger trials would also be beneficial to demonstrate any differences between TDT 064 and a placebo.

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Introduction

Knee osteoarthritis is a problem that limits function, and creates a disability in patients worldwide.^{1,2} There are many methods to decrease pain, and for improving function for those afflicted with this disease. One of these is topical therapy, which is a treatment that applies agents or medicines directly to the symptomatic knee.^{3,4} This method is one of the effective treatments that has some benefits over oral medications. One advantage of topical therapies is its limited systemic effects; such as, gastrointestinal irritation,⁵ hepatotoxicity,⁶ cardiovascular problems,⁷ renal function disturbance,⁸ or nausea and vomiting,⁹ which can be attributed to some oral medications.

Presently, there are many topical agents that are used for the treatment of knee osteoarthritis; such, as topical nonsteroidal anti-inflammatory drugs (NSAIDs),¹⁰ Capsaicin,¹¹ topical

creams; containing glucosamine sulfate and chondroitin sulfate,¹² Menthol,¹³ and Drug-free gels containing ultra-deformable phospholipid vesicles (TDT 064). TDT 064 is a topical agent that was recently reported on for its efficacy for treatment of osteoarthritis.¹⁴ This was in spite of the fact that the specific mechanism of action in pain relief of TDT 064 has not been completely clarified. TDT 064 is a gel containing hydrophilic, nano-scale lipid vesicles with a phospholipid bilayer. This is based on knowledge that phospholipid is a key function in the natural lubrication of articular cartilage.¹⁵ There was an animal study which reported that injecting phospholipid into an osteoarthritis knee impacted joint lubrication, by acting as a boundary lubricant and preserved articular cartilage from degenerative changes.¹⁶ So, the mechanism of action of TDT 064 states that it acts as a biolubricant, when it is localized on



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the articular surface. This bio lubricant effect reduces friction between the cartilage, which might minimize inflammation by reducing the release of damaged cartilage debris.¹⁴

There have been studies reporting on the effectiveness of TDT 064. Kneer et al¹⁷ reported that; in a randomized controlled trial TDT 064 had the same effectiveness on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) as did 100, 50, or 25 mg of Ketoprofen in Transfersome gel (IDEA-033). Another, randomized controlled trial in OA knee patients demonstrated that TDT 064 was not different to topical ketoprofen 50 or 100 mg in ultra-deformable vesicles and oral Celecoxib for the improvement of both WOMAC pain and function.¹⁸ However, there was 1 study which reported that patients who used TDT 064 had better pain and joint function than patients who used 100 mg Ketoprofen in Transfersome gel.¹⁹ Due to the limited number of evidences on the effectiveness of TDT 064, and that most of the previous reports were granted by pharmaceutical companies,¹⁷⁻¹⁹ the aim of this study was to evaluate the efficacy and safety of TDT 064 on pain and function compared with a topical placebo by a randomized controlled trial.

Methods

This study was a randomized placebo-controlled trial in parallel-group, 2-arm clinical trial, with allocation ratio 1:1; conducted from March 2019 to November 2019.

Patients between 45 and 80 years-old, who had primary osteoarthritis by criteria from the committee of the American Rheumatism Association²⁰ and radiographic showing Kellgren and Lawrence classification grade II to III, and whom were able to walk without support at the Orthopedic out-patient clinic of Songklanagarind hospital were approached for being potentially eligible for this study. The exclusion criteria were: inflammatory arthritis, previous knee surgery, neurological or muscular problems, skin problems around the knee, chronic kidney disease with creatinine clearance below 30 ml/minutes, and history or those who were allergic to the medication in this study protocol. The study was conducted at a tertiary care hospital. (Songklanagarind Hospital, Prince of Songkla University, Hatyai, Songkhla, Thailand).

All patients were then randomized into 2 groups. The first group; the TDT 064 group used TDT 064 for local treatment, while the control group were on a placebo. In the TDT 064 group, TDT 064 (TDT 064; Pro Bono Bio Entrepreneur Ltd) was applied twice daily, for 3 months; while in the control group a placebo, which had an identical appearance, was used instead (provided by Pharmaceutical Laboratory Service Center, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Songkhla, Thailand). The placebo consisted of water, butylene glycol, disodium EDTA, polysorbate 80, olive oil, polyacrylamide, C13 to C14 isoparaffin, laureth-7, butylated hydroxytoluene, ethanol, benzyl alcohol, methyl paraben, propyl paraben, ethyl paraben, and phenoxyethanol.

All patients were taught as to how to apply the gel twice daily; once in the morning and once in the evening. After the skin was cleaned and dried, the gel was applied around the knee; with the exception of the patellar area. After applying the gel, patients were asked to wait for 10 minutes until the gel dried before covering. Patients were prescribed meloxicam (7.5 mg oral once a day), or celecoxib (200 mg oral once a day) in case of a history of meloxicam, or conventional NSAIDs allergies as rescue medication in case of breakthrough pain. Rescue medication was not allowed within 24 hours before follow-up appointments. Patient education related to osteoarthritis disease and self-management; such as, activity modification, weight control, quadriceps, and low impact exercises were applied to patients. Patients were followed up at 2-, 6-, and 12-weeks, for evaluation of outcome and/or complications.

The primary outcome of this study was pain level, with the secondary outcomes being knee functional score and patient satisfaction. The verbal numerical rating scale (VNRS) was used for evaluating the level of pain; from 0 (no pain) to 10 (worst imaginable pain). Self-reported Knee Injury and Osteoarthritis Outcome Scores (KOOS), which consisted of 5 subscales: Pain, Symptoms, Function in daily living (ADL), Function in Sport and Recreation (Sport/Rec), and knee-related Quality of Life (QOL), were recorded separately. The score is from 0 to 100; 0 representing extreme problems and 100 representing no problems. The number of rescue medication usage at each visit was reported, additionally any skin complications at gel applied areas; such as, itching, burning sensation, rash, changes of skin color and anaphylaxis, were also recorded. Patient satisfaction with the treatment was evaluated with VNRS; wherein, 0 represented the least satisfied and 10 indicated most satisfied. All data were recorded by a staff member who was blinded as to which group of treatment the patients belonged to, with the exception of KOOS; which was self-reported by the patients.

The sample size was calculated based on the previous TDT 064 in osteoarthritis.¹⁹ Twenty-nine patients per group were required to detect a significance level of .01, and power was set at .8 to detect a difference of 2 points (SD 2.2) in the pain level after treatment. Blocks-of-4, randomization by a computer-generated sequence, were used for allocating each group of patients. The allocation concealment was performed with opaque, sealed envelopes. The envelopes were kept with the research administrators, who were not involved with patient treatment and evaluations. The envelope was opened by the patients, after the patients underwent a unify education program along with self-management information, and how to apply topical agents used at the out-patient clinic.

The patients were blinded as to their allocated group, by using containers identical in appearance of TDT 064 or the placebo. Physicians and evaluators were blinded to each group of patients.

This study was approved by the ethics committee and institutional review board of the Faculty of Medicine, Prince of Songkla University. The procedures in this study were performed in accordance with the Declaration of Helsinki's ethical principles for medical research involving human participants. Written informed consent was obtained from all individual participants included in the study.

Statistical analysis

All patients were analyzed in the groups to which they were randomized; regardless of discontinuation of treatment, loss to follow-up, or treatment conversion (intention-to-treat principle). Patient demographic data, including: gender, age, weight, height, body mass index (BMI), baseline VNRS score for the pain, VNRS score for patient satisfaction, baseline KOOS, and amount of rescue medication, were evaluated with a *t*-test. The comparison of VNRS score for the pain between groups, comparison of VNRS score for the pain at any time point with baseline and comparison of KOOS between groups were performed using repeated measures ANOVA. Pearson's chi-square test was used to compare gender, side, KL classification, and complications from applying the topical agent. The analyses were performed with R version 3.1.0 software (R Foundation for statistical computing, Vienna, Austria). Statistical significance was assumed if the *P*-value was less than .05.

Results

Participant flow

A total of 80 patients were approached for being potentially eligible for this study. Eight patients were excluded from the study, because of spinal stenosis; 2 patients had previous knee surgery, 1 patient had chronic kidney disease, and 5 patients declined to participate in the study. Finally, 64 patients were enrolled into the protocol, and then randomized into the 2 groups. The first group; the TDT 064 group included 32 patients using TDT 064 for local treatment, while the control group, consisting of 32 patients, used a placebo. There were 2 patients lost to follow-up; 1 patient in the TDT 064 group was lost to follow-up after their 6-week follow-up visit, and 1 patient in the control group was lost to follow-up after their 2-week follow-up visit (Figure 1).

There were no differences found in patient characteristics between either the TDT 064 group or control group in terms of: age, gender, weight, height, BMI, and Side and KL classification (Table 1). Thirty-two patients in each group were analyzed at the start of their treatment, and at their 2-week follow-up. At 6-week follow-up, 32 patients in the TDT 064 group and 31 patients in the control group were analyzed. Finally, 31 patients in each group were available for analysis, from start of treatment until 12-week follow-up.

VNRS for pain between both groups showed no differences at the start of the treatment, nor at any time of follow up visits

(Table 2). However, VNRS for pain at 2 weeks, 6 weeks, and 3 months were significantly improved when compared with the start time of treatment in both groups. Mean difference; TDT 064 group: 2 weeks 1.91 (95% CI, 1.37-2.44), 6 weeks 2.13 (95% CI, 1.12-3.13), and 3 months 2.71 (95% CI, 1.37-4.05). Control group: 2 weeks 1.56 (95% CI, 0.74-2.42), 6 weeks 1.65 (95% CI, 0.57-2.72), and 3 months 2.71 (95% CI, 1.57-3.85).

Knee injuries and Osteoarthritis Outcome Scores were not significantly different between both groups of patients at baseline and 3 months in all subscales (Table 3). However, the mean amount of NSAIDs usage over 3 months was different between the groups; wherein, the average amount of NSAIDs in the TDT 064 group was 26 ± 22.11 tabs, which was significantly lower than that of the control group; which used an average of 37 ± 19.22 tabs in 3 months ($P = .047$) (Table 4). VNRS for patient satisfaction did not differ between the TDT 064 or control group at 2 weeks (TDT 064: 8.56 ± 1.52 , control: 8.19 ± 1.73 , $P = .446$), 6 weeks (TDT 064: 8.39 ± 1.61 , control: 8.61 ± 1.56 , $P = .577$), and 3 months (TDT 064: 8.81 ± 1.04 , control: 8.65 ± 1.45 , $P = .617$).

In terms of safety, following the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Disease (ESCEO) recommendations on clinical trials on anti-osteoarthritis medications,²¹ this study found only 1 skin and subcutaneous tissue disorder in the TDT 064 group; which consisted of mild redness on the skin. Nevertheless, this patient continued treatment until completion of the study. Additionally, there were no general disorders or other administration site conditions, infections, infestations, or neoplasms benign and malignant.

Discussion

Topical therapy is one treatment for osteoarthritis patients, with limited, systemic adverse effects. TDT 064 is a novel topical agent that has been stated to be able to pass deep through the skin to reach the joints, so as to act as a bio lubricant.¹⁴ However, the evidences in the effectiveness of TDT 064 are limited. Therefore, the authors performed this study to equate the efficacy of TDT 064 on pain, and function compared to a topical placebo. The results of this study showed that patients who used TDT 064 had the same pain level, knee functional score and patient satisfaction that did not differ from patients who used the placebo after the treatment. However, patients in the TDT 064 group used less NSAIDs than those in the control group.

There were some limitations in this study. First, our study was likely underpowered to detect the differences between pain levels. We hypothesized that, if we limited the usage of rescue medication the results might be different; however, this would be unethical. Second, this study used NSAIDs as rescue medication instead of paracetamol, which was commonly prescribed as the rescue drug in OA trials. So, this might impair the results of the trial when comparing TDT 064 to placebo. Third, most patients in this study were middle aged, Asian woman who had

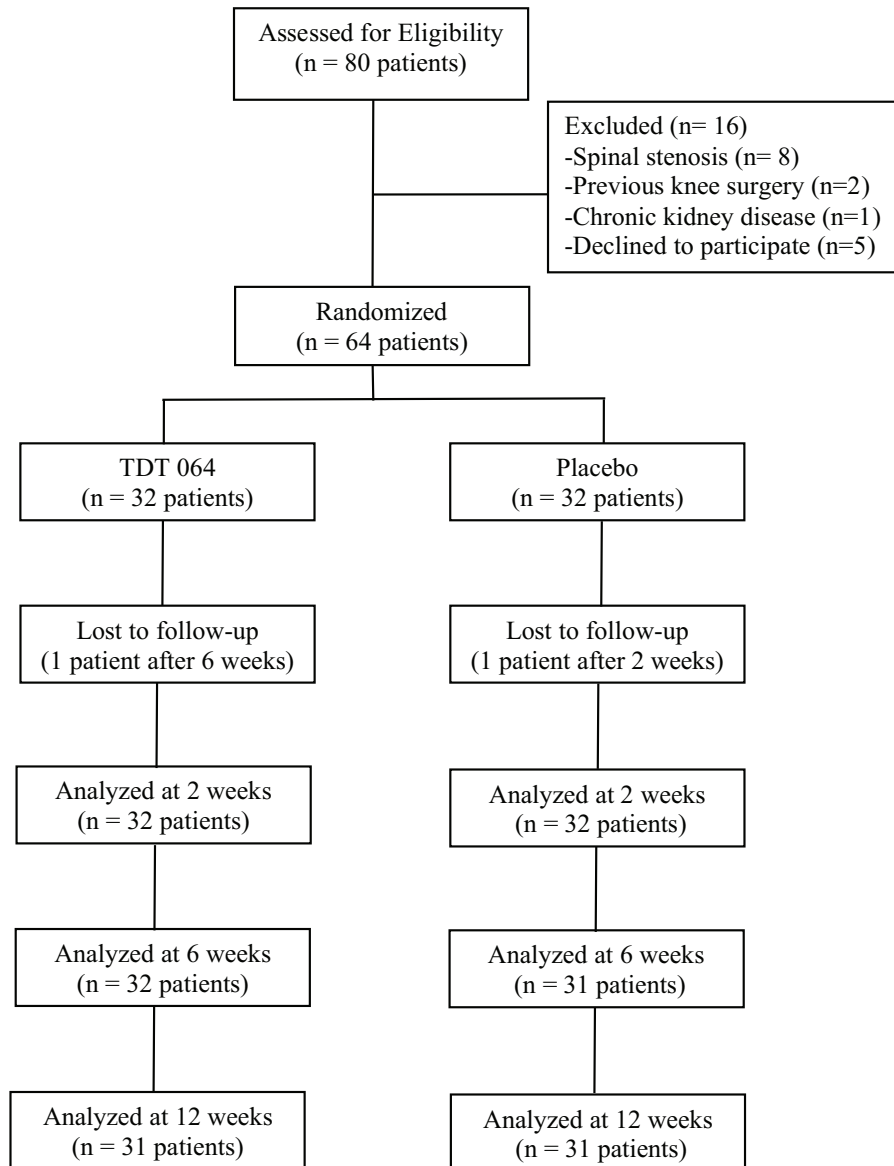


Figure 1. A diagram of the study enrollment process.

Table 1. Baseline demographic data at the beginning of the study.

CHARACTERISTIC	TDT 064 (N=32)	CONTROL GROUP (N=32)
Age (years)	65.41 ± 6.13	63.86 ± 7.21
Gender (male: female)	4:28	5:27
Weight (kg)	64.52 ± 11.14	64.88 ± 11.28
Height (cm)	157.63 ± 7.32	157.59 ± 8.4
BMI (kg/m ²)	26.17 ± 4.17	26.1 ± 4.03
Side (right: left)	16:16	15:17
KL-classification (II/III)	9:23	12:20
Verbal numerical rating scale for pain	6.18 ± 1.77	6.69 ± 1.62

Table 2. Mean verbal numerical rating scale (VNRS) for pain.

	TDT 064	CONTROL	P-VALUE
Baseline (wk)	6.81 ± 1.77	6.69 ± 1.62	.769
2	4.91 ± 1.71	5.13 ± 1.84	.491
6	4.69 ± 2.22	5 ± 1.91	.573
12	4.07 ± 2.46	3.94 ± 2.17	.698

Table 3. Mean Knee Injuries and Osteoarthritis Outcome Scores (KOOS).

	BASELINE	2WK	6WK	12WK
Pain				
TDT 064	51.88 ± 14.32	66.56 ± 12.09	69.38 ± 11.68	72.68 ± 13.69
Control	54.56 ± 15.49	63.94 ± 15.09	62.39 ± 18.1	70.36 ± 17.01
P-value	.474	.116	.021	.123
Symptoms				
TDT 064	61.59 ± 16.05	76.09 ± 12.61	78.38 ± 14.81	81.16 ± 13.36
Control	63.78 ± 20.2	73.31 ± 19.39	73.81 ± 17.83	79.71 ± 16.74
P-value	.633	.109	.15	.359
Activities of daily living				
TDT 064	48.88 ± 12.78	59.53 ± 11.42	64.1 ± 11.53	66.45 ± 13.16
Control	51.41 ± 12.75	56.84 ± 11.16	57.94 ± 15.96	63.87 ± 16.06
P-value	.43	.058	.028	.075
Sports and recreation				
TDT 064	15.97 ± 13.13	17.5 ± 13.44	19.69 ± 16.46	24.36 ± 16.77
Control	15.47 ± 12.53	18.13 ± 12.94	21.13 ± 19.65	25.81 ± 22.21
P-value	.877	.729	.845	.899
Quality of life				
TDT 064	32.34 ± 11.73	43.63 ± 12.01	49.66 ± 12.68	50.84 ± 13.89
Control	35.84 ± 13.36	41.69 ± 13.14	45.03 ± 15.52	49.10 ± 15.72
P-value	.27	.090	.037	.159

Table 4. Mean amount of nonsteroidal anti-inflammatory drugs (NSAIDs).

	TDT 064	CONTROL	P-VALUE
0-2 wk	5.66 ± 4.65	7.69 ± 4.25	.73
2-6 wk	11.28 ± 10.40	14.87 ± 9.70	.162
6-12 wk	9.26 ± 10.33	14.36 ± 10.03	.053
Total	26.39 ± 22.11	37.03 ± 19.22	.047

mild to moderate severity of osteoarthritis. However, the authors believe that the results of our findings could be applied to male patients, patients in other ranges of age, and other ethnicities with the same severity of disease. Further studies in other groups of patients and with different severity would be of interest. Fourth, the duration of oral NSAIDs at baseline was not recorded. However, NSAIDs were not allowed within 24 hours before clinical evaluation. Finally, our study used 2 types of NSAIDs (meloxicam and celecoxib), due to there being no report equating meloxicam or celecoxib dosing. So, a further study with the same rescue medication would provide more exact results.

The pain level of patients in our study, for those whom used TDT 064, improved after treatment, but was not different when compared with those using the placebo. Our study had contradicting results with previous studies. In a previous study, Kneer et al¹⁷ reported that TDT 064 had effectiveness for reduction in the WOMAC pain score of 49.5%, but this study didn't report the statistical data that compared the effectiveness of TDT 064 with other agents. A multicenter study by Conaghan PG et al. found that TDT 064 could reduce pain comparable with Transfersome gel containing 100 and 50 mg Ketoprofen and oral Celecoxib. Furthermore, TDT 064 could decrease pain better than an oral placebo.¹⁸ There was also another study comparing WOMAC pain scores between TDT 064 and 100 mg Ketoprofen in Transfersome gel. The results revealed that TDT 064 had better effectiveness to reduce pain from 6 weeks up until 3 months.¹⁹ The authors hypothesized that the different of outcome between this study and previous studies were possibly impacted by the small sample size of this study comparing with previous studies on TDT 064, which were better powered.

Our study found that Knee injuries and Osteoarthritis Outcome Scores, in all subscales, were also improved in both the TDT 064 and control group; however, there was no difference between either group. The results of this study oppose other studies. There was a multicenter study reporting that the effectiveness of TDT 064 on the WOMAC physical function subscale score had superiority to an oral placebo.¹⁸ Rother and Conaghan¹⁹ study also showed that the WOMAC function subscale score was higher in patients using TDT 064 than that of patients using 100 mg Ketoprofen in Transfersome gel, but only after 3 months of following treatment. The results of our study might not be the same as previous studies, because our study was also likely underpowered to detect the differences and the impact of outcome parameters, which used evaluated functional outcomes. Our study used KOOS, which was developed to extend the WOMAC for use in a more active patient group,²² while previous studies used WOMAC. We postulate that the demographics of patients in our study might not be active enough to demonstrate the difference in results of treatment.

To our knowledge, there have been no recent studies that report the amount of oral medicine used as rescue medication. We found that TDT 064 was able to decrease the number of NSAIDs usage in comparison with the placebo group. So, the difference of oral medication usage might obscure differences of pain level and functional scores between groups.

Conclusions

This study found no differences in the VNRS for pain and KOOS scores between TDT 064 and placebo groups in osteoarthritis patients. Although, TDT 064 could decrease usage of rescue medication the difference with use of a placebo was minimal. Due to the limitations of this study it was likely underpowered to detect the differences between pain levels, and the use of NSAIDs as rescue medication instead of paracetamol. Further, larger trials would also be beneficial to demonstrate any differences between TDT 064 and a placebo. Moreover, longer trials are warranted to assess the long-term effects of TDT 064. Finally, further research on TDT 064 for evaluation of its efficacy and cost-effectiveness would be beneficial.

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Author Contributions

VY designed the study, performed the analysis, and manuscript preparation. KI, TH, and BT designed the study and performed the data analysis. PT designed the study and manuscript preparation. All authors have read and approved the final manuscript.

Ethical Approval

This study was approved by the Ethics Committee and Institutional Review Board of the Faculty of Medicine, Prince of Songkla University (EC: 61-105-11-1).

Informed Consent

Written informed consent was obtained from all, individual participants included in this study.

Public Trials Registry

Thai Clinical Trials Registry (<http://www.clinicaltrials.in.th>). Registry number: TCTR20190302001.

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Availability of Data and Materials

The datasets generated during this current study are available from the corresponding author upon reasonable request.

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