Randomized Trial

Co-treatment with Oral Duloxetine and Intraarticular Injection of Corticosteroid plus Hyaluronic Acid Reduces Pain in the Treatment of Knee Osteoarthritis

DuoYi Li, MD[1, 2], Rong Hang, MD[3], Lang Meng, MD[1], Zhigang Zhao, MD[3], Chunmei Zhao, MD[1], and Fang Luo, MD[1]

From: [1]Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, China; [2]Department of Anesthesiology, Beijing Children's Hospital, Capital Medical University, Beijing, China; [3]Department of Pharmacy, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

Address Correspondence:
Fang Luo, MD
Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
E-mail: 13611326978@163.com

Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 07-30-2023
Revised manuscript received: 09-06-2023
Accepted for publication: 10-05-2023

Free full manuscript: www.painphysicianjournal.com

Background: Knee osteoarthritis (OA) is a common form of arthritis in elders which can lead to reduced daily activity and quality of life. It is important to administer a proper treatment with high efficacy and low side effects. In this study, we evaluated the efficacy of co-treatment with oral duloxetine and intraarticular (IA) injection of hyaluronic acid (HA) and corticosteroid (CS) in patients with knee OA.

Objectives: This study aimed to test the hypothesis that an IA injection of CS+HA combined with duloxetine could achieve pain management superior to that of an IA injection of CS+HA alone in patients experiencing knee OA related pain.

Study Design: This study adopted a prospective, randomized, open-label blind endpoint study design.

Setting: The investigation was performed at Beijing Tiantan Hospital Affiliated with the Capital Medical University from October 2019 to December 2021. The study plan was approved by the Ethics Committee of Beijing Tiantan Hospital (KY 2019-086-02).

Methods: A total of 150 patients were randomly allocated to receive either duloxetine combined with an IA injection (n = 75) or a single IA injection alone (n = 75). All patients were followed for 24 weeks. The primary outcome was the change in the weekly 24 hours average mean pain scores, and the secondary outcomes included the proportion of patients with ≥ 30% or ≥ 50% pain reduction, Brief Pain Inventory (BPI) items, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores, Patient Global Impression Improvement (PGI-I) ratings, hospital anxiety and depression scale (HADS) scores and adverse events (AEs).

Results: Patients in the experimental group had significantly greater improvement in the change of weekly mean of the 24 hours average pain scores, BPI pain severity ratings ($P < 0.001$) and WOMAC scores ($P < 0.001$) at the study endpoint. A significantly greater percentage of patients in the experimental group rated PGI-I of ≤ 2 ($P = 0.021$) and ≥ 50% pain reduction ($P = 0.029$) at 24 weeks. There was no difference in the proportion of patients with ≥30% pain reduction, the HADS scores or frequency of AEs between the 2 groups.

Limitations: The effectiveness and safety were examined only up to 24 weeks after treatment, and we did not perform a long-term follow-up as most previous studies have. Optimum dosage of duloxetine, as well as different molecular-weight HA, should be investigated in future studies.

Conclusion: Patients receiving co-treatment with oral duloxetine and IA (HA+CS) injections experienced considerable improvement in pain and knee function compared to those who received an IA injection alone.

Key words: Pain management, co-treatment, duloxetine, intraarticular injection, knee osteoarthritis, hyaluronic acid, corticosteroid

Pain Physician 2024: 27:E45-E53

Osteoarthritis (OA) is the most common form of arthritis, affecting an estimated 302 million people worldwide, and is a leading cause of disability among older adults (1). Knee OA accounts for more than 80% of OA cases and has a marked increase in prevalence in the world (2). As the disease progresses, knee OA seriously affects its patients' quality of life and can often lead to disability, which places a huge economic burden on patients worldwide (2). Therefore, it is essential to develop effective treatments that can slow knee OA progression, relieve its symptoms, and postpone the need for joint replacement surgery.

As knee OA spans over decades of a patient's life, patients are likely to be treated with several different pharmaceutical and nonpharmaceutical interventions, often in combination (3). Current pharmacological treatments such as nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, etc. focus on symptomatic management. However, long-term pharmacologic treatments may increase the risk of adverse effects (4). Intraarticular (IA) injection therapies are an alternative form of treatment for knee OA. Corticosteroid (CS) and hyaluronic acid (HA) injections are often utilized for symptomatic relief of pain in knee OA (1,5-9). The society guidelines from the American College of Rheumatology/Arthritis Foundation (ACR) highlighted that IA glucocorticoid injections are strongly recommended for patients with knee OA, due to effective short-term outcome (1,10). The latest Osteoarthritis Research Society International guidelines published in 2019 recommended HA injections in individuals with knee OA (11). Studies have also shown that the combination of CS and HA in the management of knee OA provides superior symptomatic relief (7). As the frequency of injections is increased, the incidence of adverse reactions also increases (12,13). Against this background, an ideal conservative therapy that improves symptoms and tolerability of knee OA has been the focus of research.

The mechanism underlying the osteoarthritic pain is complicated. There is evidence that central sensitization contributes to the chronic pain associated with knee OA, and that dysfunction of the descending pain inhibitory pathway contributes, at least partly, to central sensitization (14,15). Duloxetine is a selective serotonin-norepinephrine reuptake inhibitor. Its effect of increasing serotonin and norepinephrine levels in the synaptic cleft in spinal and supraspinal pathways is thought to activate the descending pain inhibitory pathway, mainly at the dorsal spinal horn, resulting in pain reduction (14,16,17). The centrally acting analgesic effect of duloxetine supports the notion that duloxetine is effective in treating central sensitization, that contributes to chronic pain associated with knee OA. It has shown efficacy in the treatment of knee OA in several randomized, placebo-controlled studies, and is accompanied by an acceptable safety profile (4,14,16-20). However, to our knowledge, no trials have studied the outcomes of IA treatments combined with duloxetine for knee OA. Therefore, the aim of this study is to determine whether the co-treatment of oral duloxetine and an IA injection of CS and HA further relieves pain and improves physical function and quality of life in comparison to an IA injection of CS and HA alone, in patients with knee OA.

Methods

Trial Design

This study was designed as a prospective, randomized, open-label blinded endpoint (PROBE) study with a planned enrollment of 150 participants with symptomatic knee OA. All knee OA participants were randomly assigned to either the experimental group or the control group in a 1:1 ratio. The investigation was performed at Beijing Tiantan Hospital from October 2019 to December 2021. The study plan was approved by the Ethics Committee of Beijing Tiantan Hospital (KY 2019-086-02). The study protocol was registered at the ClinicalTrials.gov Web site before trial commencement (NCT04117893). This study was conducted in accordance with the World Medical Association's Declaration of Helsinki. There were no substantial changes to the main study protocol after the commencement of the recruitment process. The trial protocol has previously been published elsewhere (17). All patients signed the written informed consent prior to participation and had sufficient time to decide whether to participate in this study. All participants had the right to obtain all relevant information and were allowed to withdraw their consent or discontinue participation at any time point during the study. Patients did not receive any compensation for participating in this study. The confidentiality of participant records has been protected.

Study Population

Patients who met the following criteria were included: men and women aged 50-75 years who met the American College of Rheumatology clinical and radiographic criteria for the diagnosis of knee OA with knee pain (pain for ≥ 14 days of each month for ≥ 3

months before study entry, with a mean score of ≥ 4 on the 24 hour average pain score (0-10) using the daily average of ratings before participation); dissatisfaction with conservative treatment (NSAIDs, oral analgesic drugs, physical therapy); body mass index (BMI) < 40 kg/m^2; radiographic criteria including Kellgren-Lawrence grade II-III; knee stability; no knee deformity or lumbar spondylosis with radiculopathy; good cognition; ability to understand the study protocol; and willingness to participate. Patients were excluded if they had a prior synovial fluid analysis indicative of a diagnosis other than OA; had inflammatory arthritis, an autoimmune disorder, septic arthritis or any other concomitant disease (such as liver and kidney disease); had contraindications to duloxetine or had previously undergone duloxetine therapy; previous combined use of other drugs acting on the central nervous system (such as benzodiazepines); had metabolic diseases or anticoagulation therapy; history of allergy to any of the study medications; underwent invasive therapies of the knee within the past 6 months; and a history of knee arthroplasty or a current infection in the affected limb.

Study Interventions and Protocol

Patients in both groups received a single 3.5 mL IA injection of HA+CS [25 mg of HA (Artz Dispo, Seikagaku Co.) plus 10 mg of triamcinolone acetonide (TA)] and agreed to maintain their usual daily activities throughout the course of the study. Patients in the experimental group started with 30 mg duloxetine quaque die (QD) for one week and then titrated up to 60 mg duloxetine QD for 23 weeks. All patients underwent tapering after the completion of treatment to minimize discontinuation-emergent adverse events (AE). Patients who withdrew from the study after receiving duloxetine treatment for 2 or more weeks had to contact the study investigator to obtain discontinuation advice and entered a tapering phase (4,18). Concomitant rescue medication used by the patients, including acetaminophen and NSAIDs (the use of all other pain medications was prohibited) was allowed.

All procedures were conducted in an outpatient clinic and were performed by a trained physician. The procedure was performed using the inferolateral approach under ultrasound guidance and strict aseptic conditions. Local anesthetic wheals were placed at the injection sites for patient comfort. A syringe prefilled with HA and TA mixture was prepared prior to the injection. A 21-G needle (0.8·50 mm) was inserted into the joint capsule, and then, the syringe prefilled with the HA and TA mixture was inserted to administer the study solution.

Randomization and Blinding

Randomization was performed by permuted blocks. The allocation sequence was generated by an independent researcher before the inclusion of the first participant. After randomization, all patients were randomly assigned to either the experimental group [IA (HA+CS) injection combined with oral duloxetine] or the control group [IA (HA+CS)] in a distribution ratio of 1:1. One assessor was responsible for pre-trial evaluation of eligibility and another for post-intervention evaluation. To ensure blinding, patients were given clear instructions not to disclose which treatment they had received while being interviewed by the blinded assessors.

Outcome Measures

The primary objective of this study was to compare the efficacy of duloxetine combined with an IA (HA+CS) injection to an IA (HA+CS) injection alone on the reduction of pain severity as measured by the change in the weekly mean of the 24 hours average pain scores in patients with knee OA pain. This was reported in patients' diaries based on the 11-point Likert scale (an ordinal scale with 0 indicating 'no pain', and 10 indicating 'worst pain imaginable') at weeks 1, 2, 4, 8, 16 and 24 post-injection.

Secondary outcomes comprised of aspects including the proportion of patients with ≥ 30% (corresponding to moderate improvement) or ≥ 50% (corresponding to substantial improvement) reduction in weekly mean score in 24 hour average pain severity ratings from baseline to endpoint. The severity of pain and the interference of pain with function were measured by Brief Pain Inventory-Severity (BPI-S) and Brief Pain Inventory-Interference (BPI-I) items at 24 weeks. Additionally, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), consisting of 24 questions pertaining to the patient's knee condition on three subscales (pain, stiffness, and physical function), was evaluated at weeks 1, 2, 4, 8, 16 and 24 following the injection. Furthermore, at 24 weeks patients recorded global improvement from baseline using the Patient Global Impression Improvement (PGI-I), which ranged from one (very much better) to 7 (very much worse). Lastly, depression and anxiety was assessed at 24 weeks by hospital anxiety and depression scale (HADS) which included 14 items that were equally divided in two subscales: anxiety (HADS-A) and depression (HADS-D).

The safety and tolerability of treatment were assessed according to the incidence and type of AEs. Treatment-related AEs reported by patients were collected and evaluated at each visit. A treatment-related event was any event occurring for the first time or worsening in severity during treatment, compared to baseline. Follow-up evaluations were conducted by experienced research members who were blinded to the study.

Statistical Analysis

Data were analyzed with an intention-to-treat basis, that included all enrolled patients who were randomized. The last observation carried forward method was used for missing data. Statistical analysis was performed with SPSS version 22.0 (SPSS Inc). Measurement data is presented as mean ± standard deviation, and the data between different groups was compared with a t-test for 2 independent samples. Dichotomous variables were tested with the chi-squared test. Moreover, a repeated measure analysis of variance was performed to compare the weekly mean 24 hour average pain score and the WOMAC score at different time points. All statistical analyses were performed by statisticians who were blinded to the entire allocation and intervention process.

Results

Patient Disposition and Baseline Characteristics

A total of 227 patients were screened for eligibility, out of which, 50 did not meet the inclusion criteria, 27 declined participation, and 150 patients were enrolled and randomized to either the experimental or the control group (Fig. 1). Most patients (82%) completed the 24-week study period: 62 (82.7%) in the experimental group and 61 (81.3%) in the control group. Reasons for discontinuation are shown in Fig. 1. Data was analyzed with an intention-to-treat basis, including the patients who had dropped out prior to the study completion. As shown in Table 1, the patients' demographic characteristics were similar to baseline. Most patients (60.7%) had previously taken oral analgesics, without satisfactory effect, in both treatment groups.

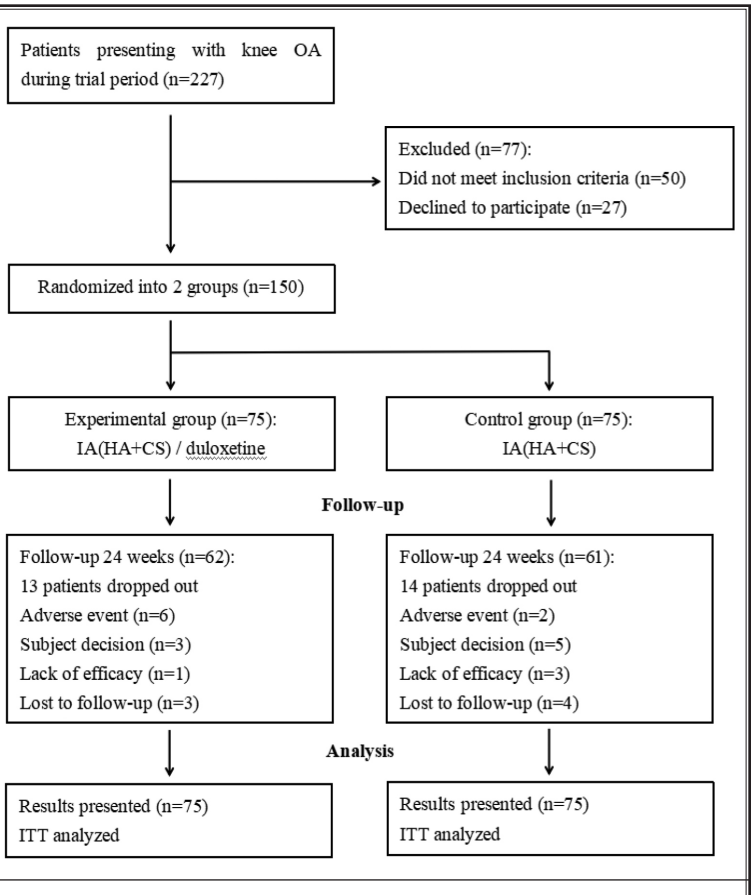

Fig. 1. *Flow diagram of the present study.*

Efficacy

Primary Outcomes

As shown in Table 2, the weekly mean 24 hour average pain score (on the 11-point Likert scale) tended to favor the experimental group at 24 weeks follow-up. Mean changes in the weekly mean 24 hour average pain scores over time are shown in Fig. 2. There were significant differences between the 2 groups at all time points ($P < 0.05$) except for week one. Following an initial pain reduction in the first 4 weeks, the pain scores in both groups increased; however, the extent of pain in the experimental group increased more gradually compared to that in the control group. Ultimately, the weekly mean 24 hour average pain score in both groups were markedly decreased at 24 weeks when compared to the baseline ($P < 0.05$).

Response Rate

At 24 weeks, the proportion of patients with ≥ 30% reduction in weekly mean 24 hour average pain scores showed no significant differences between the experimental (65.3%) and control (52%) group (*P* = 0.097). However, the proportion of patients with ≥ 50% reduction was higher in the experimental (46.7%) than that in the control (29.3%) group (*P* = 0.029).

BPI-S and BPI-I

There were no statistically significant differences in the outcome of BPI-S and BPI-I at baseline between the 2 groups (data not shown). As shown in Table 3, most BPI-S and BPI-I items tended to favor the experimental group at 24 weeks, with a significant difference between the 2 groups; except for the items normal work, relationships with people, and sleep pattern.

WOMAC Score

The WOMAC pain, stiffness, physical function, and total score were markedly decreased in both groups throughout 24 weeks follow-up period, compared to baseline. In terms of pain, physical function, and total scores, better outcome was observed in the experimental group after 2 weeks (*P* < 0.05). While the experimental group had significant improvements in WOMAC stiffness after 4 weeks. The WOMAC score over time is shown in Fig. 3.

PGI-I

At 24 weeks, there were 58 (77.3%) and 49 (65.3%) patients with PGI-I ≤ 3 (at least a little better) in the experimental and control group respectively, showing no significant difference (*P* = 0.104). However, the experimental group (53.3%) had a significantly greater percentage of patients who rated PGI-I ≤ 2 (at least much better) than the control group (34.7%) (*P* = 0.021).

HADS

At 24 weeks, the HADS-A subscale scores were 4.2 (2.7) and 4.4 (3.2) in the experimental and control group respectively (*P* = 0.722). Meanwhile the HADS-D subscale scores were 4.4 (3.1) and 4.8 (2.9) in the experimental and control group respectively (*P* = 0.462). Thus, no significant differences were found between the 2 groups.

Table 1. *Baseline and demographic characteristics of patients with knee OA.*

	Experimental group (n = 75)	Control group (n = 75)	*P* value
Age (years)	64.0 (6.0)	62.3 (7.2)	0.099
Gender (women/men)	28/47	36/39	0.187
Height (cm)	160.4 (14.6)	159.3 (10.3)	0.604
Weight (kg)	66.0 (15.0)	65.4 (12.2)	0.786
BMI (kg/m^2)	25.4 (3.4)	25.7 (4.0)	0.645
KL grade (II/III)	18/57	14/61	0.425
Analgesic use, n (%)	47 (62.7)	44 (58.7)	0.616
Comorbidities, n (%)	43 (57.3)	47 (62.7)	0.505
Pain duration (years)	6.4 (2.8)	6.7 (3.6)	0.544
BPI average pain score	6.1 (1.6)	6.2 (1.8)	0.926
24-h average pain severity[a]	6.1 (1.3)	6.3 (1.6)	0.433
Total WOMAC score	56.0 (11.8)	55.4 (12.5)	0.595
WOMAC pain score	11.9 (4.6)	12.2 (4.4)	0.685
WOMAC stiffness score	4.3 (2.6)	4.4 (2.8)	0.810
WOMAC function score	39.8 (10.3)	38.8 (11.5)	0.576
HADS-A subscale	4.9 (3.0)	5.3 (3.0)	0.418
HADS-D subscale	4.8 (2.7)	5.6 (3.2)	0.073

Measurements are given as the mean (SD);
BMI: body mass index; KL: Kellgren-Lawrence; BPI: Brief Pain Inventory; WOMAC: Western Ontario and McMaster University Osteoarthritis Index; HADS-A: hospital anxiety and depression scale - anxiety; HADS-D: hospital anxiety and depression scale - depression.
a Weekly mean of the 24 hours average pain (Likert scale)

Table 2. *Summary of results for weekly mean 24-h average pain scores.*

	Experimental group (n = 75)	Control group (n = 75)	*P* value	*P* value		
				Group	Time	Group × Time
Baseline	6.1 (1.3)	6.3 (1.6)	0.433	< 0.001	< 0.001	0.003
1 week	3.2 (1.8)	3.6 (1.8)	0.168			
2 weeks	2.1 (1.5)	3.1 (2.0)	0.001			
4 weeks	1.9 (1.3)	3.0 (2.0)	< 0.001			
8 weeks	2.0 (1.3)	3.4 (1.5)	< 0.001			
16 weeks	2.4 (1.5)	4.1 (2.2)	< 0.001			
24 weeks	2.5 (0.9)	4.3 (2.4)	< 0.001			

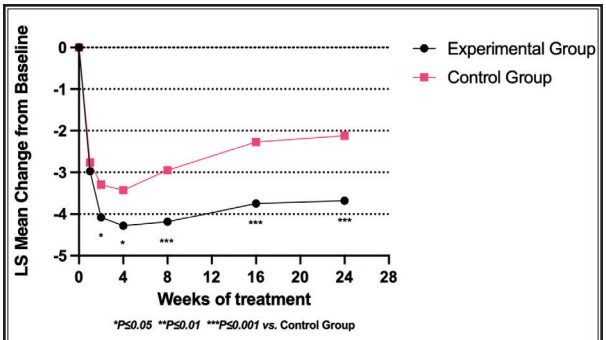

Fig. 2. *Mean change in the weekly 24 hour average pain score from baseline to each time points.*
LS: Likert scale

Table 3. *BPI-S and BPI-I scores in both groups.*

	Experimental group		Control group		*P* value
	n	Endpoint	n	Endpoint	
BPI-S					
Average pain	75	2.5 (1.1)	75	4.3 (2.5)	< 0.001
Worst pain	75	3.5 (1.8)	75	5.1 (2.0)	< 0.001
Least pain	75	1.9 (1.3)	75	3.2 (2.0)	< 0.001
Pain right now	75	2.1 (1.5)	75	3.5 (1.8)	< 0.001
BPI-I					
General activity	75	2.6 (1.6)	75	3.6 (2.4)	0.003
Mood	75	2.3 (1.7)	75	2.9 (1.6)	0.027
Walking ability	75	2.9 (1.6)	75	3.6 (2.1)	0.017
Normal work[a]	46	2.5 (1.8)	50	2.6 (1.5)	0.767
Relationships with people	75	2.1 (1.5)	75	2.5 (1.4)	0.084
Sleep	75	1.9 (1.5)	75	2.1 (1.4)	0.405
Enjoyment of life	75	2.0 (1.4)	75	2.6 (1.7)	0.021

Measurements are given as the mean (SD);
BPI-S: Brief Pain Inventory-Severity; BPI-I: Brief Pain Inventory-Interference
a Some elderly patients did not work, and the subscale was not evaluated.

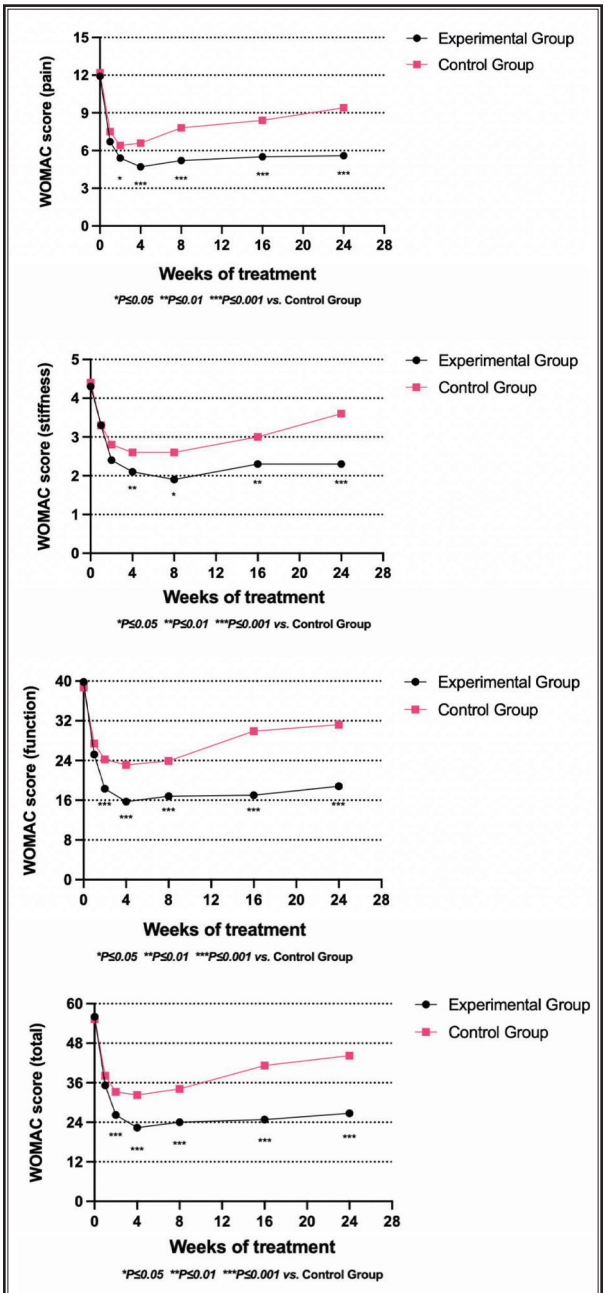

Fig. 3. *The WOMAC score from baseline to each time points.*

Concomitant Rescue Medication

Although the percentage of patients using oral rescue medications was lower in the experimental group (30.7%), the difference was not statistically significant compared to the control group (38.7%) ($P = 0.303$).

Adverse Events

No death occurred during the study; however, a total of 3 (2.0%) patients experienced serious adverse events (SAEs), including one (1.3%) patient in the experimental group who suffered a malleolus fracture due to a fall and 2 patients (2.7%) in the control group who developed coronary artery disease and bronchitis. All SAEs were not related to the study drug or treatment and had been resolved by the end of the study. A total of 77 (51.3%) patients experienced one or more treatment-emergent adverse events (TEAEs) during the treatment phase. Forty-three (57.3%) patients in the experimental group reported

81 TEAEs, while 34 (45.3%) patients in the control group reported 52 TEAEs ($P = 0.142$). AEs which occurred in 3% or more of the overall intention-to-treat (ITT) population are presented in Table 4. Constipation ($P = 0.013$), nausea ($P = 0.028$), fatigue ($P = 0.039$) and dry mouth ($P = 0.009$) occurred more commonly in the experimental group. The most common TEAEs in both groups was arthralgia. Most TEAEs were considered mild or moderate in severity. No clinically relevant differences in vital signs between the two groups were noted. Although more patients in the experimental group (n = 6) had dropped out due to adverse events than those in the control group (n = 2), the difference was not statistically significant ($P = 0.267$).

Table 4. *Adverse events with ≥ 3% incidence occurring during the study.*

Adverse events n (%)	Experimental group (n = 75)	Control group (n = 75)	*P* value
Constipation	7 (9.3)	0 (0)	0.013
Nausea	9 (12.0)	2 (2.7)	0.028
Dizziness	5 (6.7)	2 (2.7)	0.439
Fatigue	8 (10.7)	1 (1.3)	0.039
Diarrhea	5 (6.7)	2 (2.7)	0.439
Insomnia	4 (5.3)	2 (2.7)	0.677
Dry mouth	9 (12.0)	1 (1.3)	0.009
Arthralgia	11 (14.7)	13 (17.3)	0.656
Headache	3 (4.0)	6 (8.0)	0.492
Joint swelling	5 (6.7)	8 (10.7)	0.384
Injection site pain	6 (8.0)	8 (10.7)	0.575
Joint stiffness	5 (6.7)	4 (5.3)	1.000
Back pain	4 (5.3)	3 (4.0)	1.000

Discussion

As far as literature is concerned, this is the first study to compare the outcomes of oral duloxetine combined with an IA injection compared to an IA injection alone in patients with knee OA. In this study, we found that, compared to those who received an IA injection alone, patients receiving co-treatment with oral duloxetine and an IA (HA+CS) injection experienced considerable improvements in pain and knee function with acceptable AEs, suggesting that this is a promising treatment option.

In this study, we found a marked reduction in weekly mean 24 hour average pain score (Likert scale) in both groups from baseline to end-point, and the pain score tended to favor the outcome of oral duloxetine combined with an IA injection at all time points except at week one. Maximum pain reduction was observed at week 4 in the 2 groups, and then the pain sore was maintained at a similar level in the experimental group throughout the 24-week study period but increased over time in the control group. This difference in pain scores between the 2 groups may be attributed to the prescription of oral duloxetine. At one week, CS mainly provided pain relief in both groups due to its rapid anti inflammatory effect. During this period, the dose of duloxetine used in the experimental group was only 30 mg QD, which may have led to insignificant difference in pain reduction between the 2 groups due to its limited clinical effect. After 4 weeks, the pain score increased in the control group as the CS metabolized, while HA played a major role in pain control, and this effect may have lasted beyond week 8. In contrast, duloxetine could reduce pain scores constantly for 24 weeks and the improvement was sustained with continued drug administration (4,16,18). Therefore, although pain reduction in the experimental group decreased mildly as the effect of CS and HA subsided, the pain score remains significantly lower than that in the control group.

In our study, the addition of oral duloxetine therapy could have possibly improved pain relief due to the following reasons: (1) the multimodal analgesia reduced central and peripheral pain sensitization; (2) the depression and/or anxiety symptoms caused by long-term pain and functional disability was relieved, which could have also contributed to pain reduction. In the present study, the baseline mean HADS-A and HADS-D scores were less than 7, which means that most patients had no depression or anxiety before treatment. In the same way, no significant differences in HADS-A and HADS-D score were found between the two groups at the study endpoint. Therefore, we believe that the effect of oral duloxetine on the pain relief can possibly be directly attributed to its analgesic effect as opposed to its antidepressant effect.

Duloxetine combined with an IA injection also demonstrated superiority over an IA injection alone on most secondary efficacy measures, providing significant evidence for the efficacy of duloxetine in improving pain and overall function in patients with knee OA. Our study found statistically significant differences between groups with regards to the 50% response rate, BPI-I, BPI-S (except for normal work, relationships with people, and sleep pattern), and percentage of PGI-I ≤ 2 (very much better) at the final follow-up, while the outcomes such as 30% response

rate and percentage of PGI-I ≤ 3 (much better) showed no significant differences. This means that both the treatment regimens are effective in patients with knee OA, but this combination therapy can lead to a better clinical outcome. Although an IA injection alone relieves less pain, there were no differences in some items of BPI-S scale such as normal work, relationships with people, and sleep pattern between the 2 groups; perhaps because patients over the age of 50 have lower knee functional requirement for these daily activities. Similarly, this study demonstrates significant improvement on WOMAC scores in both the groups compared to the baseline. However, the WOMAC scores decreased more significantly in the experimental group, which maintained throughout the 24-week study period. Most WOMAC scores including the total score as well as the pain and function subscales showed significant differences between the two groups after week 2, while significant difference was found in stiffness subscale only after week 4. Therefore, the effect of duloxetine on knee stiffness remains controversial. Although many studies have found that duloxetine is effective in improving stiffness, some previous studies have reported that it has no effect on treating joint stiffness compared to placebo (2,4,16,18,21). In the present study, although delayed, patients in the experimental group eventually experienced significant improvement in stiffness. Therefore, we believe that the addition of oral duloxetine to CS and HA injections can also be considered beneficial for joint stiffness, but requires a longer treatment duration compared to pain relief.

Several studies have reported that both IA (HA+CS) injections and duloxetine are safe choices for the treatment of knee OA (4,14,16,18,22-25). The incidence of AEs from HA+CS injections ranges from 17% to 62%, and the most common AEs include arthralgia, knee discomfort, joint stiffness, and joint effusion (22-24). Most of these symptoms were mild to moderate (22). Meanwhile the incidence of AEs of duloxetine were reported to range from 41.8% to 51%, and the most common AEs include dry mouth, constipation, somnolence, nausea, dizziness, decreased appetite, and insomnia (4,14,16,18,26). To our knowledge, this is the first to report the safety of combination therapy with IA (HA+CS) injections and oral duloxetine. We found that patients in the experimental group suffered some minor duloxetine-related AEs such as constipation, nausea, fatigue, and dry mouth, which are similar to those reported in previous studies of duloxetine (4,14,16,18). However, there were no significant differences in the incidence of TEAEs between the treatment groups. In addition, AEs related to IA injections were similar between the 2 groups, indicating that duloxetine did not increase the potential risk associated with IA (HA+CS) injection. Therefore, the combination therapy with oral duloxetine and HA+CS injections is a safe and effective strategy for knee OA treatment.

Limitations

There are several limitations to this study. First, we did not perform a long-term follow-up as most previous studies have done. The effectiveness and safety were examined only up to 24 weeks after treatment. Further study should be conducted to evaluate the long-term effects of this treatment modality. Second, low molecular-weight (MW) HA was used in the present study; it is reported that high MW cross-linked HA may provide better results (17,23). Further investigation is necessary to determine the effects of duloxetine when combined with different MW HA. Third, duloxetine was prescribed for patients in the experimental group at a fixed dosage. The optimum dosage of duloxetine for pain relief should be further studied.

Conclusion

In summary, both oral duloxetine combined with IA HA+CS) injections and IA (HA+CS) injections alone are effective therapies for patients with knee OA. Patients who received co-treatment with oral duloxetine and IA injections experienced considerable and sustained improvements in pain and knee function with acceptable AEs compared to those who received the IA injection treatment alone.

Author Contributions

DYL performed the data analysis and wrote the first draft of the manuscript. RH and LM did all preprocessing data analyses. ZGZ and CMZ contributed to data collection. All authors discussed the results and commented on the manuscript. FL has given final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. FL is responsible as corresponding author.

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