Randomized Trial

Prolozone M Therapy's Analgesic Efficacy for Managing Moderate-to-Severe Knee Osteoarthritis: A Randomized, Double-Blind, Placebo-Controlled Trial

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

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 article.

Article received: 01-29-2026
Revised article received: 04-17-2026
Accepted for publication: 05-20-2026

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Background: Knee osteoarthritis is one of the most common disabling joint diseases in India. Nonsurgical management remains the only option for patients who are unwilling to undergo or unable to afford total knee arthroplasty.

Objective: Our study's primary objective was to compare the analgesic efficacy of intraarticular injection of either a combined hypertonic dextrose, ozone, and magnesium injectate with an injectate of corticosteroid only in patients with moderate-to-severe knee osteoarthritis. A third group received an intraarticular saline injection.

Study Design: Prospective, randomized, double-blind, placebo-controlled study

Setting: Pain medicine clinic at Sri Madhusudan Sai Institute of Medical Sciences and Research, a tertiary care medical college in the Republic of India.

Methods: Patients were randomly assigned to one of 3 groups (combined hypertonic dextrose, ozone, and magnesium; corticosteroid; or saline). Patients and the clinicians performing the injections were blinded to the treatment allocation. All study patients had moderate-to-severe primary osteoarthritis of the knee (a Kellgren Lawrence Grading Scale score of 3 or 4). They received a total of 3 intraarticular treatments—one every 3 weeks. Patients and follow-up assessors were both blinded. Follow-ups were conducted at 3, 6, 12, and 24 weeks post the first injection. The primary outcome criterion was the change from baseline to 24 weeks post the first injection in the Western Ontario and McMaster Universities Osteoarthritis Index A (pain) subscore.

Results: A total of 180 patients with a Kellgren Lawrence Grading Scale score of 3 or 4 were randomly assigned. Baseline characteristics were similar. When compared to corticosteroids, patients in the Prolotherapy M Group had statistically significant greater improvements in their Western Ontario and McMaster Universities Osteoarthritis Index A (pain) subscore at 24 weeks post the first injection (mean, -2.3 [98.3% CI, -3.8 to -0.8], $P < 0.001$, d 0.88). Radiological images showed improvement at 24 weeks in the Prolotherapy M Group when compared to baseline.

Limitation: This was a single-center study with a limited follow-up period.

Conclusion: Our placebo-controlled study showed that 3 injections of combined hypertonic dextrose, ozone, and magnesium is safe and efficacious in providing statistically significant, clinically relevant analgesia at 24 weeks post the first injection, with a significant difference vs corticosteroid only injections. There were early signs of chondroprotection with Prolozone M therapy.

Key words: Knee osteoarthritis, prolozone, intraarticular, chondrogenesis, corticosteroids

Pain Physician 2026: 29:E635-E644

Knee osteoarthritis (KOA) is a chronic, progressive degenerative disease of the entire joint. It affects the articular cartilage, subchondral bone, ligaments, capsule, and synovium (1-3). Its pathophysiology is likely to involve a combination of mechanically driven processes and inflammation (1,2). Moderate-to-severe KOA causes significant pain, distress, and an impaired quality of life. In India, KOA is among the most common disabling joint diseases with a reported prevalence of 28.7% (4,5). Risk factors include aging and heavy physical occupational activity, a required livelihood for many living in rural India.

Total knee arthroplasty is the current best practice for managing advanced KOA (6). However, it is an expensive undertaking. In 2023, only 150,000 total knee arthroplasties were performed in India despite millions who have advanced KOA (7). Patients in rural India often struggle to afford this procedure. Additionally, restrictions on deep squatting following total knee arthroplasty are seen as a hindrance in the rural population (8,9).

Nonsurgical options include intraarticular injections with corticosteroids, platelet-rich plasma, hypertonic dextrose (prolotherapy), or ozone gas (10-15). Currently, an intraarticular corticosteroid injection is the recommended intervention by most international orthopedic and rheumatology associations, although there is a potential for chondrotoxic and osteoporotic adverse effects (10,11,16). However, none of these interventions have been shown to mitigate the progression of articular cartilage deterioration.

Intraarticular ozone therapy provides short-term analgesia with a favorable safety profile (14,15). Additionally, intraarticular ozone therapy is reported to improve tissue oxygenation, inhibit inflammatory mediators, and reduce oxidative stress, thereby offering a protective immunomodulatory effect on articular cartilage (14,17-19). Hypertonic dextrose prolotherapy (HDP) involves periarticular injections that target intraarticular and extraarticular pain generators, are cost-effective, and have an excellent safety profile with potential regenerative benefits (20,21). However, HDP only provides short-term analgesia for KOA (20–22). HDP has been hypothesized to stimulate healing of chronically injured periarticular tissue by increasing inflammatory cytokines, stimulating the release of growth factors that favor soft tissue healing, thereby causing volume expansion effects in local tissue (20,21,23,24).

Animal studies have shown that an intraarticular injection of magnesium can attenuate cartilage degeneration progression (25). Additionally, magnesium enhances serum levels of antioxidants like superoxide dismutase and could antagonize inflammation by blocking N-methyl-D-aspartate (NMDA) receptors (26).

There have been no studies to date that have evaluated the effectiveness of combined hypertonic dextrose, ozone, and magnesium (Prolozone M) therapy. Our hypothesis is that by combining the regenerative, immunomodulatory, and analgesic properties of hypertonic dextrose, ozone gas, and magnesium, durable analgesia and improved function could be provided to patients with moderate to severe knee osteoarthritis. We also hypothesize that Prolozone M therapy may prevent further deterioration and potentially enhance repair of the knee joint.

Methods

Ethics

Our study was performed in accordance with the principles of good clinical practice guidelines. It was approved by the Institutional Ethics Committee at Ramaiah Medical College Ethics Committee (MSRMC/EC/AP-01/10-2023). It was registered at the Clinical Trials Registry of India (CTRI) and given the registration number CTRI/2023/11/059765. Written, informed consent was obtained from all patients.

Study Design

All study patients were from rural India and were not fluent in English. At the screening visit, they provided their written, informed consent. A weight-bearing radiographic assessment of the index knee was performed. A baseline 30-second sit-to-stand test was completed. We collected the patients' demographic data and their relevant medical history; they were then randomly assigned to one of 3 groups.

An independent assessor, unaware of each patient's group allocation, assisted the patient in completing the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index outcome measure and the Patient Global Impression of Change (PGIC) measure at the 24-week follow-up. Safety assessments, usage of concomitant medications, and vital signs were recorded at each follow-up. Follow-ups were conducted at 3, 6, 12, and 24 weeks post the first intraarticular injection.

Patient Selection

In order to be included in our study, patients had to meet the American College of Rheumatology criteria for osteoarthritis (knee pain for most days of the previous month and an osteophyte or osteophytes at the joint margin visible on x-ray) (27).

The main inclusion criteria were age 40 years or greater; a diagnosis of primary osteoarthritis of the index knee; radiographic evidence of moderate to severe osteoarthritis in the medial and/or lateral tibiofemoral compartment; and continued pain in the index knee despite conservative management. Clinical severity was defined as a mean WOMAC-A subscore of 1.5–3.5 (28,29). Radiological severity was based on the criteria defined by the Kellgren Lawrence Grading Scale, which grades KOA into 0–4 grades (30). Our study required the patient to have a grade of either 3 or 4.

The main exclusion criteria were secondary osteoarthritis; a Kellgren Lawrence Grading Scale grade of one or 2; and having an intraarticular injection of corticosteroids into the index joint within 3 months before screening.

Intervention Arms and Randomization

All patients were randomly assigned to one of 3 groups—Prolozone M Group, Corticosteroid Group, or Saline Group—by a computer-generated block randomization protocol prepared by an independent statistician. The randomization schedule was secured and was inaccessible to the members of the research team. All interventions were performed under real-time ultrasound guidance. Arthrocentesis was performed if there was joint effusion prior to the intervention.

Power and Sample Size

The sample size was based on comparing the primary outcome—the WOMAC-A subscore at the end of the study—between groups (28,29). The study was powered to detect a minimal clinically important difference of 0.44 units between groups; the standard deviation was assumed to be 0.7 units (31). The analysis used an Analysis of Covariance (ANCOVA) approach, with the WOMAC-A subscore at baseline included as a covariate. A moderate correlation of 0.4 between baseline and final outcome scores was assumed. To allow for a Bonferroni adjustment to be implemented at the analysis stage, a significance level of 1.7% (5%/3) was assumed. With 80% power, it was calculated that 45 patients per group (135 in total) were required. A dropout rate of 25% was assumed. Therefore, we recruited a total of 180 patients (60 per group).

Interventions

Prolozone M Injections

Extraarticular HDP injections: Seven tender spots around the knee joint were injected with 2 mL of 12.5% dextrose solution mixed with 0.2% bupivacaine. The injection sites were based on a modified treatment protocol first described by Sert, et al (21). The injection sites included the medial collateral ligament (femur and tibia attachment points), the lateral collateral ligament (femur and fibula attachment points), posterior muscles (hamstrings and gastrocnemius), and pes anserinus ligament-bone attachment point.

Intraarticular dextrose, ozone and magnesium injections: Under real-time ultrasound guidance, 8 mL of 12.5% dextrose mixed with 500 mg of 0.25% magnesium sulphate and 1 mL of 2% lidocaine was injected into the suprapatellar recess of the knee joint. The needle was left in situ, 10 mL of 70 µg/mL of ozone was injected, and the needle was removed.

Intraarticular Corticosteroid Injections

Under real-time ultrasound guidance, a 30 mg depot of methylprednisolone and 1 mL of 2% lidocaine diluted in 8 mL of distilled water were injected into the suprapatellar recess of the knee joint. Thereafter, 7 sham injections (0.5 mL of distilled water) were performed around the knee.

Intraarticular Saline Injections

Under real-time ultrasound guidance, 8 mL of normal saline was injected into the knee joint. Thereafter, 7 sham injections (0.5 mL normal saline) were performed around the knee.

All interventions were repeated at 3 and 6 weeks post the first injection. The patients were taught 2 exercises to enhance the strength of their quadriceps and hamstring muscles. They were advised to perform the exercises daily. They were also trained to correctly perform the 30-second sit-to-stand test prior to their follow-up assessments. If needed, rescue analgesia included oral tramadol 50 mg and oral acetaminophen one g.

All patients were reviewed at follow-up weeks 3, 6, 12, and 24 in our outpatient clinic. An independent assessor unaware of the patient's group allocation assessed them.

At 24 weeks, following the final assessment, an x-ray of the index joint was repeated in 30 patients from the Prolozone M Group to assess any change in the knee joint. An orthopedic surgeon, unaware of

the patient's group allocation, assessed the x-ray. The weight-bearing x-ray was evaluated for any change in joint space, osteophytes, and subchondral sclerosis. The assessment outcome was graded as improvement, nonprogression, or deterioration.

Efficacy Analyses

The primary efficacy analysis was performed on the intention-to-treat population (all randomly assigned patients). Data from all follow-up timepoints were analyzed together using a linear mixed model. Timepoint and study group were included as fixed factors, along with the interaction between these 2 variables. The interaction term allowed the group differences to be quantified at each timepoint. The equivalent score at baseline was included as a covariate in the analysis. Patient was included as a random effect. For outcomes measured at a single timepoint, ordinal outcomes were compared between the 3 groups using the Kruskal-Wallis test and between pairs of groups using the Mann-Whitney U test. The χ^2 test was used for binary outcomes. These analyses included the differences from baseline at 24 weeks in total WOMAC, PGIC, and the responders to treatment per the Outcome Measures in Rheumatology, Osteoarthritis Research Society International (OMERACT-OARSI) responder criteria (30). To allow for multiple group comparisons, P values from the analyses were given a Bonferroni adjustment (by a factor of 3 to allow for 3 comparisons per outcome). For the same reasons as multiple testing, 98.3% CIs are reported (where appropriate) instead of 95% CIs.

Results

From December 2023 through February 2025, a total of 207 patients were enrolled at a single tertiary care medical college hospital located in rural India. There were 27 screening failures; 180 patients were randomly assigned to one of 3 groups (Prolozone M, Corticosteroid, and Saline). All 180 patients were included in the safety population. A total of 151 patients (84%) completed the study. Nine patients assigned to the Corticosteroid Group (15%) and the Saline Group (15%), as well as 11 patients in the Prolozone M Group (18%), did not complete the study schedule (Fig. 1). Table 1 shows baseline and demographic parameters of the 3 groups. Prolozone M group patients were younger compared to the other groups. There were no other differences between the treatment groups.

The primary outcome was the change in the WOMAC-A subscore at 24 weeks post the first injection. The treatment effect with Prolozone M was both clinically and statistically significantly superior to the corticosteroid as well as the placebo intervention (Table 2, Fig. 2). Prolozone M injections resulted in an estimated change from baseline to 24 weeks of 6.9 and a mean percentage change in WOMAC-A subscore from baseline of 49%. Patients in the Corticosteroid Group had an estimated change in their WOMAC-A subscore from baseline to 24 weeks of 4.0 and a mean percentage change from baseline of 30%. Patients in the Saline Group had an estimated change in WOMAC A sub score from baseline to 24 weeks of 4.7 and a mean percentage change from baseline of 34%. The estimated treatment difference between the Prolozone M and the 2 comparator groups at 24 weeks was statistically significant (Table 2).

The secondary outcomes, including total WOMAC score, PGIC score, and 30-second sit-to-stand showed statistically significant differences between the 3 groups, favoring Prolozone M at the 24-week follow-up (Table 3, Fig. 3). All secondary outcomes, including the WOMAC-A subscore did not show statistically significant differences at the 3-, 6-, and 12-week follow-ups (Table 4).

There were no serious adverse effects related to the study procedure. The overall frequency of adverse effects was comparable between the three treatment arms (Table 1). The most common adverse effect was a flare-up in knee pain following the study treatment. The median (interquartile range) flare-up was longer in the Prolozone M Group (3 [2–4]) compared to the Corticosteroid Group (1 [0–3]) and the Saline Group (2 [1–4]).

In a 30-patient subset of the Prolozone M Group, radiological changes at 24 weeks post the first injection, when compared to the baseline, assessed by a weight-bearing x-ray of the index knee, showed signs of improvement (12/30, 40%) and nonprogression (9/30, 30%) (Table 5).

The OMERACT-OARSI responder analysis at 24 weeks following the first injection showed a statistically significant difference between the 3 groups (Table 5) (32). At 24 weeks, 45 patients (75%) in the Prolozone M Group, 30 patients in the Corticosteroid Group (50%), and 32 patients (53%) in the Saline Group were responders ($P = 0.02$ [Prolozone M Group vs Corticosteroid Group] and $P = 0.04$ [Prolozone M Group vs Saline Group]).

Discussion

Our study shows that combined hypertonic dextrose, ozone, and magnesium (Prolozone M) therapy is effective for providing statistically significant and clinically relevant improvement in pain, as measured by WOMAC subscore A at 24 weeks post the first injection when compared to intraarticular injections of corticosteroid and saline. To the best of our knowledge, this is the first study evaluating Prolozone M therapy in moderate to severe osteoarthritis of the knee. Effect size measures efficacy between clinical interventions. At 24 weeks, the effect size of Prolozone M compared to both corticosteroid and saline, as measured by Cohen d, was large (0.88 and 0.77, respectively). The OMERACT-OARSI responder analysis also favored Prolozone M (Table 5).

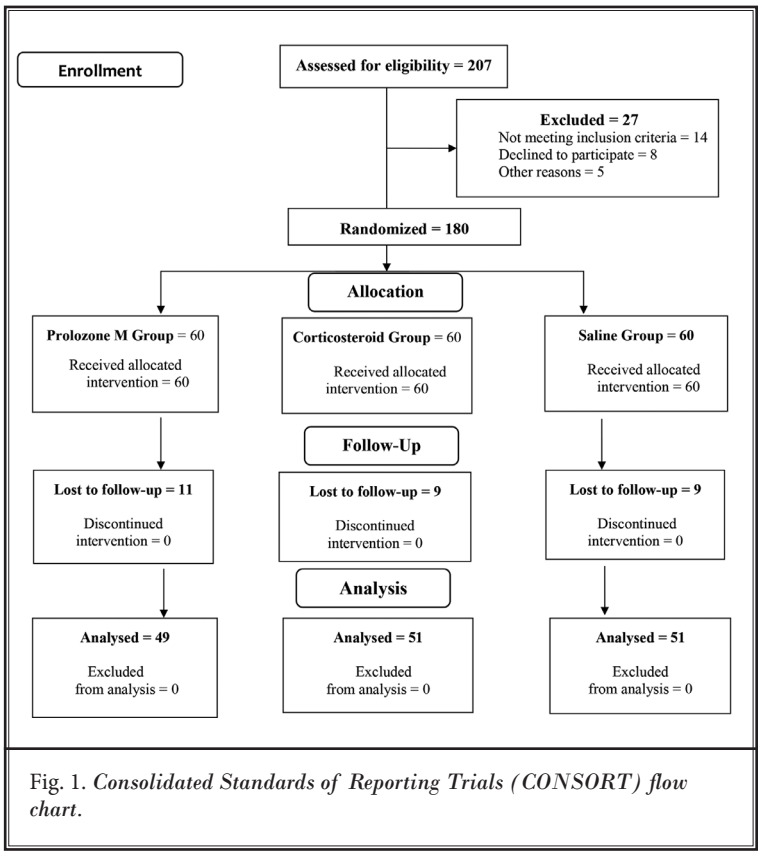


Fig. 1. *Consolidated Standards of Reporting Trials (CONSORT) flow chart.*

KOA is a multi-tissue disease, involving nearly all components within the joint. In KOA, meniscal degeneration, subchondral bone sclerosis, synovitis, and articular cartilage degeneration contribute to the metabolic and immune dysfunction that underlie OA pathology (1-3). Prolozone M therapy targets the pathophysiology of KOA at multiple levels. Periarticular injection of HDP can target both intra- and extraarticular pain generators (20,21). HDP potentiates affected periarticular tissue healing by increasing cytokine expression and releasing growth factors (20,21,23,24).

Controlled administration of ozone gas produces an initial acute oxidative stress followed by an antioxidant effect (33). The oxidative stress promotes oxidative preconditioning, while the subsequent antioxidant effect protects against further tissue damage. Administering intraarticular ozone is reported to dissolve in the synovial fluid, generating reactive oxygen species as well as lipid oxidation products. These in turn attenuate synovial inflammation while promoting proliferation of chondrocytes and fibroblasts (14).

Administering intraarticular magnesium is reported to provide analgesia following knee arthroscopy (34). In addition, magnesium can attenuate the progression of KOA by promoting the synthesis of cartilage matrix and suppressing synovial inflammation (25,35). Magnesium-based implants can promote the healing of bone fractures (36). Magnesium is also reported to enhance antioxidant levels as well as antagonize the expression of inflammatory mediators (26,37). We hypothesized that combining HDP, magnesium, and ozone was likely to have a synergistic effect when injected into the knee joint.

Advanced KOA is associated with a high economic burden. This is primarily due to disability as well as recurrent treatment expenses incurred by patients (38). The burden of KOA, especially in rural India, is substantial and is expected to increase with the rise in the aging population (39).

There was a large placebo effect in our study. The positive effect with intraarticular saline injection is well established (40). The suggested mechanisms include the therapeutic effect of arthrocentesis and possible washout of nociceptive proinflammatory cytokines. Despite the large placebo effect, Prolozone M was significantly superior to both corticosteroid and saline in the primary outcome and several of the secondary outcomes.

It is interesting to note that secondary outcomes at post first injection weeks 3, 6, and 12 were not significantly different between the 3 groups. This is possibly explained by the waning of the analgesic effects

of corticosteroids and normal saline. However, there is a possibility that the regenerative effect of Prolozone M possibly develops over time. An extended follow-up at 52 weeks may have shown an enhanced clinical and radiological benefit.

A subset of patients in the Prolozone M Group showed features suggestive of radiological improvement and OA nonprogression of the index joint at 24 weeks follow-up (Figs. 4). However, it must be noted that fluoroscopy is not as sensitive as magnetic reso-

Table 1. *Baseline characteristics.*

	Prolozone M Group (n = 60)	Corticosteroid Group (n = 60)	Saline Group (n = 60)
Age	59.4 (9.2)	62.3 (8.7)	59.8 (8.5)
Gender			
Men	23 (38%)	26 (43%)	22 (37%)
Women	37 (62%)	34 (57%)	38 (63%)
BMI	27.9 (5.1)	27.8 (5.1)	26.9 (3.9)
KOA Grade			
3	23 (38%)	28 (47%)	32 (53%)
4	37 (62%)	32 (53%)	28 (47%)
Side			
Left	26 (43%)	34 (57%)	26 (43%)
Right	34 (57%)	26 (43%)	34 (57%)
Employment			
No	3 (5%)	6 (10%)	6 (10%)
Yes	56 (95%)	54 (90%)	54 (90%)
Flare-up (days)	3 (2–4)	1 (0–3)	2 (1–4)
Contralateral knee Pain			
No	13 (22%)	15 (25%)	11 (18%)
Yes	46 (78%)	45 (75%)	49 (82%)
Duration pain (years)	5 (2–8)	3 (2–5)	3 (1–7)

Data expressed as mean (SD), median (interquartile range) or number (percentage). KOA, knee osteoarthritis; BMI, body mass index (kg/m^2).

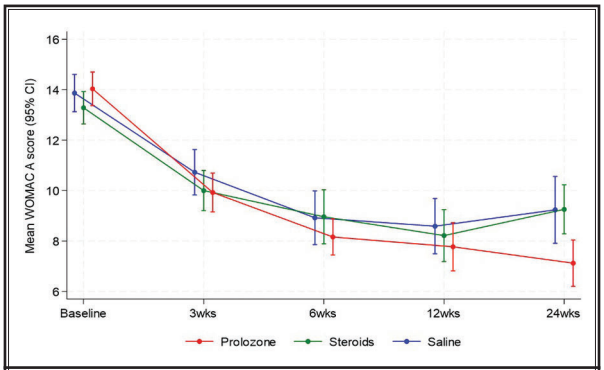


Fig. 2. *Western Ontario and McMaster (WOMAC)-A subscores over time.*

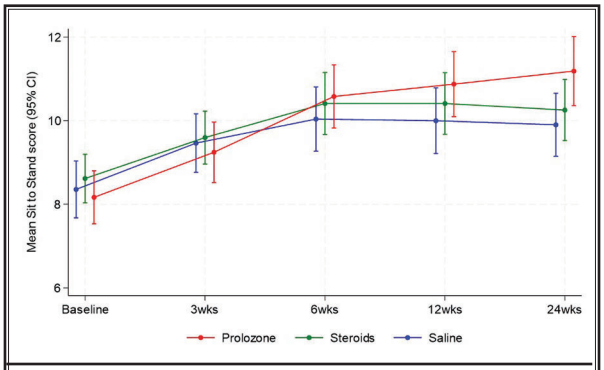


Fig. 3. *Thirty-second sit-to-stand scores over time.*

Table 2. *Group comparisons for the primary outcome (Western Ontario and McMaster Universities [WOMAC] Osteoarthritis Index A [pain]) measured at 24 weeks post the first injection.*

Outcome	Saline Group vs Corticosteroid Group(+)			Saline Group vs Prolozone M Group (++)			Corticosteroid Group vs Prolozone M Group (+++)		
	Mean diff (98.3% CI)	*P* (*)	d	Mean diff (98.3% CI)	*P* (*)	d	Mean diff (98.3% CI)	*P* (*)	d
WOMAC A	0.3 (-1.2 to 1.8)	1.00	0.11	-2.0 (-3.5 to -0.5)	0.003	0.77	-2.3 (-3.8 to -0.8)	< 0.001	0.88

d = Cohen d
(+) Differences between groups calculated as the outcome for the Corticosteroid Group minus the outcome for the Saline Group.
(++) Differences between groups calculated as the outcome for the Prolozone M Group minus the outcome for the Saline Group.
(+++) Differences between groups calculated as the outcome for the Prolozone M Group minus the outcome for the Corticosteroid Group.
(*) *P* values given a Bonferroni adjustment to allow for multiple group comparisons.

Table 3. *Group comparisons for secondary outcomes measured over time.*

Outcome	Timepoint	Saline vs. Steroids (+)			Saline vs. Prolozone M (++)			Steroids vs. Prolozone M (+++)		
		Mean diff (98.3% CI)	*P* (*)	d	Mean diff (98.3% CI)	*P* (*)	d	Mean diff (98.3% CI)	*P* (*)	d
WOMAC Total	3 weeks	-0.4 (-7.1, 6.3)	1.00	0.03	-4.2 (-10.8, 2.5)	0.40	0.31	-3.8 (-10.5, 3.0)	0.55	0.28
	6 weeks	1.7 (-5.1, 8.5)	1.00	0.13	-4.2 (-11.0, 2.6)	0.44	0.31	-5.9 (-12.7, 1.0)	0.12	0.44
	12 weeks	-0.7 (-7.5, 6.1)	1.00	0.06	-5.3 (-12.1, 1.6)	0.20	0.39	-4.5 (-11.4, 2.4)	0.35	0.34
	24 weeks	-0.1 (-6.9, 6.7)	1.00	0.01	-10.4 (-17.2, -3.6)	< 0.001	0.78	-10.3 (-17.2, -3.5)	< 0.001	0.77
30 second sit to stand test	3 weeks	-0.1 (-0.9, 0.8)	1.00	0.03	0.0 (-0.8, 0.9)	1.00	0.02	0.1 (-0.8, 1.0)	1.00	0.04
	6 weeks	0.3 (-0.6, 1.1)	1.00	0.11	0.7 (-0.2, 1.6)	0.17	0.29	0.4 (-0.4, 1.3)	0.70	0.18
	12 weeks	0.3 (-0.6, 1.2)	1.00	0.12	1.0 (0.1, 1.9)	0.03	0.40	0.7 (-0.2, 1.6)	0.22	0.27
	24 weeks	0.2 (-0.6, 1.1)	1.00	0.10	1.5 (0.6, 2.4)	< 0.001	0.61	1.2 (0.4, 2.1)	0.003	0.51

d = Cohen d
(+) Differences between groups calculated as outcome for Steroid minus outcome for Saline
(++) Differences between groups calculated as outcome for Prolozone M minus outcome for Saline
(+++) Differences between groups calculated as outcome for Prolozone M minus outcome for Steroids
(*) *P*-values given a Bonferroni adjustment to allow for multiple group comparisons

Table 4. *Summary of outcome variables measured over time.*

		Saline		Steroids		Prolozone M	
		N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
WOMAC A	Baseline	60	13.9 ± 2.9	60	13.3 ± 2.5	60	14.0 ± 2.6
	3 weeks	55	10.7 ± 3.3	52	10.0 ± 2.8	53	9.9 ± 2.8
	6 weeks	51	8.9 ± 3.8	51	9.0 ± 3.8	50	8.2 ± 2.5
	12 weeks	51	8.6 ± 3.9	51	8.2 ± 3.7	48	7.8 ± 3.3
	24 weeks	51	9.2 ± 4.7	51	9.3 ± 3.5	49	7.1 ± 3.2
WOMAC Total	Baseline	60	61.5 ± 13.8	60	58.0 ± 13.2	60	61.5 ± 12.8
	3 weeks	56	47.4 ± 15.6	52	44.7 ± 14.0	53	43.3 ± 14.8
	6 weeks	51	39.0 ± 17.5	51	39.2 ± 18.5	50	34.7 ± 12.7
	12 weeks	51	38.0 ± 18.5	51	35.7 ± 17.2	48	31.9 ± 15.6
	24 weeks	51	42.1 ± 21.3	51	40.5 ± 16.5	49	31.3 ± 13.2
30 second sit to stand test	Baseline	60	8.4 ± 2.6	60	8.6 ± 2.2	60	8.2 ± 2.5
	3 weeks	56	9.5 ± 2.3	52	9.6 ± 2.3	53	9.2 ± 2.6
	6 weeks	51	10.0 ± 2.7	51	10.4 ± 2.6	50	10.6 ± 2.7
	12 weeks	51	10.0 ± 2.8	51	10.4 ± 2.6	48	10.9 ± 2.7
	24 weeks	51	9.9 ± .7	51	10.3 ± 2.6	49	11.2 ± 2.8

WOMAC Western Ontario and McMaster Universities Osteoarthritis Index

nance imaging for evaluating disease progression (41). In addition, 24 weeks may be too short a period to measure an increase in articular cartilage volume. To the best of our knowledge, our study is the first reporting radiological improvement with Prolozone M.

Table 5. *Secondary efficacy end points.*

	Saline		Steroid		Prolozone		Group comparisons: *P*-values (*)		
	N	N (%)	N	N (%)	N	N (%)	Saline vs. Steroid	Saline vs. Prolozone	Steroid vs Prolozone
PGIC									
Very much worse	51	14 (28%)	51	11 (22%)	49	2 (4%)	1.00	0.006	< 0.001
Much worse		5 (10%)		8 (16%)		2 (4%)			
Minimally worse		3 (6%)		2 (4%)		1 (2%)			
No change		6 (12%)		10 (20%)		5 (10%)			
Minimally improved		7 (14%)		9 (18%)		17 (35%)			
Much improved		15 (29%)		11 (22%)		20 (41%)			
Very much improved		1 (2%)		0 (0%)		2 (4%)			
Responder									
No	60	28 (47%)	60	30 (50%)	60	15 (4%)	1.00	0.04	0.02
Yes		32 (53%)		30 (50%)		45 (75%)			
Radiological change									
Improvement					30	12 (40%)			
Non-progression						9 (30%)			
Worsening						9 (30%)			

(*) *P*-values given a Bonferroni adjustment to allow for multiple group comparisons
PGIC Patient Global Impression of Change

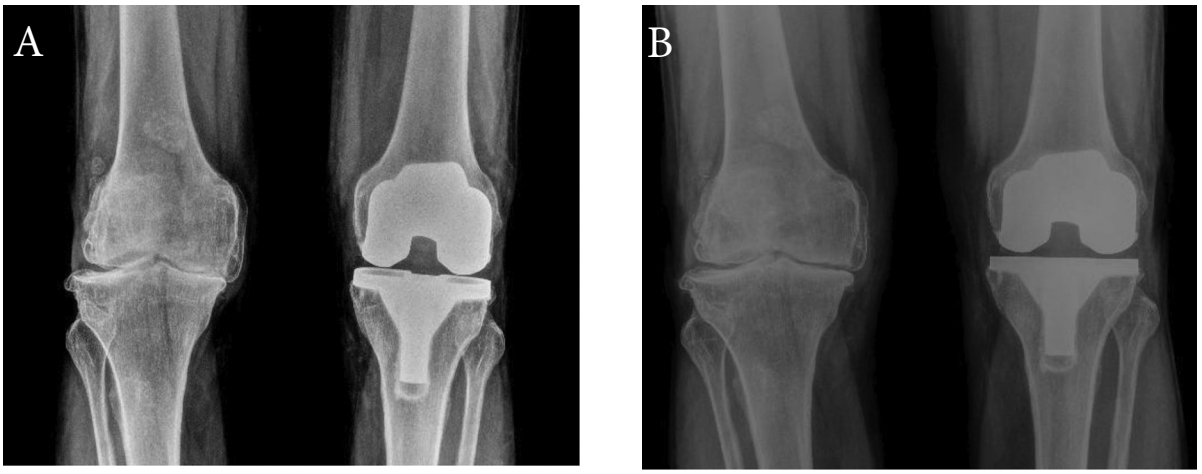


Fig. 4. *A) Baseline x-ray showing Grade 4 osteoarthritis of the right knee. B) X-ray of the right knee at 24-week follow-up showing increase in joint space and reduction in sclerosis after Prolozone M treatment.*

Limitations

Our study's limitations include that it was conducted at a single-center with a follow-up restricted to 24 weeks. In addition, goniometric assessments and a formal assessment of blinding efficacy were not performed. Also, disease progression was evaluated using fluoroscopy rather than magnetic resonance imaging, which is reported to be more sensitive for identifying disease progression as well as any improvement in cartilage volume (41). Finally, despite randomization,

the Prolozone M Group included a younger cohort of patients with a greater number of severe osteoarthritis (Kellgren-Lawrence Grade 4 KOA) compared with the other 2 groups (Table 1).

Conclusion

In conclusion, our placebo-controlled study shows that, in patients with moderate to severe KOA, 3 serial intrarticular injections of Prolozone M are safe and effective in providing statistically significant, clinically relevant pain relief at 24 weeks post the first injection, compared with intraarticular corticosteroid injections as well as placebo injections. There were early signs of chondrogenic potential at the 24-week follow-up in patients who received Prolozone M. The authors recommend large-scale, multicenter studies with an extended follow-up period to confirm these results.

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