Anesth Pain Med. 2015 October; 5(5): e27585. doi: 10.5812/aapm.27585

Published online 2015 October 17. **Research Article**

The Effects of Prolotherapy With Hypertonic Dextrose Versus Prolozone (Intraarticular Ozone) in Patients With Knee Osteoarthritis

Masoud Hashemi,[1] Parviz Jalili,[1] Shirin Mennati,[2] Alireza Koosha,[1] Ramin Rohanifar,[1] Firouz Madadi,[2] Seyed Sajad Razavi,[1,*] and Farinaz Taheri[2]

[1]Anesthesiology Research Center, Mofid Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Anesthesiology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

*Corresponding authors: Seyed Sajad Razavi, Anesthesiology Research Center, Mofid Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Tel: +98-2122908383, E-mail: s.razavi@sbmu.ac.ir

Received February 1, 2015; **Revised** May 20, 2015; **Accepted** June 20, 2015

Background: Knee osteoarthritis (KOA) is a common disabling disease. Limited studies have demonstrated that prolotherapy with dextrose or with prolozone can be helpful in the treatment of patients with KOA.
Objectives: In the current study, we compared the results between these two treatment methods.
Patients and Methods: In the current randomized clinical trial, 80 patients with mild to moderate KOA were randomly assigned equally into two groups (ozone group and dextrose group). In each group, injections were repeated three times with 10-day intervals. Before the treatment and 3 months after the injections, the pain intensity was measured by using a visual analogue scale and the Western Ontario and McMaster university arthritis index scores. Finally, the results were compared between the two groups.
Results: In the two groups, the pain intensity and WOMAC scores significantly decreased and increased, respectively ($P < 0.001$). However, there was no significant difference between the two groups.
Conclusions: Prolotherapy with dextrose and with prolozone result in the same pain relief or functional improvement in patients with mild to moderate KOA.

Keywords: Osteoarthritis, Knee; Prolotherapy, Prolozone, Dextrose

1. Background

Knee osteoarthritis (KOA) is a degenerative disease leading to painful joints, articular stiffness, and decreased function (1). The high prevalence of KOA, especially in older persons, makes it a costly health-care problem. Radiologic changes of osteoarthritis (OA) are usually observed at around 65 years, the age at which almost 11% of patients become symptomatic (2-4). The exact mechanism of pain and disability is not well recognized. The origin of pain has been attributed to various body parts such as the articular capsule, ligaments, synovium, bone, lateral part of the meniscus, and extraarticular ligaments and tendons (5, 6). Total knee arthroplasty (TKA) is the definitive treatment of KOA in severe cases. However, surgeons tend to delay TKA as much as possible because of the limited survival of knee prostheses. In addition, revision surgery is a complicated and difficult procedure. The nonoperative treatment of these patients is a multimodal approach that includes physical therapy, anti-inflammatory drug use, intraarticular injections, acupuncture, and use of wedge insoles; this approach has resulted in satisfactory outcomes in patients at the earlier stages of the disease (7, 8). However, none of these modalities completely relieves the knee pain and dissolves the symptoms. In a recent report, none of these treatments was shown to have an advantage over the others (4). Prolotherapy was first introduced by Hackett in 1950, followed by several preclinical and clinical studies (9). Prolotherapy seems to stimulate the healing process of tissues with chronic injuries (10, 11). In some animal models, prolotherapy resulted in increased inflammatory markers (12). The mechanism of action of dextrose prolotherapy is not clearly understood. Hypertonic dextrose can cause the osmotic rupture of local cells (13). Increased extracellular glucose leads to increased growth factors in different types of human cells (14-16). In addition, a hypertonic environment results in increased DNA-encoding growth factors (17). Although some studies have demonstrated the promising effects of prolotherapy with hypertonic dextrose on pain and function in patients with KOA (18-22), more prospective randomized studies are required to prove the efficacy and safety of this treatment meth-

od for KOA.

The medical effects of ozone are increasingly being considered in recent years especially for musculoskeletal disorders, including low back pain, lumbar disk herniation, failed back surgery syndrome, degenerative spinal disease, shoulder disorders, and KOA (23-31). There is limited evidence on the efficacy of ozone therapy for patients with KOA, and its mechanism of action is unknown. Several biological effects have been suggested for ozone. The increased oxygenation of tissues, and analgesic and anti-inflammatory effects through the stimulation of the antinociceptive system may explain the therapeutic effects of ozone in musculoskeletal disorders (26, 32).

2. Objectives

In the current randomized clinical trial, we compared the effects of prolotherapy with hypertonic dextrose and prolotherapy with ozone on pain and function in patients with KOA.

3. Patients and Methods

During 2013, 80 patients with mild to moderate OA of the medial knee compartment (Kellgren-Lawrence grade I and II), aged 40 - 75 years, were enrolled in the current randomized clinical trial. All patients gave their written informed consent before the study. The diagnosis of KOA was made on the basis of the results of clinical examination and anteroposterior standing radiography. The exclusion criteria included pregnancy, severe underlying diseases such as diabetes, anticoagulant use, being a candidate for knee joint replacement (Kellgren-Lawrence grade III and IV), OA of the lateral knee compartment, previous prolotherapy or any intraarticular injection during the last year, with suspicion for infectious or inflammatory arthritis, and daily use of opioid or nonopioid analgesic drugs. Before the treatment, the pain intensity was determined by using a 10-cm ruler (visual analogue scale). In this scale, 0 indicated no pain and 10 indicated the worst pain. Moreover, all patients completed the Western Ontario and McMaster university arthritis index (WOMAC) assessment, which varies between 0 and 100 points and in which lower scores indicate better knee status.

Patients were randomly assigned equally into two groups: the ozone prolotherapy (OP) group and the hypertonic dextrose prolotherapy (HDP) group. Through the inferomedial approach, 15 g/mL of ozone-oxygen mixture (5 - 7 cm^3) was injected intraarticularly in the OP group, and 7 cm^3 of 12.5% hypertonic dextrose was injected intraarticularly in the HDP group, by using a 25-G needle under ultrasound guidance. Before the prolotherapy, 1% lidocaine was injected as a local anesthetic to the skin and underlying tissues. The injections were repeated three times with 7–10 days interval for each patient. Three months after the last injection, the pain intensity was measured and the WOMAC scores were determined. Finally, the pretreatment and posttreatment outcomes were compared in each group and between the two groups.

3.1. Statistics

Statistical analysis was performed by using SPSS statistical software ver. 15.0. The pretreatment and posttreatment outcomes were compared by using a paired t-test for quantitative data and the McNemar test for qualitative data. The two groups were compared by using an independent-samples t-test for quantitative data and the ^{2} test for qualitative data. $P < 0.05$ was considered significant.

4. Results

The demographic characteristics of the patients are presented in Table 1, which shows no statistically significant difference between the two groups. In addition, before the treatment, the pain intensity and WOMAC scores were the same between the two groups ($P < 0.05$) (Table 2). After the treatment, the pain and function significantly improved in the two groups ($P < 0.001$) (Table 2). However, there was no statistically significant difference in pain and WOMAC scores at the last visit between the two groups ($P < 0.05$) (Table 2).

Table 1. Comparison of Demographic Findings between the Two Groups (n = 40)

Variable	Ozone	Hypertonic Dextrose	P Value
Age, y	59.1 ± 12.3	57.3 ± 15.1	0.349
Sex			0.491
Male	17	14	
Female	23	26	
Body mass index, kg/m^2	31.2 ± 1.1	31.8±0.9	0.751
Duration of pain (before injection), months	7.6 ± 0.8	8.1 ± 0.9	0.1

Table 2. Comparison of the Visual Analogue Scale and WOMAC Scores in Each Group and between the Two Groups (n = 40)

Group	Ozone	Hypertonic Dextrose	P Value (Intergroup)	P Value (Intragroup)
Visual analogue scale				< 0.001
Before	7.6 ± 1.3	8.1 ± 1.1	0.146	
After	2.8 ± 1.1	3 ± 1.2	0.512	
WOMAC score				< 0.001
Before	56.3 ± 11.5	58.5 ± 13.3	0.835	
After	81.6 ± 13.7	83.7 ± 15.3	0.173	

5. Discussion

The current study shows that prolotherapy with hypertonic dextrose or prolozone (intraarticular ozone injection) can be effectively used in the nonoperative management of patients with KOA. Prolotherapy is an injection therapy for the management of chronic musculoskeletal disorders such as KOA (10). Although prolotherapy is being increasingly used worldwide, its mechanism of action in pain relief is not yet clearly understood. Several mechanisms have been proposed, such as accelerating the healing process of damaged tissue (10, 11), releasing growth factors (14-16), having a positive effect on the nociceptive system (33), and the effect of needle insertion and volume enhancement (34).

Reeves and Hassanein found that prolotherapy with 10% dextrose resulted in significant pain relief, decrease in knee swelling, decrease in bulking episodes, and improvement in the knee range of motion. They also found, on the basis of radiographic images, that prolotherapy was associated with improvement in OA severity.

In recent years, the treatment of several musculoskeletal disorders with ozone has increasingly attracted attention. Ozone is a toxic and soluble gas with high oxidative activity (35). Ozone has an antinociceptive effect with several mechanisms (35, 36). Paoloni et al. treated patients with lumbar disc herniation by using intramuscular oxygen-ozone injection. They observed that 61% of the patients became pain free compared with 33% of the control group (30). Li et al. and Mishra et al. reported improved function and decreased pain intensity after intraarticular injection of ozone in patients with KOA (24, 25). To our knowledge, there is no study comparing the effects of prolotherapy with hypertonic dextrose and injection of ozone. Therefore, it is possible to compare the outcomes of the current study with those of others. However, our findings confirmed the outcome of previous studies indicating the pain killing and therapeutic effects of prolotherapy with ozone or dextrose. In our study, the pain intensity was significantly reduced after the treatment. However, there was no statistically significant difference between the two groups.

We believe that our study is limited by the small sample size; if more patients were investigated, it is possible that we could have found some differences between the two groups. In addition, we only investigated the short-term results; mid-term and long-term follow-up are required.

5.1. Conclusion

Intraarticular injection of hypertonic dextrose or ozone could significantly decrease pain in patients with mild to moderate KOA, and improve their functional status. There was no significant difference between dextrose and ozone in the outcomes, and more studies are required in the future.

Footenote

Authors' Contributions: Study concept and design: Masoud Hashemi and Parviz Jalili; acquisition of data: Masoud Hashemi, Parviz Jalili, Firuz Madadi, Shirin Mennati, and Ramin Rohanifar; analysis and interpretation of data: Parviz Jalili, Shirin Mennati, and Firuz Madadi; drafting of the manuscript: Masoud Hashemi, Firuz Madadi, and Alireza Koosha; critical revision of the manuscript for important intellectual content: Masoud Hashemi and Alireza Koosha; statistical analysis: Farshad Safdari; administrative, technical, and material support: Masoud Hashemi, Parviz Jalili, Firuz Madadi, and Shirin Mennati; study supervision: Masoud Hashemi and Shirin Mennati.

References

1. Hawamdeh ZM, Al-Ajlouni JM. The clinical pattern of knee osteoarthritis in Jordan: a hospital based study. *Int J Med Sci.* 2013;**10**(6):790–5.
2. Gupta S, Hawker GA, Laporte A, Croxford R, Coyte PC. The economic burden of disabling hip and knee osteoarthritis (OA) from the perspective of individuals living with this condition. *Rheumatology (Oxford).* 2005;**44**(12):1531–7.
3. Li Y, Wei X, Zhou J, Wei L. The age-related changes in cartilage and osteoarthritis. *Biomed Res Int.* 2013;**2013**:916530.
4. Samson DJ, Grant MD, Ratko TA, Bonnell CJ, Ziegler KM, Aronson N. Treatment of primary and secondary osteoarthritis of the knee. *Evid Rep Technol Assess (Full Rep).* 2007;(157):1–157.
5. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Ann Rheum Dis.* 2001;**60**(2):91–7.

6. Felson DT. The sources of pain in knee osteoarthritis. *Curr Opin Rheumatol.* 2005;**17**(5):624–8.
7. Shengelia R, Parker SJ, Ballin M, George T, Reid MC. Complementary therapies for osteoarthritis: are they effective? *Pain Manag Nurs.* 2013;**14**(4):e274–88.
8. Buckwalter JA, Stanish WD, Rosier RN, Schenck RJ, Dennis DA, Coutts RD. The increasing need for nonoperative treatment of patients with osteoarthritis. *Clin Orthop Relat Res.* 2001;(385):36–45.
9. Hackett GMG. *Ligament and tendon relaxation treated by prolotherapy.* 5 ed 1993.
10. Linetsky F, Botwin K, Gorfine L, Jay GW, McComb B, Miguel R, et al. *Regenerative injection therapy (RIT): effectiveness and appropriate usage.* Florida Academy of Pain Medicine (FAPM); 2001.
11. Banks AR. A rationale for prolotherapy. *J Orthopa Med.* 1991;**13**(3)
12. Jensen KT, Rabago DP, Best TM, Patterson JJ, Vanderby RJ. Early inflammatory response of knee ligaments to prolotherapy in a rat model. *J Orthop Res.* 2008;**26**(6):816–23.
13. Rabago D, Slattengren A, Zgierska A. Prolotherapy in primary care practice. *Prim Care.* 2010;**37**(1):65–80.
14. Scarpone M, Rabago DP, Zgierska A, Arbogast G, Snell E. The efficacy of prolotherapy for lateral epicondylosis: a pilot study. *Clin J Sport Med.* 2008;**18**(3):248–54.
15. Di Paolo S, Gesualdo L, Ranieri E, Grandaliano G, Schena FP. High glucose concentration induces the overexpression of transforming growth factor-beta through the activation of a platelet-derived growth factor loop in human mesangial cells. *Am J Pathol.* 1996;**149**(6):2095–106.
16. Murphy M, Godson C, Cannon S, Kato S, Mackenzie HS, Martin F, et al. Suppression subtractive hybridization identifies high glucose levels as a stimulus for expression of connective tissue growth factor and other genes in human mesangial cells. *J Biol Chem.* 1999;**274**(9):5830–4.
17. Krump E, Nikitas K, Grinstein S. Induction of tyrosine phosphorylation and Na+/H+ exchanger activation during shrinkage of human neutrophils. *J Biol Chem.* 1997;**272**(28):17303–11.
18. Reeves KD, Hassanein K. Randomized prospective double-blind placebo-controlled study of dextrose prolotherapy for knee osteoarthritis with or without ACL laxity. *Altern Ther Health Med.* 2000;**6**(2):68–74.
19. Rabago D, Zgierska A, Fortney L, Kijowski R, Mundt M, Ryan M, et al. Hypertonic dextrose injections (prolotherapy) for knee osteoarthritis: results of a single-arm uncontrolled study with 1-year follow-up. *J Altern Complement Med.* 2012;**18**(4):408–14.
20. Rabago D, Patterson JJ, Mundt M, Kijowski R, Grettie J, Segal NA, et al. Dextrose prolotherapy for knee osteoarthritis: a randomized controlled trial. *Ann Fam Med.* 2013;**11**(3):229–37.
21. Rabago D, Patterson JJ, Mundt M, Zgierska A, Fortney L, Grettie J, et al. Dextrose and morrhuate sodium injections (prolotherapy) for knee osteoarthritis: a prospective open-label trial. *J Altern Complement Med.* 2014;**20**(5):383–91.
22. Rahimzadeh P, Imani F, Faiz SH, Entezary SR, Nasiri AA, Ziaeefard M. Investigation the efficacy of intra-articular prolotherapy with erythropoietin and dextrose and intra-articular pulsed radiofrequency on pain level reduction and range of motion improvement in primary osteoarthritis of knee. *J Res Med Sci.* 2014;**19**(8):696–702.
23. Al-Jaziri AA, Mahmoodi SM. Painkilling effect of ozone-oxygen injection on spine and joint osteoarthritis. *Saudi Med J.* 2008;**29**(4):553–7.
24. Li JH, Zhou LX, Li GY, Cheng B. [Treatment of middle-aged and aged patients with knee osteoarthritis of yang-deficiency induced cold-damp syndrome by ozone combined Chinese materia medica: a clinical research]. *Zhongguo Zhong Xi Yi Jie He Za Zhi.* 2013;**33**(4):471–5.
25. Mishra SK, Pramanik R, Das P, Das PP, Palit AK, Roy J, et al. Role of intra-articular ozone in osteo-arthritis of knee for functional and symptomatic improvement. *Ind J Phys Med Rehabil.* 2011;**22**(2):65–9.
26. Andreula CF, Simonetti L, De Santis F, Agati R, Ricci R, Leonardi M. Minimally invasive oxygen-ozone therapy for lumbar disk herniation. *AJNR Am J Neuroradiol.* 2003;**24**(5):996–1000.
27. Bonetti M, Fontana A, Martinelli F, Andreula C. Oxygen-ozone therapy for degenerative spine disease in the elderly: a prospective study. *Acta Neurochir Suppl.* 2011;**108**:137–42.
28. Gallucci M, Limbucci N, Zugaro L, Barile A, Stavroulis E, Ricci A, et al. Sciatica: treatment with intradiscal and intraforaminal injections of steroid and oxygen-ozone versus steroid only. *Radiology.* 2007;**242**(3):907–13.
29. Oder B, Loewe M, Reisegger M, Lang W, Ilias W, Thurnher SA. CT-guided ozone/steroid therapy for the treatment of degenerative spinal disease–effect of age, gender, disc pathology and multisegmental changes. *Neuroradiology.* 2008;**50**(9):777–85.
30. Paoloni M, Di Sante L, Cacchio A, Apuzzo D, Marotta S, Razzano M, et al. Intramuscular oxygen-ozone therapy in the treatment of acute back pain with lumbar disc herniation: a multicenter, randomized, double-blind, clinical trial of active and simulated lumbar paravertebral injection. *Spine (Phila Pa 1976).* 2009;**34**(13):1337–44.
31. Apuzzo D, Giotti C, Pasqualetti P, Ferrazza P, Soldati P, Zucco GM. An observational retrospective/horizontal study to compare oxygen-ozone therapy and/or global postural re-education in complicated chronic low back pain. *Funct Neurol.* 2014;**29**(1):31–9.
32. Benvenuti P. Oxygen-ozone treatment of the knee, shoulder and hip. A personal experience. *Rivista italiana di ossigeno-ozonoterapia.* 2006;**5**:135–44.
33. Yelland MJ, Sweeting KR, Lyftogt JA, Ng SK, Scuffham PA, Evans KA. Prolotherapy injections and eccentric loading exercises for painful Achilles tendinosis: a randomised trial. *Br J Sports Med.* 2011;**45**(5):421–8.
34. Rabago D, Kijowski R, Woods M, Patterson JJ, Mundt M, Zgierska A, et al. Association between disease-specific quality of life and magnetic resonance imaging outcomes in a clinical trial of prolotherapy for knee osteoarthritis. *Arch Phys Med Rehabil.* 2013;**94**(11):2075–82.
35. Bocci V. Ozone as Janus: this controversial gas can be either toxic or medically useful. *Mediators Inflamm.* 2004;**13**(1):3–11.
36. Shallenberger F. Prolozone™–Regenerating Joints and Eliminating Pain. *J Prolother.* 2011;**3**(2):630–8.