The effect of Hypertonic Dextrose injection on the control of pain associated with knee osteoarthritis

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Abstract

Introduction: The purpose of this study was to evaluate the effect of dextrose injection on controlling pain associated with knee osteoarthritis.

Methods: To achieve the research objectives, available sampling was done using 80 patients with knee osteoarthritis referring to Taleghani Hospital in 2017 and samples were divided into two groups: 15% dextrose injection and 25% hypertonic dextrose injection. This injection was performed at the beginning of the study, the first week, the fifth week and the ninth week. During these weeks, participants were asked to complete the WOMAC questionnaire implementing the VAS scale. After data collection, independent t-test and two-way variance analysis with repeated measures were used.

Findings: The findings showed that 15% and 25% dextrose injection had a significant effect on the visual scale of pain and function of patients, so that, during weekly treatment, scales showed improvement in treatment in these patients. Also, other findings showed that injection of 25% dextrose had a significant visual analog of patient's pain and function compared to 15%.

Conclusion: In general, it can be suggested that the use of dextrose prolotherapy is a simple, safe, inexpensive, accessible and less complicated method than other treatments in these patients.

Key words: Osteoarthritis, Prolotherapy, Treatment, Health.

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Introduction

Osteoarthritis (OA) is the most common joint disease in humans and is characterized by the degradation of the hyaline cartilage and can lead to chronic pain and severe disability in the patient (1). The morning and the decrease in the movement range of the joint are important characteristics of this disease (2). The greatest risk factor for this disease is age (3), but high blood pressure, severe strokes, excessive use of the joint, inoperative anterior cruciate ligament and damage to the meniscus can also result in knee OA (4-5). OA levels in all societies are rising due to increased longevity. Pain, stiffness and knee pain during active knee movements are common symptoms of OA, which not only reduces the ability of patients, but also adversely affects the quality of life of patients (6).

Osteoarthritis is one of the five main causes of physical disability in the elderly (1, 7). It is estimated that 90% of people over 40 in the United States suffer from osteoarthritis (8). Studies show that the prevalence of knee osteoarthritis is 60 to 90% as a cause of musculoskeletal pain among people 65 years of age or older (9). By 2020, it is estimated approximately 4.55 million Americans, i.e. 18.2% of the US population will have osteoarthritis (10). According to the World Health Organization, the prevalence of osteoarthritis in the Iranian urban population is reported to be about 19.3% (5). The findings of a similar study in Iran show that osteoarthritis is higher in the Iranian population than in the other studied populations, and the prevalence in women is more than in men (11). OA costs 60 billion dollars a year for the US economy (12). This disease is one of the main causes of functional impairment and has greatly influenced people's lives, including their mobility, independence, and daily activities, resulting in limited recreational activities, sports, and work (13). The results of a 2004 study in Iran investigating 200 patients with osteoarthritis showed that high BMI, high age, and live in a village were the main factors affecting the inability of these patients (14). Sex also plays a major role in this issue, about 2.3% to 3.4% of the knee OA patients are female (15).

The inflammation process also plays an important role in osteoarthritis, and cytokines such as IL-1 beta, IL-6, tumor necrosis factor, and IL-15 play a role in this disease (16-17). The disease is divided into two primary and secondary forms. In the primary type, the degeneration process and joint destruction occurs without previous anomalies. Its main cause is unknown, usually it is seen in individuals over 40 years of age with slow progressive and multiple arthroplasty, and is seen through normal or abnormal pressure on the weak joint (8, 15). Secondary osteoarthritis is followed by an underlying cause such as fractures, bone and joint injuries, infections, rheumatoid arthritis, and congenital and metabolic diseases (18).

In terms of pathology, this disease is caused by three biological, mechanical and biomechanical causes. Symptoms begin with mild pain in one or more joints and gradually intensify. This pain is improved with exertion and relaxation, with the advancement of pain, it develops and joint stiffness lasts for a few minutes (19).

Failure to use a joint with OA due to pain results in rapid atrophy of the muscles around the joint, and therefore, lead to muscle loss, which is one of the most important factors for joint support. Eventually, in the last stages of the disease or when there is severe pain (20), it disturbs patients' quality of life, and ultimately leads to surgery such as joint replacement (21). Pain is a multidimensional phenomenon that has physical, psychological, social, and spiritual components, and is, in fact, a kind of unpleasant sensory and psychological experience that is associated with actual or potential tissue damage and it is expressed with a series of words from people who experience it (22). The lack of management of chronic pain affects the physical and mental condition of individuals, decreases their quality of life and that of their families, and on the other hand, along with the physical and psychological disabilities, it imposes a significant cost to the economic resources of countries, health systems and insurance (23). In addition to the direct medical costs caused by pain, it imposes the following indirect costs, such as complications of therapeutic measures, the number of days someone cannot handle, movement restrictions, being useless and ineffective, functional disorders, pain-related disabilities, and compensation for these disabilities on the individual and the community (24).

In industrialized countries and developing countries attention to knee osteoarthritis is an important cause of pain and disability, the loss of proper joint performance, and joint instability and deformity are increasing (25). Therefore, several therapeutic approaches have been proposed for the treatment or improvement of this disease. Multiple treatments for this disease include medication, lifestyle changes, weight loss, muscle strengthening, using cane, brace, heel wedge and surgical procedures. All of these methods have a sedative effect and only delay the onset of the disease (26). The standard of care and treatment is multifactorial in osteoarthritis, and often involves physical therapy, prescribing and taking anti-inflammatory drugs, intracranial injection of hyaluronic acid (visco-supplementation) and arthroscopic surgery. New studies also show no therapeutic effect left alone (27).
Unfortunately, no definitive treatment for this disease has been found despite the many used therapeutic methods. Therefore, given the long duration, high financial costs, widespread side effects, non-steroidal anti-inflammatory drugs, and finally, the symptoms of the disease lead to limitation of movement and severe disability and loss of muscle performance and muscle weakness; therapeutic goals of the disease should include reducing pain and weakness, improving performance and range of motion, and facilitating day-to-day activities. Treatment of the disease includes medical treatments and non-pharmacological treatments including physiotherapy. Another promising treatment that has recently been used to treat musculoskeletal pain is prolotherapy (28, 29). Prolotherapy is a selective therapeutic and complementary injection for chronic musculoskeletal pain. Prolotherapy techniques and injected intra-articular materials are very different and are related to the patient's condition, severity of symptoms and clinical manifestations of patients. Prolotherapy involves infusion of a very small amount of

an anti-inflammatory or sclerosis agent into the tendon, inflamed or painful joint or ligament (30).

It is assumed that prolotherapy leads to stimulate recovery in chronic soft tissue injuries; typically, dextrose hypertonic is used in prolotherapy for intramuscular injection (30). The study of Reeves et al. (2003) showed that the pain of the patients was significantly decreased after the injection of into the hip (31). Jo et al. also found that intra-joint 15% dextrose injection can reduce knee pain in these individuals (32). A study by Rabago et al showed that in adults with osteoarthritis, using intra-articular dextrose reduces pain, rigidity and increased function of patients without side effects (33).

Knee osteoarthritis can result in severe physical and mental disability, and the therapeutic goals in this disease include reducing weakness, improving performance, reducing pain, increasing the range of motion, reducing the morning stiffness of the joints, and facilitating the daily functioning of life (34) and due to the need to find safe, simple and inexpensive non-surgical treatments to reduce pain and improve the function of patients with knee osteoarthritis and the limited number of studies in this field, this study aimed to investigate the effect of dextrose injection on the control of pain associated with knee osteoarthritis in patients referred to Taleghani Hospital (2017).

Methodology

The study was a single-blind clinical trial. The research population was all patients with knee osteoarthritis, who were selected by available sampling method from 80 knee osteoarthritis patients referred to Taleghani Hospital. They were randomly divided into two groups: 15% dextrose injection and injection of hypertonic dextrose 25% divided. The sample size was 80 individuals based on similar research ($p \leq 0.05$) and a test power of 80%. The criteria for entering the study included: unilateral idiopathic OA of the knee, age range of 45-75 years, walking ability, local knee pain with a score of more than 5 based on VAS criteria and exit criteria including: other knee diseases, hip joint OA, and ankle sprain, radicular pain due to lumbar spine disorders, intraocular effusion, history of physiotherapy and intra-articular injection in the past 6 months, psycho-mental diseases, knee necrotic tissue, infection and tissue in the blood, neurological, sensory and motor disorders, history of knee surgery and obesity. Ethical Criteria of this study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences.

Method of implementation

After diagnosis of the patient as an appropriate case, education about the method of implementation and the benefits and possible complications of participating in the project, written consent was taken from the patient. They were informed about the necessity of regular referral for follow up, but that it was not imposed. The intervention was performed without the cost to the patient. Before the intervention, a questionnaire was filled out including patient's demographic information, such as: gender, age, occupation, involved side (upper leg), history of previous treatments, and history of underlying illness and the duration of symptoms. In addition to providing an educational brochure on how to inject, the time for referrals to perform tests and the next visit was presented face to face. Regarding moral considerations, the patient was assured that they could be excluded from the study whenever they wished, and that their failure to cooperate with the doctor and the hospital would not affect their treatment and all patient information would be kept confidential. The injection procedure was performed in such a way that the patient was placed in a supine position and marked with a knee flexion of 10-15 degrees on the medial side of the knee, marking the injection area, and then the injection site was disinfected with Povidone iodine and the injected area was anesthetized with 1 ml 1% Lidocaine solution and using needle number 25-27 after aspiration and ensuring proper placement of needle for intra-articular injection (35).

In the 25% dextrose group, solution was made of 5 cc 50% dextrose and 5 cc 1% lidocaine. Then, 6 cc of this 25% dextrose solution was injected into the patient's joint and injection was performed with the inferomedial approach (33). In the 15% dextrose group, solution was made of 6.75 cc 50% dextrose and 4.5 cc of 1% lidocaine and 11.25 cc of normal saline 0.9%. Then, 0.5 cc of this solution was 15% dextrose that was injected as subdermal with peppering technique with needle number 25 in the bone ligament. There were 15 injections for each patient (33). This injection was performed at the beginning of the study, the first week, the fifth week and the ninth week. The completion of the WOMAC questionnaire and the implementation of the VAS scale were performed before the intervention, and in the first week, the fifth week, the ninth week and the thirteenth week. To measure the variables, the Western Ontario and McMaster Universities (WOMAC) index and the VAS Scale (Visual Analogue Scale) were used as follows.

Visual Analogue Scale

The visual analogue scale (VAS) indicates the pain of the patients in general. This scale is plotted as a 10 cm line, and the degree of pain is graded from zero to 10 cm. The zero number does not show any pain, 1 to 3 mild pain, 4 to 6 moderate pain and 7 to 10 severe pain [36]. The internal reliability of this tool has been reported as 0.85 to 0.95 (37).

Functional questionnaire of WOMAC

The WOMAC functional questionnaire consists of 24 questions, 5 questions regarding pain, 2 questions related to stiffness and 16 questions regarding the performance of patients with osteoarthritis. The score for each question varies from zero to four. This criterion is scored from zero to 96. If the patient has no problem, then, the score is zero and if they have a maximum problem, score will be 96. Validity and reliability of this tool have been investigated by Ebrahimzadeh et al. and has been validated in the Persian language. Cronbach's alpha was estimated 0.9 in Persian language (5).

In analyzing data, the mean, standard deviations, frequencies, tables and charts were used to categorize

and summarize the collected data. In the study of statistical pre-requisites, the number of observations per distribution was used to test the natural distribution of the data using the Kolmogorov-Smirnov test. Regarding the existence of statistical hypotheses, independent t-test and two way-analysis of variance with repeated measures (p≤0.05) and using the Statistical package of version 22 were used.

Results

The participants in the present study consisted of 48 (60%) women and 32 (40%) men. The age range of patients was (45-75) years and the mean age was 64.3 years.

VAS variable

The results of Kolmogorov-Smirnov test showed that the distribution of data was normal (P> 0.05). T-test showed that there was no significant difference in VAS scale between the two groups before intervention (t=0.781, p> 0.05). Two-way analysis of variance (week × group) of 3×2 was used to analyze the data. The results are presented in Table 1.

Table 1: The results of variance analysis of VAS scale in two groups

Variables	df	Sum of squares	F	Sig.
Group	1	7.004	14127.948	0.00
Week	2	859.400	2596.509	0.00
Week × Group	2	1.117	3.373	0.037
Error	78	16.410		

The findings showed that the main effect of the group (F2.78 = 14127.948, p<0/05), the main effect of week (F2.78 = 2596.509, p<0.05) and the interaction between the group and the week was significant. The significance effect of the group means that there is a significant difference between the two groups in the visual analogue scale. According to Chart 1, the group of 25% Dextrose injection experienced more pain relief than the 15% group. Significance of the weeks of treatment meant that during the weeks of injection, the process of pain reduction continued significantly (Figure 1).

WOMAC variable

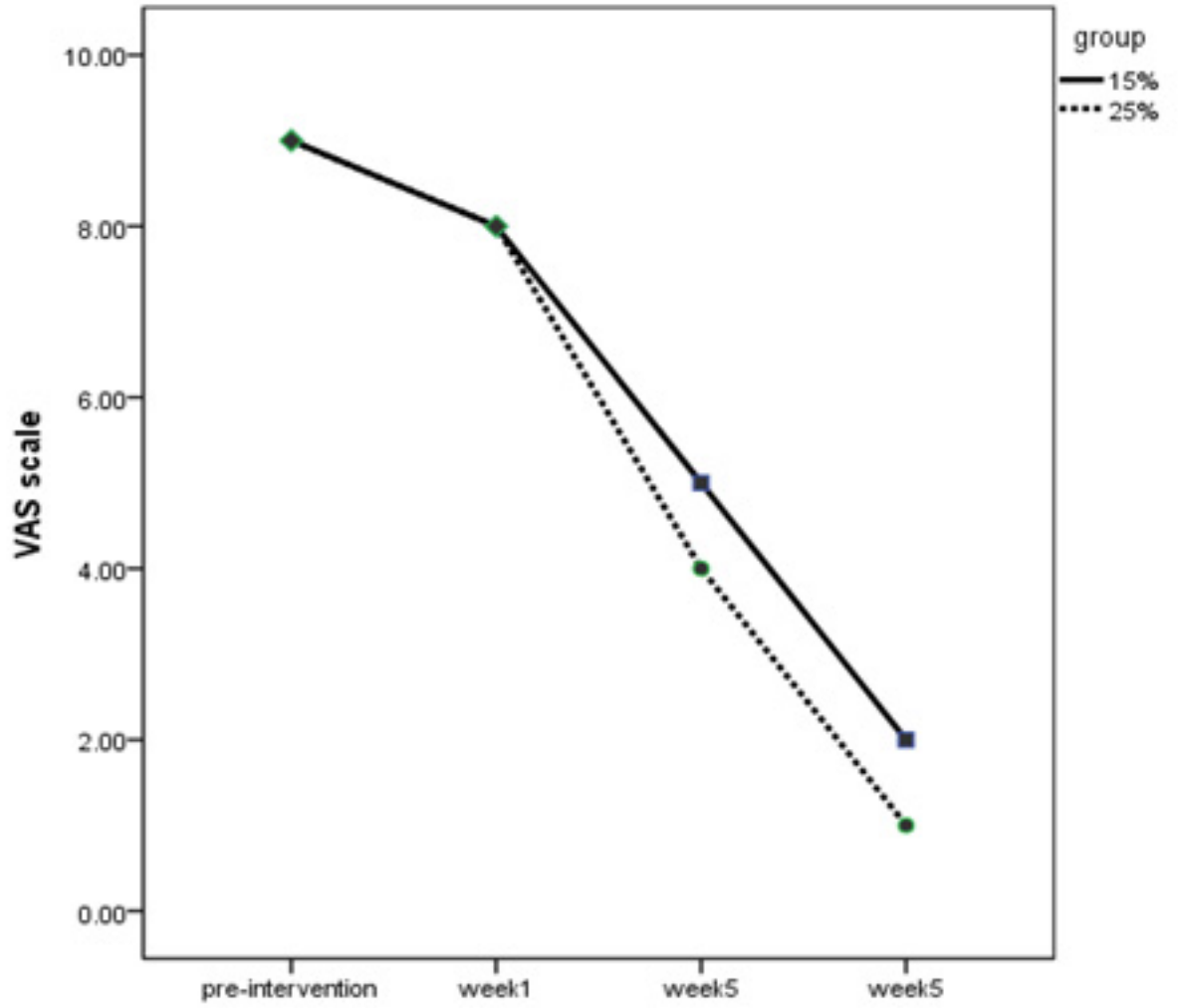
The results of Kolmogorov-Smirnov test showed that the distribution of data was normal (P>0.05). T-test showed that there was no significant difference in the WOMAC scale between the two groups before the intervention (t = 0.841, p>0.05). Two-way analysis of variance (week × group) of 3×2 was used to analyze the data. The results are presented in Table 2.

The findings showed that the main effect of the group (F2.78 = 5671/901, p <0.05), the main effect of week (F2.78 = 797/595, p <0.05) and the interaction between the group and the week was significant. The significance of the effect of the group means that there is a significant difference between the two groups on the WOMAC scale. According to Figure 2, it can be said that 25% dextrose injection group had a better experience. Significantly, the weeks of treatment means that during the weeks of injection, the improvement in performance was significantly increased (Figure. 2 - page 197).

Table 2: The results of variance analysis of WOMAC scale in two groups

Variables	df	Sum of squares	F	Sig.
Group	1	2368.817	5671.901	0.000
Week	2	22381.904	797.595	0.000
Week × Group	2	326.279	12.91	0.000
Error	78	35.558		

Figure 1: VAS scale of the two groups in the weeks of treatment



Discussion

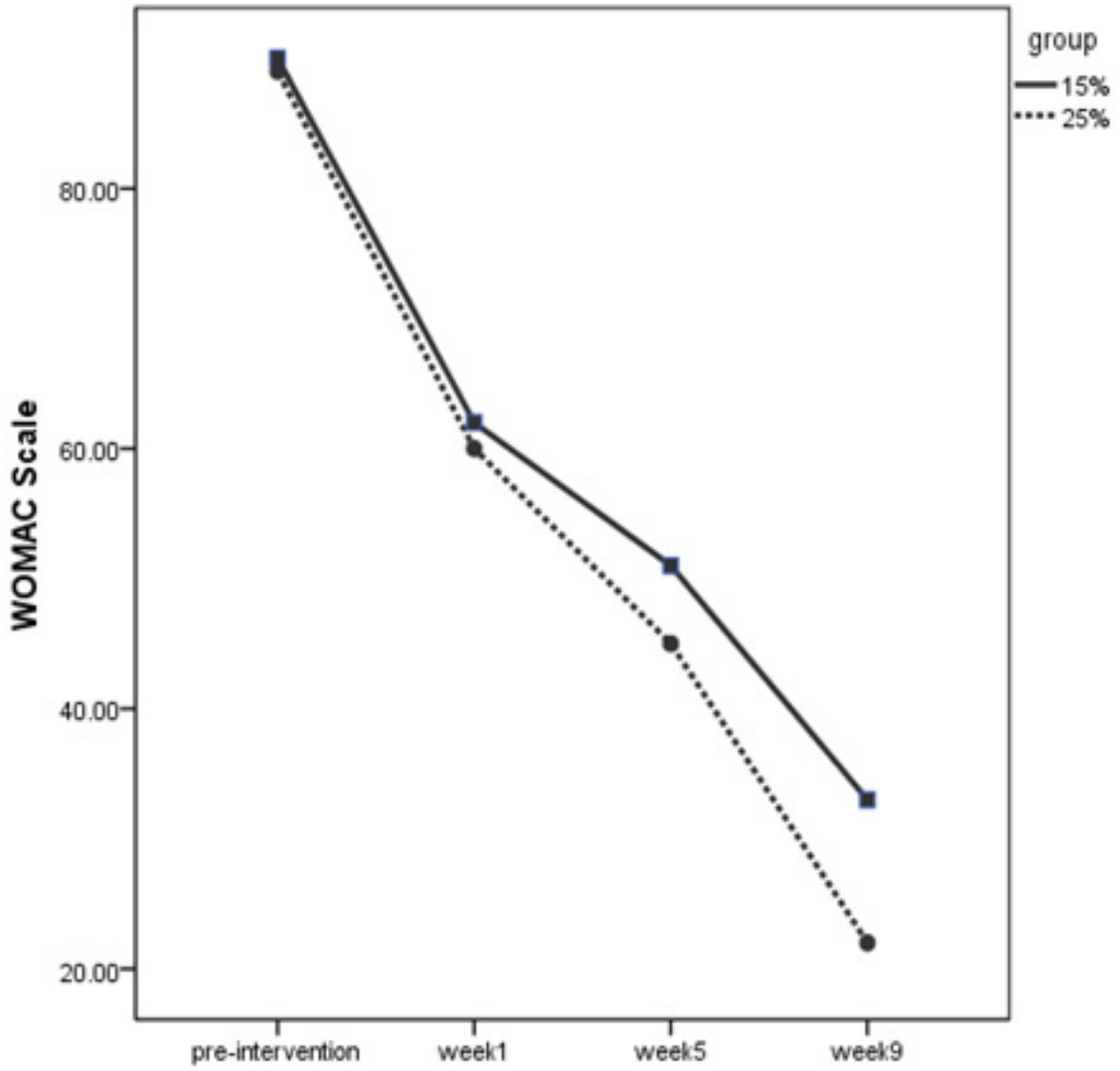
The purpose of this study was to investigate the effect of dextrose injection on pain control associated with knee osteoarthritis. The findings showed that injection of 15% and 25% of dextrose had a significant effect on the visual scale of pain and function of patients so that during treatment, scales showed improvement in treatment in these patients.

Also, other findings showed that injection of 25% dextrose compared to 15% had a significant effect on visual scale of pain and function of patients. These findings are consistent with the results of Reeves and Hassanin (2004), Rabago (2012), Jo (2004), Reeves and Hassanin (2000), Hashemi (2015) and Reeves (2003). For example, the findings of Rabago (2012) showed that in adults with osteoarthritis, using intra-arterial dextrose reduces pain, stiffness and increased function of the patients without any side effects (33). Joe et al. (2004) showed that the pain of patients was significantly reduced by 15% dextrose injection. They also concluded that intra-articular injection of 15% dextrose can reduce knee pain in these individuals (32). In another study, Hashemi et al. (2015) attempted to compare the effect of ozone therapy and dextrose injection in patients with osteoarthritis. They evaluated the patients using the WOMAC and VAS scales. The findings showed that in both groups, pain significantly decreased and function was significantly increased. They concluded that both treatments were effective in reducing pain and increasing the function of patients (38). In subsequent studies, Reeves and Hassanein (2000) evaluated the effect of 10% dextrose on osteoarthritis of fingers. After six months of follow up, they found that in the dextrose group, a significant improvement was observed in the case of xylocaine group during fingers movement and joint flexion, but there was no significant improvement in pain during rest and recovery. Another study on knee osteoarthritis and anterior AC ligation showed significant improvement in pain and knee swelling and flexion, but in the ACL group, there was no significant improvement in instability (40).

Also, Hassanein and Reeves (2002) conducted a study on patients with joint instability associated with ACL rupture. Their findings showed that in patients with a three year follow up, there was a significant decrease in pain during walking, joint swelling and joint flexion (40).

In another study for the treatment of osteoarthritis, finger joints used 10% dextrose over two months, which was associated with beneficial therapeutic effects (41). In another study, it has been reported that in third world countries where knee insertion surgery is not available, in contrast to symptomatic patients, exercise, physiotherapy or NSAIDs

Figure 2: WOMAC scale of the two groups in the weeks of treatment



are prescribed. The researchers found that 10% dextrose could modify ACL ligament laxity, which was not associated with rupture, and also prevented gradual salivation after surgery in joints with a potential displacement (42). The mechanism of dextrose effect is that injection of a stimulant such as dextrose into a damaged joint, possibly with local inflammatory reactions, may lead to an increase in blood flow around the joint and damaged tissue, thereby causing self-repair in that area.

The dextrose effect has another mechanism of effect (43). They showed that in treatment with 10% Dextrose, the response rate, the accumulation and tightening of the uterus, was significantly better than oxytocin treatment (40 units per liter).

These researchers argued that the mechanism of dextrose effect is that since the activity of the sympathetic nervous system and the level of adrenalin of the blood increases at an advanced age, this increase in adrenalin increases the level of cAMP by binding to beta receptors and thus, activates the protein kina dependent to cAMP, which in turn has a moderating role in kinase adhesion to the myosin-like chain and calcium-calmodulin molecule, and therefore, result in reduction in the contractile power of the smooth muscle. Hence, at an advanced age, it is necessary to increase the level of dextrose and consequently increase the level of ATP for exposure to high levels of catecholamines to help accumulate and tighten the uterus.

According to the results, it can be concluded that the mechanism of the effect of Dextrose Prolotherapy is direct effects, osmotic and inflammatory growth. Dextrose injection with a concentration of less than 10% directly promotes cell and tissue proliferation without inflammatory reaction and a high concentration of 10% results in an extracellular osmotic gradient at the injection site resulting in loss of intracellular and lyse cellular cells and invasion of growth factors and inflammatory cells that start the wound healing cascade in that particular area. Dextrose is an ideal proliferrant because it is water-soluble and is a mixture of blood that can be safely injected into several areas and in large quantities, and the final result is the insertion of new collagen into damaged tissues such as Ligaments and tendons.

When extracellular dextrose concentrations reach 5%, normal cells begin to proliferate and produce a number of growth factors such as platelet growth factor, TGF-β, epidermal growth factor, basal growth factor fibroblast growth factor, insulin-like growth factor, and connective tissue growth factor that repairs the tendon, ligaments and other soft tissues.

Conclusion

Finally, according to human and animal studies, dextrose Prolotherapy has a significant effect on musculoskeletal pain, disability and cost of treatment. Major complications from dextrose have not been reported, and include mostly side effects of injection (pain in injection site, hematoma, infection, and skin pigmentation) (38, 39). According to the findings of this study, the use of Dextrose Prolotherapy is a simple, safe, inexpensive, available and uncomplicated method for other remedies in these patients, which has been confirmed by other studies.

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