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Is Regenerative Injection Therapy (Prolotherapy) Effective at Reducing Pain Associated With Knee Osteoarthritis?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not "Is regenerative injection therapy (prolotherapy) effective at reducing pain associated with knee osteoarthritis?"

Study Design: Review of all English language primary studies published in 2012 and 2013.

Data Sources: One randomized control trial, one randomized crossover study and one single-arm uncontrolled study were found using PubMed and Ebscohost.

Outcomes Measured: Clinical outcome for all three articles was measured using the Western Ontario McMaster University Osteoarthritis Index (WOMAC); which specifically focuses on quality of life, function, and pain reduction after the use of prolotherapy versus the saline placebo.

Results: In a randomized control study (RCT) by Rabago et al. (2012) they found that patients given prolotherapy sustained significant improvement of pain, function, and stiffness scores for knee osteoarthritis compared with the blinded saline injection group. The randomized crossover study by Dumais et al. also came to the conclusion that prolotherapy is associated with a marked reduction in symptoms that was sustained for over 24 weeks. The Rabago et al. (2013) single-arm uncontrolled study also found similar results; 36% improvement on the WOMAC.

Conclusions: Both randomized controlled trials and the single-arm uncontrolled studies included in this review indicate that regenerative injection therapy, also known as RIT or prolotherapy, is an effective treatment for knee osteoarthritis in regards to quality of life, pain, and function.

Keywords: Prolotherapy, knee osteoarthritis, regenerative injection therapy

Introduction

Osteoarthritis is becoming extremely prevalent as the population is increasing in age and living longer. It is the most frequent form of arthritis in older adults; most commonly affecting the knees, hips, spine, and hands.[1] Although joint replacement is the definitive treatment, patients and providers are searching for less invasive treatments to prolong quality of life, improve function, and relieve symptoms. This paper evaluates two randomized control studies and one single-arm uncontrolled study, looking at the effectiveness of intra-articular injections of dextrose mixed with lidocaine on function and pain in an osteoarthritic knee.

Osteoarthritis of the knee is one of the five leading causes of disability among non-institutionalized adults.[1] In the United States alone, osteoarthritis affects 13.9% of adults aged 25 and older; 33.6% of those are adults over the age of 65 which amounts to roughly 12.4 million Americans. In 2005, it was conservatively estimated that there were a total of 26.9 million Americans living with OA, which had significantly increased from 21 million in 1990.[1]

Everyday both physician assistants and physicians are working to treat their patients' knee osteoarthritis, with the goal to improve their function and reduce pain. Although the exact number of visits for OA alone is not reported, the American Academy of Orthopaedic Surgeons stated that in 2004 healthcare visits by persons with arthritis or other rheumatic conditions included 44.2 million ambulatory care visits. This represents 5% of all care visits to doctor's offices, ERs, and outpatient clinics.[2] According to the CDC in 2009 the costs due to hospital expenditures of total knee replacements amounted to $28.5 billion, with the total annual costs of OA per patient amounting to $5,700 per year.[1] Nationally, the rate (per 100,000) of knee

replacements has increased 187% from 1991 to 2007, which can be attributed to our growing older population.[1]

The specific causes of OA remain unknown, but is it believed to be a result of both mechanical and molecular events in the affected joint. There are both modifiable and non-modifiable risk factors for OA some of which include; excess body mass, joint injury, occupations that put more stress on the joints, gender, age, race, and genetic disposition. The disease onset is gradual and usually begins after the age of 40. The etiology of pain and disability in knee OA is also not well understood but it is thought that the source of pain most likely includes the joint capsule, ligaments, synovium, bone, and the supportive extra-articular ligaments and tendons.[1]

The diagnosis of knee OA is a clinical diagnosis but the use of X-rays, MRI, and laboratory tests are often used to confirm or solidify the diagnosis. The criteria for OA of the knee include the presence of knee pain plus at least three of the following characteristics: Age >50, morning stiffness lasting less than 30 minutes, crepitus, bone tenderness of the knee, bony enlargement of the knee, and no detectable warmth of the joint to the touch.[3]

There are multiple methods available to help treat osteoarthritis. Some non-medical treatments used are weight loss, physical therapy, orthotics, assistive devices like canes or walkers, dietary supplements like glucosamine and chondroitin, or even the use of capsaicin cream. However, a key component to treating OA is drug therapy which include; NSAIDS, aspirin, glucocorticoid injections, and Hyaluronate injections. The definitive treatment for OA is a total joint replacement, but this is usually reserved for severe OA or OA that is refractory to the less invasive methods.[3]

When lifestyle modifications are not effective, and patients have tried all the medications but are not ready to have a joint replacement, practitioners look for other options to help the individual achieve the outcomes they want. Regenerative Injection therapy (Prolotherapy), is a current pharmacological treatment that may be an alternative beneficial treatment for knee OA that is noninvasive. Prolotherapy is an injection therapy currently used for chronic musculoskeletal injury in which small volumes of a hypertonic dextrose solution are injected into multiple painful areas over several treatment sessions. It is thought that it works by stimulating local healing. [4]

Objective

The objective of this selective EBM review is to determine whether or not "Is regenerative injection therapy (Prolotherapy) effective at reducing pain associated with knee osteoarthritis?"

Methods

This investigation looks at two randomized controlled trials and one single-arm crossover study. In order to participate in the study the participants had to meet specific criteria which included the following; aged 18 and older or between the ages of 40 and 76, diagnosis of knee OA, diagnosed by a radiologist within 5 years of their enrollment, and moderate to severe knee pain for at least 3 months. All studies included regeneration injection therapy (RIT) of dextrose and lidocaine as the intervention therapy. In the randomized controlled crossover study by Dumas et al. and the single-arm uncontrolled trial by Rabago et al. no comparison group was used. In the RCT by Rabago et al. the groups being compared were RIT to a saline placebo and

exercise group. The main outcomes looked at for the purpose of this paper are function and pain reduction.

The author performed searches using the PubMed and Ebscohost databases using the key words of prolotherapy, regenerative injection therapy, and knee osteoarthritis. All searches performed were set for English language. All articles searched were published in peer-reviewed journals after the year 1999 and were selected based on relevance and importance of outcome to the patient. Inclusion criteria for the purpose of this paper included randomized controlled studies, cohort studies, and studies that included POEMs. Exclusion criteria included previous Cochrane reviews, and previous student published systematic reviews. All studies used similar statistics to evaluate the outcomes where p-value is considered statistically significant if it is less than or equal to 0.05. The demographics of the studies are included and outlined below in **Table 1**.

Table 1- Demographics and Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion criteria	Exclusion Criteria	W/D	Intervention
Dumais, 2012 (1)	RCT cross-over	45	18 and older	Dx of knee OA, knee pain for min 6 mo, be able to understand and execute physio-therapy exercises, 18 years and older	Previous knee operation, abnormal coagulation, infection of skin surrounding knee, allergy to lidocaine, pregnancy or breast feeding	9	Regenerative Inj Tx (RIT)- 1cc 15% dextrose & 0.6% lido-caine in 8 collateral ligaments, 5cc 20% dextrose & 0.5% lido-caine inside knee joint
Rabago, 2013 (2)	RCT	98	40-76	Dx of knee OA, dx by radiologist w/in 5 yrs of	Pregnancy, DM, anticoagulation tx, hx of TKR, prior knee prolo-	8	Intra-articular Inj of 5ml 50% dextrose & 5mL lido-

				enrollment, tenderness of ≥1 anterior knee structures on PE, self-reported mod-severe pain for ≥3 months.	therapy, post-infectious knee arthritis, daily opioid use, allergy to study meds, BMI >40kg/m2, severe comor-bidity preventing participation		caine, 1% saline & extra-articular inj of 6.75 mL 50% dextrose, 4.5mL of 1% lidocaine. 11.25mL 0.9% saline
Rabago, 2012 (3)	Single arm uncon-trolled	36	40-76	Dx of knee OA based on clin-ical criteria, identification by a radiologist of knee OA on existing knee radiograph within 5 years, tenderness of one or more anterior knee structures on PE, and mod-severe pain for ≥3 mos prior.	Pregnancy, sig-nificant comor-bidity, anticoag-ulation tx, hx of or planned TKR, prolotherapy or other knee inj w/in past 3 mos, inflammatory or post-infx knee arthritis, daily opioid use, intol/ allergy to study meds, no x-ray of affected knee, BMI >45kg.m2.	2	Intra and extra-articular injections of 25% dextrose

Outcomes Measured

All studies measured the outcomes using the Western Ontario McMaster University Osteoarthritis index (WOMAC), which specifically focuses on pain and functioning.

Results

In the Rabago et al. RCT, 98 patients were used to compare RIT to a saline placebo and were recruited based on a set of inclusion/exclusion criteria provided in **Table 1**. The sample consisted of 66% women with a mean age of 56.7, 74% were either overweight or obese. Patients were randomly assigned to either a dextrose injection group or a saline injection group

(this paper will not focus on the exercise group). The injections were performed at 1, 5, and 9 weeks in an outpatient setting and injected intra- and extra-articularly according to a published protocol. After the injections, participants were offered acetaminophen and eight 5mg oxycodone tablets to use as needed for up to 1 week and were advised to rest the knee for 2-3 days following the injection. The primary outcome measured was the change in knee-related quality of life as assed by the composite score of WOMAC, a questionnaire evaluating OA severity using pain, stiffness, and function. The minimal clinical important difference on the WOMAC for knee OA has been reported as 12 points of change on a 0- to 100-mm visual analog scale. Secondary outcomes were measured using the knee pain scale (KPS). Data was analyzed using SAS 9.1 statistical software; and analysis was by intention-to-treat. Percentage improvement in WOMAC scores was calculated as the change in total WOMAC scores from baseline to 52 weeks.[4] A summary of results can be seen in **Table 2**.

Table 2- WOMAC composite score change, Mean (SE)

	Dextrose	Saline	P Value
52 weeks	15.32	7.59	.022

This study demonstrates that after 52 weeks participants who received the dextrose injection reported improved composite WOMAC scores, a 24% improvement (compared with baseline status) compared with those in the saline placebo group. The P value is .022 which is considered statistically significant. All injection group participants experienced mild to moderate post-injection pain, 3 participants in the dextrose group and 5 in the saline group experienced self-limiting bruising. There were no other side effects or adverse events noted. Overall, 91% of those in the dextrose group would recommend the treatment to other patients.

In the Rabago et al. single-arm uncontrolled study 36 patients were included in the analysis of whom were recruited from outpatient clinics or former control groups. The study consisted of Caucasian adults with an age range of 40-71, the majority were women with a BMI over 25 kg/m^2. The remaining inclusion/exclusion criteria that participants needed to meet can be found in **Table 1**. There were 22 participants that had both knees treated, and 14 who only had a single knee injected totaling 58 total knees. Prolotherapy injections (dextrose and lidocaine) were injected at 1, 5, and 9 weeks according to an existing protocol. Patients were offered acetaminophen and eight 5mg oxycodone tablets to use as needed for pain for up to 1 week post injection and advised to rest for the first 2 days. The primary outcome measured was the change in knee-related quality of life as assed by the composite score of WOMAC. The minimal clinical important difference on the WOMAC for knee OA has been reported as 12 points of change on a 0- to 100-mm visual analog scale. Secondary outcomes were measured using the knee pain scale (KPS). Data was analyzed using SAS 9.1 statistical software; and analysis was by intention-to-treat. Percentage improvement in WOMAC scores was calculated as the change in total WOMAC scores from baseline to 52 weeks.[5] A summary of results can be seen in **Table 3**.

Table 3- total and change in WOMAC score

	Dextrose	P value
52 weeks	+15.9	<.001

This study demonstrates that the WOMAC scores progressively improved from baseline to 52 weeks; the p-value falling within the statistically significant range. The NNT to achieve minimal clinical importance difference of 12% was 2. At the end of the 52 weeks, 38% of the participants achieved a 50% improvement in the total WOMAC score.

In the study done by Dumais et al. they conducted a two-period crossover design in which the experiment was conducted over two consecutive time periods separated by a washout phase. The patients included in this study had to have a diagnosis of knee OA, experience pain for a minimum of 6 months, be 18 years or older, and be able to execute the exercises. The exclusion criteria can be found in **Table 1**. There were a total of 45 enrolled in the study. Group A was given home-based exercise program for 32 weeks in combination with RIT on weeks 0, 4, 8, and 12. Group B was also given the exercise program but had RIT on weeks 20, 24, 28, and 32. The injections were placed using a pre-existing protocol. The primary outcome was assessed using the WOMAC. For the first period, the changes were between week 16 and 0, and for the second period, the change between week 36 and 20 were compared using t-tests.[6] The overall crossover design test results can be found in **Table 4**.

Table 4- Overall Crossover design test

	Est. Change RIT vs control	95% Cl	P value
WOMAC total	-11.9	(-18.4, -5.5)	<0.001

As shown in the results, the use of RIT was associated with marked improvements in WOMAC scores. The statistical analysis suggests that 29.5% of the improvement in WOMAC score can be attributed to RIT, which is considered statistically significant. The RIT regimen was stopped in one participant in group B after reports of diffuse edema of both legs; however, no other adverse events were noted.

Discussion

These three articles showed that the use of RIT for knee OA has been effective in improving the overall quality of life, reducing pain, and increasing functioning. As this becomes

a more popular treatment for knee OA patients must consider the cost of having these injections done. Since prolotherapy is relatively new in the medical field and still experimental, all insurance companies have yet to accept it as a cost-effective treatment. Therefore, depending on one's insurance, the injections may or may not be covered. In instances where it is not covered, providers will oftentimes work with their patients on the payment. The exact price also depends on how many injections the patient needs, but one can expect it to cost between $150-$500 per session.[7]

Limitations of searching for studies were due to the fact that the use of prolotherapy is still very new and experimental. Its specific use in knee OA has not been studied to great extent thus far. A major limitation of these three studies was the small study size. The Dumais et al. study states that the limitations of their study were that it was not sufficiently powered for the secondary outcomes. The analyses would have resulted in more secondary outcomes had there been a larger sample. In addition, another limitation of this study was that no placebo or saline injection control group existed. In the single-arm controlled study by Rabago et al. the limitations were the small sample size, and the assessment of participant satisfaction was indirect and subject to bias. Lastly, the RCT by Rabago et al. stated that the limitation in their study was also the small sample size which did not allow the detection of uncommon adverse events. Another limitation was the relative lack of participants with very severe baseline WOMAC scores.

Conclusion

Although further studies are warranted, after reviewing these three studies evidence strongly suggests that regenerative injection therapy is effective at reducing pain associated with

knee osteoarthritis.[4,5,6] The studies followed the participants for an appropriate amount of time and although the sample size was relatively small in each study, the results found were still considered statistically significant and in favor of RIT. However, all trials could have had larger sample sizes to provide stronger evidence that RIT is effective at reducing pain in knee OA. Future study is warranted to evaluate how many rounds of RIT are needed for substantial pain relief, and if there is a point at which patients become stagnant and do not improve. In addition, it would be beneficial to know how long the effects of RIT last; whether it needs to be repeated yearly or every 5 years etc.

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