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Original Research Article

Effectiveness of dextrose prolotherapy for chronic musculoskeletal pain: A prospective observational study

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ABSTRACT

Background: The increasing prevalence and burden of musculoskeletal conditions has led to an interest in effective nonsurgical solutions, which are more cost efficient and minimally invasive. Prolotherapy is an alternative therapeutic procedure used for management of chronic musculoskeletal conditions which involves injection of irritant solution into affected area. Primary objective of this study was to assess effectiveness of prolotherapy in relieving pain.

Aim & Objective: This study was undertaken to assess the effectiveness of prolotherapy with Inj. Ropivacaine 0.25% & Dextrose 12.5% in patients with chronic musculoskeletal pain. The primary objective was to evaluate reduction in pain 3 months after procedure. Secondary objectives were to assess number of sessions of prolotherapy required, patient satisfaction and complications if any.

Materials and Methods: Seventy patients of either sex aged 18 years and above, diagnosed with a chronic musculoskeletal pain condition, who were selected for the prolotherapy as the treatment modality, were included in the study. All patients received prolotherapy with 0.25% ropivacaine and 12.5% in the involved area.

Results: A Wilcoxon signed-rank test showed that there was statistically significant difference in mean VAS, 3 months after prolotherapy as compared to mean VAS pre-procedure. The mean VAS reduced from 6.61 ± 0.95 at the beginning of the study, reduced to 0.88 ± 1.95 by the end of the study (p = 0.000.) Maximum volume of drug required for adequate pain relief by prolotherapy was 30 cc with the mean of 17.53 ± 7.28. 58.3% of the study population needed 2 sessions of prolotherapy while 10% required 3 sessions. 80% of patients, had more than 50% pain relief at the end of 3rd month after prolotherapy.

Conclusion: Prolotherapy using 12.5% Dextrose + 0.25% Ropivacaine offers minimally invasive, cost effective and safe management option for patient with chronic musculoskeletal pain.

1. Introduction

Musculoskeletal disorders are the most common source of chronic pain. Of all the musculoskeletal complaints, cervical and lumbar back pains are the most common symptoms for which adult patients seek medical intervention. Joints of the upper and lower extremities are other common sites of musculoskeletal pain.[1]

Knee osteoarthritis (OA) affects majority of population and causes significant pain and disability, particularly in older individuals. The prevalence of knee cartilage degeneration is expected to rise with aging world population, thus representing a significant global societal challenge.[2] There is increased interest in regenerative therapy for musculoskeletal disorders and joint degeneration

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induced chronic pain. Regenerative therapies are reported to not only reduce pain but also alter the course of disease. Clinical effectiveness of prolotherapy has been established in lateral epicondylitis as well as chronic back pain.[3–5] Prolotherapy is a regenerative therapy that involves the injection of irritant solutions into tender ligamentous and tendinous attachments and adjacent joint spaces. Irritant solutions produce an inflammatory response, which in turn promotes ligamentous and tendinous regeneration.[6] Different solutions have been studied in the past are hyperosmolar dextrose, phenol glycerine glucose and morrhuate sodium.[7] Dextrose is considered to be an ideal proliferant because it is water soluble, a normal constituent of blood chemistry, and can be injected safely into multiple areas and in large quantity.[8]

The mechanism of regeneration is multifactorial, and is hypothesized to work through stimulation of fibroblast and vascular proliferation, dense collagen deposition, and cartilage growth.[9] Previous researchers have studies different formulations in varied concentrations administered once or in multiple sessions for chronic pain.[10] Hypertonic dextrose solutions act by dehydrating cells at the injection site, leading to local tissue trauma, which in turn attracts granulocytes and macrophages and induce the activation of platelet derived growth factor (PDGF), which stimulates TGF-beta, epidermal growth factor, basic fibroblast growth factor, insulin-like growth factor, and connective tissue growth factor.[11] Hypertonic glucose concentrations is believed to increase the DNA encoding growth factors in different types of human cells and subsequent healing. Dextrose is considered to be an ideal proliferant because it is water soluble, a normal constituent of blood chemistry, and can be injected safely into multiple areas and in large quantity. When used clinically, dextrose concentrations higher than 10% operate in part through inflammatory mechanisms, while concentrations less than 10% are considered noninflammatory.[8] Previous studies have used dextrose concentration of 12.5% with promising results in chronic musculoskeletal pain.[1,12,13] Majority of studies were done in western population and there is paucity of literature in Indian population.So, this study was undertaken to assess the effectiveness of prolotherapy with Inj. Ropivacaine 0.25% & Dextrose 12.5% in patients with chronic musculoskeletal pain. The primary objective was to evaluate reduction in pain 3 months after procedure. Secondary objectives were to assess number of sessions of prolotherapy required, patient satisfaction and complications if any.

2. Materials and Methods

This prospective observational study was carried out from October 2019 to September 2021 at a public teaching tertiary care hospital in India after approval from the Institutional ethics committee. (IEC NO. D02019056). A written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. The research was conducted in accordance with the principles of Declaration of Helsinki, 2013.

A previous study by Rabago D et al.[14] using dextrose prolotherapy for knee osteoarthritis found average 15% change in WOMAC score, 12 weeks after the dextrose prolotherapy. Considering this mean change, with 95% confidence interval and 80% as power of study, sample size was calculated to be 60 using the formula:

$$N = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \times 2\sigma^2}{d^2}$$

where $Z_{\alpha/2}$ is the critical value of the Normal distribution at $\alpha/2$ (for a confidence level of 95%, α is 0.05 and the critical value is 1.96), Z_{β} is the critical value of the Normal distribution at β (for a power of 80%, β is 0.2 and the critical value is 0.84), σ^2 is the population variance, and d is the difference.

Seventy patients of either sex aged 18 years and above, diagnosed with a chronic musculoskeletal pain condition, who were selected for the prolotherapy as the treatment modality, were included in the study. Obstetric patients were excluded from the study.

Pain was assessed using Visual analogue scale (VAS:0-10). Before the procedure patients enrolled for study were explained about VAS. They were asked to rate their pain on a scale of 0 to 0, where 0 represented no pain while 10 represented maximum unbearable pain. As per the protocol, after confirming the basic investigation such as complete blood count, bleeding time and clotting time, 12.5% dextrose mixture was prepared by diluting 25% dextrose (5 ml) with 0.5% Ropivacaine (5 ml) and this prepared mixture was injected by the attending pain physician into a joint space, ligaments or tendon insertion site of the involved area under all aseptic precautions using fluoroscopy or ultrasound guidance. After the procedure patients were advised to take oral Paracetamol (650 mg) three times a day for 7 days after which then they were advised to take tablet paracetamol whenever they experience unbearable pain.

Patients were followed up and pain reduction was assessed using VAS on each follow up visit. VAS was reassessed on post procedure day 1, every week up to 4 weeks then at 2^{nd} and 3^{rd} month. If more than 50% reduction in VAS (as compared to pre intervention VAS) was not achieved at 3 weeks then prolotherapy was repeated.

Total number of injections required, volume of drug used, post-procedure complications if any, and patient satisfaction by using 1-5 satisfaction score (Likert Scale) at 3 months were recorded for all cases. Percentage of patients having pain relief more than 50%, at 3 months was recorded.

2.1. Statistical analysis

Data was entered into Microsoft Excel (Windows 7; Version 2007) and analyses were done using the Statistical Package

for Social Sciences (SPSS) for Windows software (version 22.0; SPSS Inc, Chicago). Descriptive statistics such as mean and standard deviation (SD) for continuous variables, frequencies and percentages were calculated for categorical Variables were determined.

Statistical analysis for calculating VAS was done using a non-parametric test Wilcoxon t test, students paired test and Rank Test. The Wilcoxon signed rank test was used on data obtained before and after procedure to assess changes caused by procedure. The Wilcoxon signed rank test examines information on differences and on magnitude of differences between two studied parameters. Differences of visual analogue scale scores, between sessions were calculated, by taking one from another. Differences were ranked. (Smallest difference was ranked 1 and so on. Scores with no differences were removed. Ranks of positive differences were added up and ranks of negative differences were added up. T was the smallest total rank (+ or -) N was the number of scores (excluding 0 difference) T, the rank was looked up in statistical tables to see if the result is significant. Statistical significance was set at a p value < 0.05. All other objectives were calculated using their mean values before and after study, to find out statistically significant difference between the parameters

3. Results

A total of 60 patients with chronic musculoskeletal pain were given prolotherapy over the period of 2 years. (Table 1) shows demographic characteristics of patients. The Mean BMI of our study population was 29.42 ± 4.54. Forty nine out of sixty patients were obese and had BMI> 30 kg/ m^2, 5 were overweight (BMI > 25 kg/m^2) while 6 were having BMI in normal range. Out of 60 patients 20 patients (33.3%) were presented with shoulder pain. Another 20 patients (33.3%) had coccygodynia, and 18 patients (30%) were having knee pain, one patient had wrist pain and one had ankle pain.

Table 1: Demographic characteristics

Parameter	Mean ± SD/ number (%) N= 60
Age	46.13 ± 9.65
Weight (kg)	72.93 ± 9.60
Height (cms)	157.87 ± 6.90
BMI	29.42 ± 4.54
Male /female	26(43.3)/34(56.7)
Shoulder/ coccygodynia/ knee/ wrist/ankle	20(33.3)/20(33.3)/ 18(30)/1(1.7)/1(1.7)

The Mean VAS of our study population initially was 6.61 ± 0.95, which reduced to 0.91 ± 2.02 after prolotherapy.

A Wilcoxon signed-rank test showed that after 3 months of prolotherapy sessions, there were high statistically significant changes in VAS as compared to day 1 VAS with Z = -6.59 and p = 0.000 as shown in (Tables 2 and 3)

Table 2: Wilcoxon signed-rank

Rank	N	Mean Rank	Sum of Ranks
Negative Ranks	56[a]	28.50	1596.00
Positive Ranks	0[b]	.00	.00
Ties	4[c]		
Total	60		

a. 3 month VAS < Day 1 VAS; b. 3 month VAS > Day 1 VAS; c. 3 month VAS = Day 1 VAS

Table 3: Test statistics[a]

Test applied	3-month VAS - Day 1 VAS
Z	-6.594[b]
Asymp. Sig. (2-tailed)	.000

[a] Wilcoxon Signed Ranks Test; b Based on positive ranks

48 out of 60 (majority) patients, who comprise 80% of the population, had more than complete pain relief at the end of 3^{rd} month after receiving prolotherapy. 4 patients had more than 50% relief as shown in (Table 4). 52 patients out of 60 patients had more than 50% of pain relief (86%) as shown in (Table 4).

Table 4: Percentage of pain relief

% Pain reduction at 3 months	No. of patients	% of patients
10	1	1.67%
20	1	1.67%
30	2	3.33%
40	2	3.33%
50	2	3.33%
60	1	1.67%
80	2	3.33%
90	1	1.67%
100	48	80.00%

35 patients (58.3%) comprising the maximum of the study population needed 2 injections(sessions) of prolotherapy for pain relief. 19 patients (31.7%) required 1 injection and 6 patients (10%) required 3 injections of prolotherapy for adequate pain relief.

43 (71.7%) out of 60 patients gave a satisfaction score of 5, stating they were highly satisfied with the treatment. 9 patients (15%) gave a score of 4 stating that they were satisfied. 8 patients (13.3%) had a neutral response to the procedure, giving a score of 3 out of 5 as shown in (Table 5).

Table 5: Patient satisfaction score

Patient satisfaction score at 3 months	N	Percentage (%)
3	8	13.3%
4	9	15.0%
5	43	71.7%
Totals	60	100.0%

Subgroup analysis (Table 6) of the study population showed following results. 20 cases of the study population were diagnosed with frozen shoulder. On analysis reduction in the VAS score at the beginning from 6.80 ± 0.89 to 1.3 ± 2.36, was found statistically significant with p values of 0.00 and z= -3.77. Average volume required for prolotherapy in shoulder pain patients was 25.45 ± 6.20 ml. Out of 20 patients who received prolotherapy for shoulder pain few required multiple injections for adequate pain relief 11 patients (55%) needed 2 injections and 3 patients (15%) required 3 injections. 75% of patients gained complete pain relief after prolotherapy, 2 patients had 50% pain relief, while in 3 cases pain persisted despite three sessions of prolotherapy.

Another subgroup consisted of 20 patients diagnosed with coccygodynia, the mean of VAS after prolotherapy for coccygodynia was reduced from 6.8 ± 0.89 to 1.3 ± 2.36. 14 patients (15%) required 2 sessions of injection, 3 patients (15%) required 1 injection, while the remaining 3 (15%) required 3 sessions of prolotherapy for desired pain relief. 90% of the study population of coccygodynia who received prolotherapy, gained 100% pain relief after prolotherapy.

Another subgroup of 18 patients having knee pain, forming 30% of the study population who received prolotherapy showed that the mean VAS for this patient was 6.55 ± 04 at the beginning of the study was reduced to 0.5 ± 1.09 by the end of the study. 50% of this study population required 2 injections and another 50% required 3 injections of prolotherapy for adequate pain relief. Complete pain relief was achieved in 72.1% of patient. Overall, 17 patients out of 18, comprising of 94% of population received more than 50% pain relief after prolotherapy.

4. Discussion

Chronic pain is now recognised as a separate speciality and non- surgical methods to relieve chronic pain are increasingly becoming popular. Regenerative injection therapy (RIT) commonly known as Prolotherapy (assumingly named after Proliferative effect of therapy) is alluring option due to its effect on altering the degenerating effects of primary pathology.[15,16]

This prospective observational study showed that prolotherapy causes statistically significant reduction in pain. The mean VAS which was 6.61 ± 0.95 at the beginning of the study, reduced to 0.88 ± 1.95 by the end of the study. 80% of patients, had more than 50% pain relief at the end of 3rd month after prolotherapy leading to reduction in the analgesics requirement to almost zero in 83% of patients. A previous review which aimed at reviewing dextrose (D-glucose) prolotherapy efficacy in the treatment of chronic musculoskeletal pain, concluded that the use of dextrose prolotherapy is supported for the treatment of tendinopathies, knee and finger joint OA, and spinal/pelvic pain due to ligament dysfunction.[1]

The most common prolotherapy agent used in clinical practice is dextrose, with concentrations ranging from 12.5% to 25%. Dextrose is considered to be an ideal proliferant because it is water soluble, a normal constituent of blood chemistry, and can be injected safely into multiple areas and in large quantity. When used clinically, dextrose concentrations higher than 10% operate in part through inflammatory mechanisms, while concentrations less than 10% are considered noninflammatory.[8] Injecting a hyperosmolar solution is believed to remodulate the local vascular hemodynamic, and a consequent decrease in nociceptive activity.[17] The exact mechanism leading a rapid improvement in pain experienced by these patients is not known. On the other hand, the demonstrated durability of the response is not associated only with chemo modulatory effects: lasting benefit results from the growth factor release and tissue-stabilizing effects of dextrose. The potential tissue stabilizing benefits of prolotherapy dextrose injection may occur in ligaments, tendons and cartilage, since in chondrocytes and fibroblasts an anabolic response is triggered by platelet derived growth factor, transforming growth factor beta, insulin like growth factor, basic fibroblast growth factor and connective tissue growth factor. The hyperosmolarity of the dextrose solution activates enzymes such as phosphate donors, i.e. kinases, which may exert a beneficial growth effect.[18,19]

Our results show that prolotherapy was effective treatment modality for chronic shoulder pain. Previous researchers have also reported similar reduction in VAS score after dextrose prolotherapy of shoulder joint.[20,21] In a systematic review of 272 patients, where hyperosmolar dextrose solution was injected for rotator cuff tendinopathy reported found statistically significant reduction in pain intensity with multisite injection protocols compared to physical therapy and medical management.[21] The mean volume of drug used for this subgroup was 25.45 ± 6.20. this was in accordance to the previous studies.[21] Most patients in our study required 2 sessions of prolotherapy while a previous study used minimum of 2 and maximum of 6 injections of prolotherapy, according to the requirement for shoulder prolotherapy.[20] Some studies have reported use of 3 injections of prolotherapy for adequate pain relief.[22]

We had 20 cases with coccygodynia. The most common cause of coccygodynia is trauma. Non traumatic coccygodynia include a number of causes like degenerative joint or disc disease, hypermobility or hypomobility of the sacrococcygeal joint, infectious aetiology, and variants of coccygeal morphology. Khan SA et al. reported reduction in mean VAS from 8.5 to 3.4 with 81% of patients having good pain relief after prolotherapy for coccygodynia. While most patients in study by Khan et al. required 2 injections of prolotherapy for coccygodynia, 8 patients required 3 sessions.[23] A similar reduction in VAS was also reported by other researchers[24,25] after 6 months follow up.

Table 6: Subgroup analysis

	VAS Pre	VAS at 3 Month	Vol (ml)	No. Injections (inj)	Percentage of Pain relief
Shoulder pain (20)	6.80 ± 0.89	1.3 ±2.36	25.45 ± 6.20	6 – 1 inj 11 – 2 inj 3 – 3 inj	15 – 100% 2 – 50% 3 – No relief
Knee pain (18)	6.55 ± 04	0.5 ± 1.09	15.5 ± 2.89	9 – 2 inj 9 – 3 inj	13 – 100% 2 – 80% 3 – No relief
Coccygodynia (20)	6.8 ± 0.89	1.3 ± 2.36	11.2 ± 2.42	3 – 1 inj 14 – 2 inj 3 – 3 inj	18 – 100% 2 – No relief

30% of our study population were patients with chronic knee pain due to osteoarthritis. In recent years, regenerative medicine has emerged as a promising non-surgical approach for treating osteoarthritis of the knee. This approach involves using various biological materials, such as growth factors, stem cells, platelet-rich plasma (PRP), and prolotherapy to stimulate tissue repair and reduce inflammation. Among which prolotherapy was feasible option as its easily available with minimum cost as compared to various biological factors. Prolotherapy was found to be helpful in reducing the pain with statistically significant reduction in pain (p value 0.000). This was in accordance with previous studies[16,26] on prolotherapy for knee pain. Prolotherapy is reported to confer a positive and significantly beneficial effect in the treatment of knee OA with reduction in pain scores and improvement in WOMAC score. Intraarticular dextrose prolotherapy was found to be superior to normal saline in reducing pain while improving function and quality of life.[27] Most previous researchers have used 3-5 injections of dextrose prolotherapy for knee OA. Half of our study population with knee OA required 2 injections while other half required 3 injections. Previoius studies have used average of 3-5 injections.[17,26] A systematic review that included 10 randomised controlled trials and 328 patients treated with hypertonic dextrose prolotherapy reported use of 1 to 5 number of prolotherapy sessions with mode of 3.[10]

Prolotherapy is effective in treating many conditions with few adverse effects. While most studies have reported no major complication, mild to moderate pain, inflammation and self-limiting hematomas have been reported in few studies.[10] Patients may report a sense of fullness or an occasional numbness at the injection site. These side effects are usually self-limiting.[8] Acetaminophen is usually effective for post-injection pain in first 72 hours. If pain persists beyond this time, it could be because of residual ligament, tendon trigger points, excess volume injection or a stronger proliferant resulting in central hypersensitivity reaction. Light headedness, an allergic reaction, infection, or neurological damage are all potential side effects of prolotherapy injections. Most previous studies have not mentioned the volume of drug used in prolotherapy. We required minimum of 10 cc and maximum of 20 cc with a mean of 15.5 ± 2.89 drug volume for prolotherapy. This was similar to study done by Rabago D et al. who used average of 28 cc Dextrose 15% with local anaesthetic agent.[15]

There is great heterogeneity among the studies in term of patients characteristic, study design, concentration of injected ingredients, outcome measures, number of injections, time span between each injection and length of post-treatment follow-up. Optimal volume and concentration of injected substances, the number of treatment sessions and time interval between administration have to be unified.[16]

This study has few limitations. The sample size of only 60 patients was relatively smaller for concluding significant results of effects of prolotherapy. Absence of control group limits the strength of the findings. Due to logistics and infrastructural constraints, imaging studies could not be done to have objective evidence of improvement. Patient reported outcome was used to assess the effectiveness of intervention.

5. Conclusion

Prolotherapy using 12.5% Dextrose + 0.25% Ropivacaine may offer a minimally invasive, cost effective, and safe management option for patients with chronic musculoskeletal pain.

6. Source of Funding

None.

7. Conflict of Interest

None.

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