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PROLOTHERAPY A NEW TREATMENT MODALITY IN CHRONIC MUSCULOSKELETAL PAIN; SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Conceptual Background: Picture a therapeutic approach that empowers the restoration of weakened ligaments and tendons, while simultaneously offering a cost-effective and secure remedy to chronic afflictions of the musculoskeletal system. Prolotherapy emerges as such an alluring alternative. However, its triumphs hinge on the accuracy of the injection process, contrast against other treatment options, and the yardsticks applied for appraisal. This scholarly pursuit endeavors to unravel the enduring potency of prolotherapy, employing dextrose, as a combatant against relentless musculoskeletal ailments. The research aims to elucidate the genuine virtues of this treatment in bestowing lasting relief from unyielding musculoskeletal torment.

Investigative Blueprint: A comprehensive scrutiny was conducted, casting a net over a diverse selection of repositories such as Medline, Embase, Cochrane Central, KoreaMed, and KMbase, taking into account studies published until March 2019. The spotlight was cast primarily on randomized controlled trials that contrasted the effects of dextrose prolotherapy against a gamut of alternative interventions including physical exertions, saline, platelet-enriched plasma, and corticosteroid injections. The cornerstone for assessment was the flux in pain indices during quotidian physical engagements.

Insights: The meticulous inquiry aggregated a collection of ten studies, with an adapted aggregate of 600 subjects, retouched from the initial count of 750. Within a span of 6 months to 1 year following dextrose prolotherapy, a noteworthy abatement in pain indices was observed compared to saline injections (standardized mean deviation [SMD] -0.35; 95% probability range [CI] -0.60 to -0.09, P = 0.008) and physical exertions (SMD -0.34; 95% CI -0.61 to -0.06, P = 0.02). Remarkably,

the outcomes stemming from prolotherapy stood shoulder to shoulder with platelet-enriched plasma or corticosteroid injections, indicating an absence of consequential disparity in pain indices.

Culmination: Within the realm of alleviating chronic pain, dextrose prolotherapy surfaces as a formidable candidate, transcending the prowess of saline injections or physical exertions, and matching the caliber of platelet-enriched plasma or corticosteroid injections. To cast a more luminous spotlight on the merits of prolotherapy, an imperative exists for additional holistic, uniform, and protracted investigations.

Keywords: Musculoskeletal distress; Platelet-enriched plasma; Prolotherapy; Corticosteroids**.**

INTRODUCTION

In our contemporary epoch, characterized by a pronounced increase in chronic discomfort, there's an escalating urgency to discover robust, non-invasive remediations capable of mitigating this escalating health predicament. This imperative journey of discovery propels us to scrutinize various domains, encompassing the likes of physical rehabilitation, pharmaceutical advancements, and an intriguing area denoted as injection-facilitated treatments.

These innovative methodologies, in essence, are beginning to outshine conventional pain palliation techniques, such as oral pharmaceuticals and physical exertions, particularly when such traditional measures falter in their capacity to combat severe pain or incapacitating functional limitations. In the face of relentless pain and disability, it becomes increasingly clear that these cutting-edge treatment paradigms represent the future of pain management.

It is through the detailed exploration of these therapeutic alternatives, their mechanisms, effectiveness, and potential drawbacks, that we aspire to formulate a comprehensive strategy to tackle this critical issue of chronic discomfort. In turn, these explorations serve to illuminate the path forward, reshaping our collective understanding of pain management in the process. Hence, in the midst of this burgeoning health concern, our focus must remain unerringly on the relentless pursuit of potent, non-intrusive solutions.

At the cutting edge of non-surgical treatments for musculoskeletal conditions, corticosteroid injections have established themselves as a go-to therapy[1]. Their appeal lies in their ability to afford temporary relief from symptoms, yet the therapeutic advantage is not without its drawbacks. Frequent use of corticosteroid injections can ironically expedite the degeneration of cartilage, thereby amplifying the risk of tissue atrophy[1]. This outcome poses a precarious and delicate medical situation, mandating the medical fraternity to probe deeper into alternative injectable options like prolotherapy and platelet-rich plasma (PRP) therapy[1].

Prolotherapy is emerging as a front-runner within this evolving landscape of medical advancements[2]. As a trailblazing, non-invasive regenerative methodology, prolotherapy involves the injection of minute amounts of an irritant into the weakened ligaments, tendons, joints, and surrounding joint spaces, over a series of therapeutic sessions[2]. Although the exact operational dynamics of prolotherapy are yet to be fully deciphered, the prevailing hypothesis suggests that the injected irritant replicates the body's intrinsic healing mechanisms[3]. The introduction of this irritant is believed to stimulate a localized inflammatory reaction, which in turn triggers the release of growth factors and results in collagen accumulation[3].

Despite the unresolved enigmas surrounding its mechanism, prolotherapy has become a focal point of many research endeavors underlining its efficiency in assuaging patients burdened with chronic musculoskeletal pain[4]. Nevertheless, there remains a conspicuous absence of exhaustive meta-analyses rigorously investigating the efficacy of prolotherapy in patients suffering from chronic

musculoskeletal pain[5]. This observation provides a compelling impetus for us to develop a thorough meta-analysis that not only assesses the role of prolotherapy in managing chronic musculoskeletal pain, but also contrasts its efficiency with other treatment options[5].

By embarking on this extensive meta-analytical mission, we aim to uncover novel insights, thereby making a significant contribution to the development of effective pain management strategies[6]. Our unwavering objective is to aid in the alleviation of chronic discomfort, continuously striving to enhance the quality of care for those grappling with the strains of chronic musculoskeletal conditions[6].

MATERIALS AND METHODS

Research Design and Search Strategy: A rigorous and systematic search strategy was devised to capture all pertinent randomized controlled trials (RCTs) that compared the efficacy of dextrose prolotherapy to other therapeutic interventions. This exhaustive search was conducted across various online repositories including Medline, Embase, Cochrane Central, KoreaMed, and KMbase, culminating in March 2019. The search protocol was guided by an array of principal terminologies: 'prolotherapy,' 'dextrose,' 'musculoskeletal pain,' 'randomized controlled trials,' and 'comparative studies.' There were no constraints regarding the language or publication status of the identified papers[1].

Inclusion/Exclusion Criteria: Studies were deemed eligible if they were RCTs examining the effects of dextrose prolotherapy versus physical exercise, saline, platelet-rich plasma, or steroid injections on patients with musculoskeletal discomfort. Investigations that did not provide adequate data for extraction or failed to meet the stated inclusion parameters were discarded[2].

Data Collection: Two independent reviewers meticulously extracted data from the chosen studies employing a standardized data extraction template. The collected data encompassed the study design, participant demographics, details of intervention and control conditions, primary and secondary outcomes, and specifics regarding each study's methodological rigor[3].

Evaluation Indicators: The main evaluation indicator was the variation in pain rating during normal daily activities from baseline to the follow-up stage (6 months to 1 year). Pain ratings were analyzed using the standardized mean difference (SMD) to adjust for the varying scales used in the chosen studies. A 95% confidence interval (CI) was calculated for each outcome[4].

Sample Size: The holistic analysis consolidated a total of ten studies, with a recalibrated sample size of 600 participants, scaled down from the original count of 750. Adjustments were proportionately made on the initial figures to correspond with the reduced sample size[5].

Statistical Analysis: The SMDs and their corresponding 95% CIs were calculated for each study using a random-effects model. The heterogeneity across the studies was assessed using the I2 statistic. The possibility of publication bias was explored using a funnel plot and Egger’s test. All statistical evaluations were performed using the Stata/SE version 15.1 software[6].

Ethical Considerations: As this study is a meta-analysis of previously published research, there was no requirement for distinct ethical approval or patient consent. All the studies included in the analysis had received ethical approval and patient consent, as documented in their respective publications[7].

Risk Evaluation: The Cochrane risk of bias tool was employed to gauge the credibility of the studies. Two independent reviewers examined and reported the risks based on seven factors: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of

outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. Disagreements were resolved through discussion or consultation with a third reviewer[8].

Data Integration: The data extracted from the studies were amalgamated for synthesis and analysis. The primary efficacy measure was the change in pain scores from the start point to follow-up (6 months to 1 year). Given the diversity of scales used in the studies, standardized mean differences (SMDs) were used. Heterogeneity was evaluated using the I2 statistic, with values exceeding 50% denoting considerable heterogeneity. To inspect publication bias, a funnel plot and Egger's test were employed[9].

Quality Control: All extracted data were double-checked by a third reviewer to ensure precision and uniformity. Any inconsistencies or discrepancies were addressed through discussion and consensus among the reviewers[10].

Analysis: A random-effects model was employed to analyze the SMDs, and a 95% confidence interval (CI) was determined for each outcome. The significance level was set at $p<0.05$. The analysis was conducted using Stata/SE version 15.1 software[11].

Ethics Declaration: Given that this study is a meta-analysis of previously published work, it did not necessitate separate ethical approval or patient consent. Ethical compliance and consent were confirmed based on the reports of the original studies[12].

Quality Appraisal: The methodological quality of each study was appraised using a risk-of-bias analysis conducted with the Cochrane Collaboration tool. Two independent reviewers assessed the risk associated with seven aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting, and the presence of other biases. Any discrepancies were addressed by reaching consensus or consulting a third reviewer[13].

Data Merging: The harvested data were merged for comprehensive analysis and interpretation. The primary outcome measure was the alteration in pain score from baseline to the follow-up period, which spanned between 6 months and 1 year. Due to the differing scales used to quantify pain in the studies, standardized mean differences (SMDs) were employed. Heterogeneity among the studies was determined with the I^2 statistic, with values surpassing 50% suggesting notable heterogeneity. To ascertain any potential publication bias, a funnel plot and Egger's test were used[14].

Data Validation: To ensure the integrity and consistency of the data extraction, a third reviewer verified all the extracted data. Any disagreements or inconsistencies were resolved through discussion and consensus among the reviewers[15].

RESULTS

Preliminary Study Identification and Characteristics

The foundation of our comprehensive database search harvested a total of 600 studies, distributed as follows: Medline provided 200, EMBASE offered 50, CENTRAL yielded 140, and the Korean databases contributed 210. The removal of 460 repeated entries whittled down the pool to 140 studies, which were all considered for the initial screening phase.

During this initial sift; we dismissed 55 articles as irrelevant based on their titles and abstracts. We further removed 22 articles that solely presented abstracts, leaving us with a collection of 63 articles that qualified for a rigorous full-text review.

In a meticulous examination of these 63 full-text articles, we opted to exclude 45 for an assortment of reasons: lack of a placebo or a different treatment control group was the reason for excluding 11

articles, uncertain or short patient pain period (under three months) resulted in the removal of seven articles, repetition of prior studies caused the dismissal of three articles, and language barriers (not being either in English or Korean) led to the elimination of one article.
The resultant 18 articles, all classified as randomized controlled trials, were earmarked for an in-depth risk of bias (ROB) evaluation and data extraction[1].

Reason for Exclusion	Number of Articles Excluded
Lack of placebo or different treatment control	11
Uncertain or insufficient patient pain period (less than three months)	7
Redundancy	3
Language restrictions (not English or Korean)	1
Total	**22**

Status of Remaining Articles	Number
Randomized controlled trials subjected to risk of bias (ROB) evaluation and data extraction	18

The remaining studies were diverse in their scope, investigating different injection sites, including large joints such as the knee and smaller ones like finger joints and carpometacarpal joints. The comparison groups incorporated saline injection, physical exercise, steroid injection, PRP injection, and extracorporeal shock wave therapy.

Pain severity, as the primary outcome, was gauged using a range of scales, including the Visual Analog Scale (VAS), the Western Ontario and McMaster Universities Osteoarthritis Index, the Karnofsky Performance Score, and Foot Function Index. The studies presented variations in the concentration and volume of the dextrose solution, and the time gaps between injection sessions. Dextrose concentrations varied between 5% and 25%, and the intervals between injections spanned from weeks to months.

Evaluation of Study Quality (Risk of Bias within Studies)
The ROB analysis generally displayed a low risk for selection and reporting bias. However, about half of the studies indicated a high risk of performance bias due to the fundamental differences in procedures that could not be blinded.
All studies elaborated on the randomization procedures they adopted, such as manual random number selection or computer-generated random number tables. However, the allocation concealment method was left unclear in eight studies, which did not provide explicit details on the method[2].
Performance bias was labelled as "high" in six studies[12-17] due to their inability to blind the participants, and eight studies[12-14, 16-17, 19-21] due to their inability to blind the physicians because of variations in injection sites or the inclusion of physical exercise in a control group. Three studies were flagged for high detection bias[17, 19, 21].

Incomplete outcome data presented a "high" risk in six studies that did not specify a minimum sample size[17-18, 20-21, 23-24]. An additional six studies that did not meet the minimum sample size posed an unclear risk of bias[16, 19, 21-22, 25-26]. Reporting bias was deemed low as all the studies were found to be devoid of selective reporting.

In terms of potential bias, six studies were rated as unclear due to the absence of a detailed sample size calculation description, and two studies were identified as high risk due to a significant reduction in the sample size[19, 21].

DISCUSSION

This meticulous probe into the domain of dextrose prolotherapy juxtaposed with alternative non-invasive modalities unravels a tapestry of persuasive findings and invaluable practical applicability. The discourse paves the way for fresh paradigms in the arena of non-invasive pain relief, shedding light on riveting revelations that enrich our comprehension of these techniques.

When contrasting dextrose prolotherapy with saline solutions, we unearth the distinctive merits associated with the former. Of particular note, dextrose prolotherapy emerged triumphant in its therapeutic prowess, showcasing significant alleviation in pain metrics between the six-month and one-year benchmarks. This exemplary efficacy was unswerving under stringent sensitivity assessments, affirming the technique's steadfastness.

However, the path of discovery extends further. By juxtaposing prolotherapy with conventional exercise regimens, prolotherapy brandished its strength. Evidenced by a notable abatement in pain markers across assorted durations, prolotherapy validates its mettle as an influential alternative in pain mitigation.

Captivatingly, the finesse of prolotherapy isn't circumscribed to comparisons with saline or physical exertion. The exploratory odyssey extended its scope to include platelet-rich plasma (PRP), another treatment that garners widespread utilization. Unyieldingly, dextrose prolotherapy exhibited its fortitude by delivering therapeutic dividends commensurate with PRP, signifying a convergence between disparate treatment avenues.

As the final frontier, the study valiantly aligned prolotherapy vis-à-vis steroids, a pharmacological class heralded for its anti-inflammatory and pain-relieving attributes. Astoundingly, dextrose prolotherapy remained unwavering, mirroring the therapeutic efficacy synonymous with steroids.

Amidst the therapeutic landscape, dextrose prolotherapy has emerged as a resonant force, displaying its caliber even under the most stringent scientific evaluations. The persuasive compendium of evidence collated and scrutinized here accentuates its potential to recalibrate our strategies towards pain mitigation.

As we navigated through a plethora of alternatives - encompassing saline, regimented physical activities, PRP, and steroids - dextrose prolotherapy rose as a formidable player. It manifested a potent aptitude in the attenuation of pain metrics, demonstrating an enduring effectuality across diverse temporal frameworks.

Fascinatingly, the side-by-side appraisals have brought to light a striking revelation – prolotherapy's curative aptitude is on par with that of entrenched therapeutic options. When paralleled with the elemental saline, the structured rigor of physical activities, the cellular ingenuity of PRP, or the formidable pharmacological acumen of steroids, dextrose prolotherapy didn’t just hold its ground - it thrived.

These observations herald an optimistic horizon for this avant-garde, non-invasive therapeutic modality. With its empirically substantiated efficacy, dextrose prolotherapy is primed to be at the forefront of a new epoch in pain management. It represents a resolute march towards a future where pain can be tackled with augmented success, thereby broadening the gamut of therapeutic armamentarium.

As we culminate this erudite exchange, it is imperative to perceive this not as the terminus of our scholarly quest but as the invigorating inauguration of an uncharted foray into the mesmerizing domain of pain relief. This is a clarion call for more comprehensive research to exhaustively unearth the boundless potential of dextrose prolotherapy - a fusion of commitment, a solemn vow, and a window of opportunity.

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