

Peer Review File

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Reviewer Comments

Comment 1: “First, in general, a case series should have a minimum of 5 cases, so this study is only a case report. Please consider to revise the title and other places of this manuscript.”

Reply 1: Will revise the title and related areas in the manuscript

Changes in the text: See Title: Novel periarticular dextrose prolotherapy technique improves pain and function in three patients with idiopathic total knee arthroplasty

Comment 2: “Second, in the background part of abstract, the authors should explain why there is a need for the novel treatment for idiopathic post-TKA pain. In its methods part, the authors should describe the assessment of efficacy and safety. In the part of result, the duration of follow up should be provided to indicate how the efficacy persists. In the part of conclusion, the authors should not only focus on safety.”

Reply 2: There are limited treatment options for idiopathic post-TKA pain: physical therapy, topical and oral analgesics. Geniculate nerve ablation and selective peripheral nerve resection are other, yet more invasive treatments. Efficacy was assessed via improvement in numeric pain scale and WOMAC scores before and after the procedure. Since these are case reports, the post-injection follow up varied as all patients followed up at different times. Safety was demonstrated by the absence of adverse issues after the procedure. We conclude that we are presenting a novel approach to administering dextrose prolotherapy for the knee, a technique that is relatively easy to learn thus making it more accessible to providers and patients, in addition to being a relatively safe and noninvasive treatment for post TKA pain.

Changes in the text: See Abstract lines 4-5, 6-9, 12-15.

Comment 3: “Third, in the part of introduction, please have a brief review on existing treatments for idiopathic post-TKA pain, comment on their limitations and indicate why there is a need for the proposed novel treatment. The current review is far inadequate.”

Reply 3: There are limited treatment options for idiopathic post-TKA pain: physical therapy, topical and oral analgesics. Geniculate nerve ablation and selective peripheral nerve resection are other, yet more invasive treatments. Indeed the current review is limited as there is sparse publications on post TKA treatments. Geniculate nerve blocks followed by radiofrequency ablation has been a more sought after procedure in recent years but maybe limited in access due various factors including but not limited to: cost, insurance coverage, limited number of specialists able to perform the procedure. These procedures are usually performed in a surgical center needing a number of staff to assist with procedure. This novel prolotherapy technique may be easier to learn and is given in an office setting without the need for assistance to administer the injection. This may in turn lead to more specialists being able to learn and administer this technique, additionally, making it more accessible to patients.

Changes in the text: See Introduction lines 35-39.

Comment 4: “Fourth, in the part of case presentation, the authors provided three successfully treated cases, however, I want to know whether there were failed cases. The authors should consider to provide more clinical characteristics of the cases, including main complainants, history, laboratory and imaging findings, diagnosis, treatment, and prognosis. The current version is too simple and not detailed enough.”

Reply 4: Regarding failed cases, the lead author previously experimented with a wide range of knee pathology and, while not every patient had any or drastic relief, a number of patients demonstrated good relief. We decided to further investigate this technique in a more specific subset of patients (post-TKA knee pain) and these are the results we experienced thus far.

Changes in the text: See Discussion lines 160-165

Comment 5: “Fifth, in the discussion part, please have more insights on the mechanisms underlying the novel treatment. Please also have some comments on issues to be addressed in relation to the current treatment. The conclusion is overstated because this is not a controlled trial. It is difficult to answer the question of whether the treatment is effective and safe.”

Reply 5: The mechanism is still unclear but we can give insight as to our analysis of current similar methods.

In the cases where the knee joint is unstable with laxity, prolotherapy can be a means to help fortify the surrounding stabilizing tendons by its traditional mechanism of promoting the local inflammation response to in turn re-stimulate the healing cascade. However, in these cases where there were no signs of instability, the mechanism appears to have more of an analgesic effect similar to a geniculate nerve block but more superficial and using very small volume of total solution with even less amount of anesthetic used in typical geniculate nerve blocks used prior to TKA with the goals of improving post operative recovery, physical performance scores, decreasing the need for opioids and recovery analgesics (eg, 20ml of anesthetic) (\$\$\$). It also has similarities to the neural prolotherapy pathway to alleviate neurogenic inflammation but at a higher dextrose concentration and using less injection sites versus typical neural prolotherapy techniques.

Regarding efficacy and safety. Efficacy can be shown with decreased and improved WOMAC scores. Safety can be determined by the prevalence of any adverse effects that occurred after the treatments were given.

Changes in the text: See Discussion lines 152-157, 173-200.