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### Qualitative Assessment of Patients Receiving Prolotherapy for Knee Osteoarthritis in a Multimethod Study

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#### Abstract

**Objective:** Randomized and open-label studies assessing prolotherapy for knee osteoarthritis have found quantitative improvement on the validated Western Ontario McMaster University Osteoarthritis Index (WOMAC) compared with baseline status and control therapies. This study assessed the qualitative response of participants receiving prolotherapy, an injection-based complementary treatment for symptomatic knee osteoarthritis (OA).

**Design:** Qualitative study using semi-structured in-depth interviews at 52 weeks after enrollment; transcribed responses were discussed by coauthors to identify themes; disagreement was resolved by consensus.

**Setting:** Outpatient.

**Participants:** Twenty-two participants treated with prolotherapy for symptomatic knee OA who were exited from three randomized and open-label studies.

**Interventions:** Intra- and extra-articular hypertonic dextrose injection (prolotherapy).

**Main outcome measures:** Patient narrative and composite WOMAC questionnaire (0–100 points) scores.

**Results:** Participants had baseline demographic and knee OA severity similar to those of participants in three prior intervention trials, as well as similar robust follow-up WOMAC score change ( $19.9 \pm 12.6$  points), suggesting a representative subsample. Seven themes were identified from participant narratives: (1) improvement in knee-specific quality of life ( $n = 18$ ), (2) safety and comfort, (3) pretreatment counseling enhanced treatment adherence and optimism, (4) overall positive experience with prolotherapy, (5) limited response to prolotherapy ( $n = 4$ ), (6) consistency with anecdotal clinical prolotherapy experience; and (7) functional improvement without pain reduction.

**Conclusions:** Most participants reported substantially improved knee-specific effects, resulting in improved quality of life and activities of daily living; four participants reported minimal or no effect. Clear, complete description of procedural rationale may enhance optimism about and adherence to treatment appointments.

**Keywords:** : prolotherapy, regenerative medicine, dextrose injection, knee osteoarthritis, qualitative study

## Introduction

KNEE OSTEOARTHRITIS (OA) is a chronic disease resulting in joint pain, stiffness, and decreased function.<sup>1</sup> The disease is common and expensive.<sup>2</sup> By age 65 years, one third of the U.S. population has radiographic evidence of osteoarthritis.<sup>3</sup> Authors of a recent systematic review of common therapies reported no clear benefit of any one therapy for knee OA;<sup>3</sup> several studies of alternative treatments have reported variable or modest positive results,<sup>4–6</sup> including acupuncture<sup>7</sup> and *t'ai chi*.<sup>8</sup> National agencies have prioritized the assessment of new treatments for knee OA.<sup>3,9</sup>

Prolotherapy is a complementary injection therapy for chronic musculoskeletal injury,<sup>10,11</sup> including knee OA.<sup>12</sup> The therapy targets multiple potential pain generators in and around the knee joint. Three randomized controlled trials (RCTs)<sup>12–14</sup> and two open-label studies<sup>15,16</sup> reported longitudinal improvement in self-reported knee OA outcomes in response to prolotherapy compared with baseline status, blinded placebo control injections, and active treatment. The improvement met benchmarks for minimal clinically important improvement on the WOMAC measure, side effects were minimal, and participant satisfaction was high. A recent systematic review with meta-analysis concurred with these findings.<sup>17</sup>

Potential translation to routine care for knee OA is limited by lack of familiarity with the procedure, fear of injection-based therapy, and the absence of qualitative assessment of the patient's experience, which can provide important information about the context of interventions. Such qualitative assessment may facilitate patient understanding of what a treatment might mean for quality of life while empowering clinicians to personalize therapy to individual patients. The current investigation, a qualitative study, was conducted to assess perceptions and experiences among participants who received prolotherapy for knee OA.

## Materials and Methods

The study protocol was approved by the University of Wisconsin Health Sciences Institutional Review Board. The inclusion criterion for the current study was participation in, and completion of, prolotherapy intervention for knee OA in one of three clinical trials assessing prolotherapy for knee OA.<sup>15,16,18</sup> The eligibility criteria of the three intervention studies have been published and were

similar to one another; the primary criteria for each were a clinical diagnosis of knee OA (American College of Rheumatology),<sup>19</sup> identification by a radiologist of knee OA on an existing knee radiograph obtained within 5 years of intervention trial enrollment, tenderness of one or more anterior knee structures on physical examination, and self-reported moderate-to-severe knee pain for at least 3 months. The self-reported pain was assessed with the question, “What is the average level of your left/right knee pain over the last week?”; “moderate-to-severe” was defined as a score of greater than 3 on a 0–6 ordinal response scale.

Potential participants were given a brief description of knee OA, a slide presentation about prolotherapy, and a description of expected procedures and possible outcomes. They received a minimum of three, and maximum of five, injection sets over 17 weeks depending on participant preference and physician recommendation according to a published protocol<sup>15</sup> and consistent with training and standardization efforts of content leaders (<http://www.hacketthemwall.org/WELCOME.html>; <http://www.fammed.wisc.edu/prolotherapy/research>). Participants were then followed for 52 weeks. Quantitative assessment at baseline and 12 and 52 weeks included the Western Ontario McMaster University Osteoarthritis Index (WOMAC), a validated disease-specific measure.<sup>20</sup> Participants receiving prolotherapy in these studies reported improvements of  $12.4 \pm 3.5$  to  $19.4 \pm 7.0$  points at 52 weeks compared with baseline status on a 0–100 WOMAC scale, in excess of the benchmark for a minimal clinically important improvement.<sup>21</sup>

For the current study, the planned sample size was 20–25 patients, based on expected content saturation.<sup>22</sup> Twenty-seven participants were consecutively approached as they completed the studies. The 22 patients who consented to participate were interviewed as they completed the 52-week follow-up assessments. Participants and interviewers were not masked to allocation group when interviewing participants from the initial RCT. For the quantitative analysis, descriptive statistics were applied to describe baseline demographic characteristics and WOMAC outcomes at each of three time points; mean value  $\pm$  SD was reported.

For the qualitative analysis, trained study personnel conducted interviews by phone or in person at the study institution from July 2006 to July 2009. A standard qualitative research method of transcribing in-person long interviews was used.<sup>22</sup> The semi-structured interview consisted of open-ended questions with several prompts that the interviewer could use to encourage salient discussion ([Table 1](#)). Transcripts were stripped of identifiers and reviewed individually by using a standardized coding worksheet, then discussed by coauthors (L.B., D.R., L.F., A.S., J.G., L.vL.) in a group setting using an iterative approach for identification of major themes. Disagreements were resolved through discussion and consensus. Direct quotes are integrated into the “Themes” section of the Results and presented in table form; occasional bracketed text is used to clarify the participant's intent or to eliminate wordiness. Themes were defined as ideas expressed by 50% or more of the cohort or those whose import and clinical relevance were high in the authors' opinion. Transcribed interviews were initially analyzed in six meetings (June–August 2012), then in three subsequent sessions (June–July 2015) after publication of quantitative data describing long-term quantitative follow-up, which revealed nonresponsiveness to prolotherapy among some participants.<sup>23</sup>

**TABLE 1.**

OPEN-ENDED QUESTIONS FOR PARTICIPANT INTERVIEWS

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What were your general symptoms of knee osteoarthritis before the study?

How did prolotherapy affect you?

Did you experience anything that was especially good or bad about prolotherapy or its after effects?

Did you get any reactions from friends or family from being a part of the study?

What were your emotional reactions from using prolotherapy?

What was the informational meeting at the beginning of the study like for you?

Is there anything else you would like to say about prolotherapy or being in the study?

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## Results

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### Quantitative data

Consent from 22 participants was obtained from the first 27 participants queried, resulting in a cohort that was similar to the 104 participants of the intervention studies in terms of age, sex, number of injection sessions, and baseline and average WOMAC composite score improvement ( $19.9 \pm 12.6$  points) at 52-week follow-up ([Tables 2](#) and [3](#)).<sup>15,16,18</sup> Eight participants came from the dextrose arm of the RCT and 14 came from the two open-label studies.<sup>15,16,18</sup> The data were highly variable. Eighteen participants qualitatively described an overall positive effect of prolotherapy, which is reflected in WOMAC scores for this subsample ([Table 3](#)). Four participants described no, very little, or temporary effect, which is reflected in their lower mean WOMAC score change ([Table 3](#)). Participants' reporting of short-term injection-related pain also varied; most ( $n = 14$ ) found the injections painful or very painful, but tolerable. The study team identified seven major themes ([Table 4](#)).



**TABLE 3.**

AVERAGE WOMAC SCORE CHANGE AMONG ALL QUALITATIVE STUDY PARTICIPANTS AND THOSE WHO REPORTED “NO IMPROVEMENT”

<i>Variable</i>	<i>Baseline</i>	<i>Week 12</i>	<i>Week 52</i>
All qualitative study participants ( <i>N</i> = 22)			
WOMAC composite score	61.0 ± 12.3	76.6 ± 12.3	80.9 ± 12.6
Subscale score change			
Pain	65.4 ± 13.1	78.2 ± 11.8	82.7 ± 14.9
Stiffness	57.1 ± 19.2	72.7 ± 18.4	76.7 ± 16.5
Function	60.5 ± 12.8	78.8 ± 11.8	83.4 ± 11.9
Participants who reported “no improvement” at 52 weeks ( <i>N</i> = 4)			
WOMAC composite score	62.6 ± 3.2	70.0 ± 11.0	65.6 ± 8.7
Subscale score change			
Pain	68.8 ± 8.5	63.3 ± 10.4	62.5 ± 9.6
Stiffness	59.4 ± 12.0	70.8 ± 26.0	59.4 ± 12.0
Function	59.5 ± 8.4	76.0 ± 10.6	74.8 ± 10.8

Values are expressed as mean ± SD. For baseline, week 12, and week 52, numbers of participants were 22, 22, and 22 for all study participants and 4, 4, and 4 for those reporting “no improvement” at 52 weeks, respectively.

*N*, number.

**TABLE 4.**

## MAJOR QUALITATIVE THEMES

## 1. Improvement in knee-specific quality of life

“Now ... [the knees] are much better. I still can't kneel down comfortably. But I can go up and down stairs, I don't have any problems getting out of the car. I've jogged a little bit.”

“Having my activity level being inhibited by something like arthritis was kind of difficult. And having the prolotherapy to work against that and help me, I think was a huge benefit emotionally.”

“I think it increased the stability laterally in both my knees so that I don't feel so wobbly when I walk, which I think caused more pain after a while....”

“...before I was taking prescription [pain] medication through the day, and now I am managing better [with less].”

“I always say that I've gotten my knees back. I don't have the grinding, bone on bone, pain and noise that I did before and I feel much more capable of being able to walk normally.... I feel more stable, I feel like I have sturdy legs underneath me again.”

## 2. Safety and comfort

“...[The injection pain] was so short lived ... it wouldn't deter me from having it done....” “I did have some swelling and redness but that dissipated pretty quickly....”

“...the actual treatment itself was a little bit nerve racking the first time.” “The needles were the worst thing ... I just don't like needles.”

“...the worst thing is the pain of getting the injections ... the benefits far outweighed any of the discomfort of that.”

## 3. Pretreatment counseling enhanced treatment adherence and optimism

“...I liked everybody who was in the program, they seemed ... friendly and helpful, and it was a positive experience.”

“You were very willing to answer questions that I asked and that's the biggest thing for me ... having the knowledge of what was going to happen beforehand made that tenseness a lot less.”

“You put me at ease ... I felt very good about it.”

## 4. Overall positive experience with prolotherapy

“I really would recommend prolotherapy to anyone. I thought it was a big help for me....” “I was telling all my friends what a difference it made in my life....”

## 5. Limited response to prolotherapy

“I think there is absolutely no change.”

“After the prolotherapy, my knee felt much better, [but later] the effects wore off.”

## 6. Aspects of treatment consistent current prolotherapy clinical practice

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**Themes****Improvement in knee-specific quality of life**

Most participants endorsed positive results for quality of life. When asked about the overall effect of prolotherapy on pain and function, most participants agreed with one participant who noted that “it does seem to work.” Knee pain and stiffness was reduced, and function improved, in 18 participants who reported improved WOMAC scores compared with baseline status. One participant noted: “If I look at my [injected] knee, it's still going...right along with no pain...” Sixteen participants also reported lasting improvements in ability to perform activities of daily living (ADLs); “Here I am doing things I couldn't do for 2–3 years. I'm out raking. I'm planting, mulching!” Several participants also reported improved quality of life and emotional benefits due to improved functional ability and participation in important family events; one participant noted: “I have been so much improved. I'm doing pretty much most things by now ... I danced at my son's wedding ... [I am so happy] being able to dance at my son's wedding after therapy.” The same participant however, also had modest expectations, noting “There's still a few things I won't ever be able to do. I have arthritis in my knees.... But I can dance, I can walk, I can, you know ... do things.”

**Safety and comfort** Prolotherapy was perceived to be a safe treatment with no long-term side effects by all 22 participants interviewed. Side effects were infrequent and included the experience of a tingling sensation for 3 days after treatment by one participant and a visible injection skin pattern that lasted 2–4 weeks for another participant. Other self-limited side effects were more common and included mild bruising, pain, swelling, and redness at the injection sites. Fourteen participants described the injections as painful, with one participant finding it painful enough to opt out of the fourth and fifth optional treatment sessions. Most others noted that short-term side effects were worth the benefit of the therapy: “The benefits far outweighed any of the discomfort.” When asked to identify the most challenging part of prolotherapy, a common response was “the pain of the injections.” Individual experience varied, with such reports as “It hurt like a normal shot” and “It felt like when you get shots in your jaw at the dentist.” Other participants reported that a fear of needles brought some treatment anxiety at the first injection session that was decreased by experience in return visits.

**Pretreatment counseling enhanced treatment adherence and optimism** All participants reported that the initial informational meeting allowed them to gain a thorough understanding of prolotherapy that made their participation easier. Participants reported reduced apprehension toward the therapy, with such comments as: “You put me at ease” and “Having the knowledge of what was going to happen beforehand made that tenseness a lot less.” Eleven participants reported increased optimism regarding prolotherapy after the informational meeting, with reports such as “The whole program was explained very well and I just thought it was a very good meeting. I came out feeling very positive.” Many expressed satisfaction regarding interactions with study personnel, including the physician performing the prolotherapy.

**Overall positive experience with prolotherapy** All 22 interviewed participants, including those with limited response, would recommend or have recommended prolotherapy to others. One participant noted: “I recommend it to anybody who ever tells me about their knee [OA].” All participants indicated that they would consider trying prolotherapy for other conditions. Most participants ( $n = 15$ ) said they would consider receiving prolotherapy again for their knee OA.

**Limited response to prolotherapy** Four participants stated their knee symptoms were not improved at the 52-week follow-up, noting: “I think there is absolutely no change,” “The treatment had little effect,” and “[Prolotherapy] had little to no [effect].” One of the four experienced no short- or long-term benefit and went on to have a total knee arthroplasty on the affected knee after the study's conclusion. The remaining three reported a more nuanced but limited symptom improvement, noting that an initial positive effect waned by 52 weeks: “After the prolotherapy, my knee felt much better, [but later] the effects wore off” and “I felt [the effect] was really positive at first but it felt like it didn't seem to help afterwards.” A positive initial symptom improvement that waned over time is captured quantitatively in the mean aggregate WOMAC scores for these four participants ([Table 3](#)).



**Consistency with anecdotal clinical prolotherapy experience** A minimum of three treatment sessions, postinjection rest with slow ramp-up of activity, and pretreatment with oral pain medication are standards of care among prolotherapists. Twelve participants reported little to no improvement until after the second or third injection session of a planned three-treatment minimum. Six participants commented on the perceived necessity to engage in less activity involving the knee joint for at least 1 day after treatment, with such comments as “I was usually ... restricted for two if not three days.” Eight participants mentioned the usefulness of taking a prescribed 5 mg of oxycodone a half-hour before injections to reduce treatment pain.

The interviewers also addressed social concerns. Because prolotherapy is new to most patients and could engender stigma or embarrassment, patients were asked whether social issues played a role in prolotherapy adherence in the study. All participants reported reactions from family and friends that ranged from relative disinterest to encouragement, surprise, or amusement; none reported that reactions from family or friends limited their use of or adherence to prolotherapy.

**Functional improvement without pain reduction** Of the 18 participants who experienced an overall improvement from prolotherapy, most reported an improvement in both pain and ability to perform ADLs. However, four reported minimal reductions in pain in the context of more substantial functional improvements. One participant explained: “I still have kind of a chronic pain. I don't have the restriction due to swelling [and so can be more active].” Other reported functional improvements without pain reduction included increased joint stability, range of motion, and ability to perform ADLs.

## Discussion

The current study is the first to formally report the qualitative experience of study participants receiving prolotherapy for any condition. Most participants experienced a safe, satisfactory, and substantial decrease in pain and improved ability to perform activities of daily living throughout the study period. A minority reported no or minimal, short-lived improvement, but still reported an overall positive experience with prolotherapy and their study involvement. These qualitative data are consistent with quantitative self-report data from three RCTs,<sup>12–14</sup> two open-label studies,<sup>15,16</sup> and a recent systematic review with meta-analysis.<sup>17</sup>

Each reported that prolotherapy resulted in sustained significant and clinically meaningful improvement on the WOMAC measure for participants with mild-to-severe pain related to knee OA compared with baseline status, or saline and exercise controls. Data from these three studies are consistent with two other quantitative RCTs, one of which used the WOMAC outcome measure.<sup>12,24</sup> However, not all the data from existing studies report a positive effect of prolotherapy for all participants. These qualitative data are also consistent with results of a longer-term (130 weeks) quantitative outcomes study suggesting a 20% nonresponse rate during a 1.5- to 3-year follow-up time period.<sup>23</sup> While the baseline patient phenotype predicting responsiveness is not known, the current study helps to bridge the gap between trials reporting overall efficacy and the individual patient experience regarding effectiveness.

A new finding is the report of improved function in the context of unchanged pain after prolotherapy. Pain and functional impairment due to knee OA are likely multifactorial and may not be uniformly correlated; similar pain levels may show dramatic differences in functional ability.<sup>25</sup> Additionally, improved function may be partially independent of pain; active persons with pain have a lower likelihood of having pain-related disability than those with pain who avoid activity.<sup>26</sup> No standard of care conservative therapy for knee OA directly treats both pain generators and degenerative tissue of the symptomatic arthritic knee. The mechanism of action is not clear but is likely multifactorial; contemporary hypotheses suggest that prolotherapy promotes local healing of chronically injured extra- and intra-articular articular and connective tissue (tendon and ligament attachments, and fascia)

through inflammatory mechanisms, and may also include direct sensorineural analgesic effects.<sup>27</sup> A recent pilot study suggested that dextrose may be associated with intra-articular chondrogenesis.<sup>28</sup> Participant reports from the current study suggest that prolotherapy may exert independent effects on pain and functional outcomes.

Consistent with procedural interventions generally, participants reported that clear comprehensive descriptive information in an introductory informational meeting eased apprehensions and provided clear expectations, suggesting the need for an initial consultation. Effective instruction about the rationale and nature of prolotherapy, clear discussion about treatment expectations and side effects, and a patient-oriented treatment environment led to a positive outlook toward prolotherapy, even though nearly all participants described the treatment as painful.

The study confirms several prolotherapy practice patterns understood anecdotally, including the experience of knee soreness for 1–5 days after treatment, minimal or nonresponsiveness to the first one or two treatment sessions among some recipients, the utility of pretreatment with opioid medication in pain-sensitive patients receiving prolotherapy, and the suggestion that procedural pain generally does not cause patients to opt out of therapy.

The current study has several limitations. Of the 22 participants, only 8 were blinded to therapy in their intervention group. Therefore, expectation bias might have influenced reporting of experience. However, the effect size of prolotherapy among current participants was similar to that of prolotherapy injection in both blinded RCTs and open-label studies. Many participants reported a strong sense of hopefulness about the treatment, which might also have increased expectation bias. Recollection of initial experiences and feelings toward prolotherapy may have been inaccurate because participants were interviewed several months after the last set of injections. An iterative process was not used to guide the formulation of interview questions, and thus issues important to participants may have been missed.

This study has implications for clinicians. Prolotherapy can confidently be performed by trained physicians for symptomatic knee OA. An initial consultation, including visual and written details of therapy protocol, injection nature of therapy, pain as a side effect, clinical expectations, and after-care, appears to increase treatment adherence and optimism. Establishing a treatment plan that ensures at least three treatment sessions may provide the greatest benefit.

The study of prolotherapy for knee OA is emerging. This study suggests further research is warranted. Questions remain about core issues, such as the participant phenotype predicting responsiveness to treatment; mechanism of action; the optimal clinical protocol; and effect on functional, biological, and radiologic measures. These issues require study in a larger patient population with more identified subgroups. Relevant to both clinicians and researchers is the issue of standardization of injection protocols for given indications. The studies from which participants in the current study were recruited received an identical injection technique and protocol refined and taught by physicians associated with the Hackett Hemwall Patterson Foundation (<http://www.hacketthemwall.org/WELCOME.html>). Efforts to standardize prolotherapy injection protocols and certify physicians in their use are now underway through this organization and the University of Wisconsin Prolotherapy Education and Research Lab (<http://www.fammed.wisc.edu/prolotherapy/research>).

## Conclusions

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Qualitative analysis of participant narratives from three clinical trials support quantitative data suggesting efficacy of prolotherapy as a treatment for knee OA. Eighty-two percent of participants described decreased knee pain and improved knee function without substantial side effects. Clinical

response is likely improved by patient education about the prolotherapy procedure. These data enable patients to better understand what treatment with prolotherapy for knee OA might mean for them, and they empower clinicians to better personalize treatment to individual patients.

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## Author Disclosure Statement

No competing financial interests exist.

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