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Efficacy of neural prolotherapy versus local corticosteroid soft tissue injection for treatment of chronic anserine bursitis: a prospective randomized clinical trial

Emmanuel Kamal Aziz Saba

Abstract

Background: Anserine bursitis is characterized by the presence of spontaneous pain with tenderness at the inferomedial aspect of the knee joint. Neural prolotherapy aims to relieve pain of a variety of chronic musculoskeletal disorders. The study aim was to explore the short-term efficacy of neural prolotherapy (subcutaneous perineural injection of dextrose 5% solution) versus local corticosteroid injection for pain relief and improvement of function in patients with chronic anserine bursitis. The enrolled patients were randomly assigned to receive neural prolotherapy (subcutaneous perineural injection of dextrose 5% solution) (neural prolotherapy group) or a single local soft tissue injection of corticosteroid (corticosteroid group). Outcome measures included Western Ontario McMasters Universities osteoarthritis index, assessment of overall anserine bursitis pain severity using the visual analogue scale, patient's global assessment of anserine bursitis severity using the visual analogue scale, and clinical assessment for the presence of tenderness on the anserine bursa region. Patients were evaluated before injection and after intervention by 4 weeks.

Results: The study included 67 lower limbs from 43 patients with chronic anserine bursitis. No significant differences were found between both treatment groups regarding all assessed parameters at the start of the study. After 4 weeks, within-group analysis showed that there was a statistically significant improvement in Western Ontario McMasters Universities osteoarthritis index and its subscales ($P \leq 0.0001$), overall anserine bursitis pain severity ($P \leq 0.0001$), and patient's global assessment of anserine bursitis severity ($P \leq 0.0001$), as well as there was significant improvement regarding the presence of tenderness at the anserine bursa region in both groups in comparison to the preinjection assessment. At the postinjection assessment, between-group analysis showed that there were no significant differences regarding all assessed outcome parameters. All patients in both groups tolerated the injection procedure and were satisfied with the procedure. There was no significant difference between the two groups regarding patients' satisfaction to the procedure results. Improvement was achieved in 86.4% of patients included in the neural prolotherapy group versus 95.2% of patients included in the corticosteroid group.

Conclusions: Neural prolotherapy was effective in relieving pain, improving local tenderness and function in patients with chronic anserine bursitis similar to local corticosteroid injection.

Correspondence: emadaziz55@yahoo.com
Current address: Physical Medicine, Rheumatology and Rehabilitation Department, Faculty of Medicine, Alexandria University, Alexandria, Alexandria Governorate 21131, Egypt

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Background

Anserine bursitis (AB) is characterized by the presence of spontaneous pain with tenderness at the inferomedial aspect of the knee joint (Helfenstein & Kuromoto, 2010). It can be bursitis, tendinitis, or both (Helfenstein & Kuromoto, 2010). The differentiation between the two pathologies is difficult clinically due to the close proximity of the bursa and the tendon. Also, the treatment of both of them is the same (Helfenstein & Kuromoto, 2010; Nemegyei & Canoso, 2004; Uysal et al., 2015).

Treatment of AB constitutes conservative and surgical treatment. Conservative treatment comprises non-pharmacologic treatment and drug therapy. Their purpose is to relieve pain, which improves functional performance and quality of life. Non-pharmacologic treatment comprises activity modification and physiotherapy. Drug therapy consists of non-steroidal anti-inflammatory drugs, oral analgesics such as acetaminophen or topical preparations, or local injection of corticosteroid. Surgical treatment is only indicated after failure of conservative treatment in severe and resistant chronic cases (Helfenstein & Kuromoto, 2010; Nemegyei & Canoso, 2004; Khosrawi et al., 2017; Sarifakioglu et al., 2016; Morales et al., 2012).

Neural prolotherapy (NP) is the subcutaneous perineural injection of isotonic dextrose 5% in water (D5W) solution around the cutaneous sensory nerves especially at their fascial penetration points, where the nerves reach the subcutaneous plane. It was reported that it led to improvement and relief of pain of a wide variety of chronic musculoskeletal disorders (Reeves & Lyftogt, 2011; Soliman et al., 2016; Lyftogt, 2005; Lyftogt, 2007a; Lyftogt, 2007b; Lyftogt, 2008; Alyan & El-Rouby, 2018). There were no previous studies that assessed the efficacy of NP in the treatment of chronic AB.

This research aimed to explore the short-term efficacy of NP (subcutaneous perineural injection of D5W solution) versus local corticosteroid injection therapy for pain relief and improvement of function in patients with chronic AB.

Methods

Study design and ethics statement

The current study was a prospective, randomized, comparative clinical study. The researcher informed all patients about the research and explained the study to them. Each one gave informed consent prior to participation. Faculty Medical Ethics Committee sanctioned the study. The study was registered in the ClinicalTrials.gov (a trial registry) with an identifier number of NCT04509440.

Study participants and patient selection

Random sampling was done to select the participated patients from those attending the Physical Medicine, Rheumatology and Rehabilitation department. The study extended from May 2018 to October 2019.

The clinical diagnosis of chronic AB was based on clinical manifestations as illustrated in Fig. 1 (Helfenstein & Kuromoto, 2010; Yoon et al., 2005). Each knee region was assessed separately for eligibility. The exclusion criteria are shown in Fig. 1 (Grover & Rakhra, 2010; Cohen et al., 1997).

For the calculation of the sample size, data obtained from previous research were utilized (Morales et al., 2012). From which the proportion of patients with complete improvement with the injection of the active drug and the proportion of patients with complete

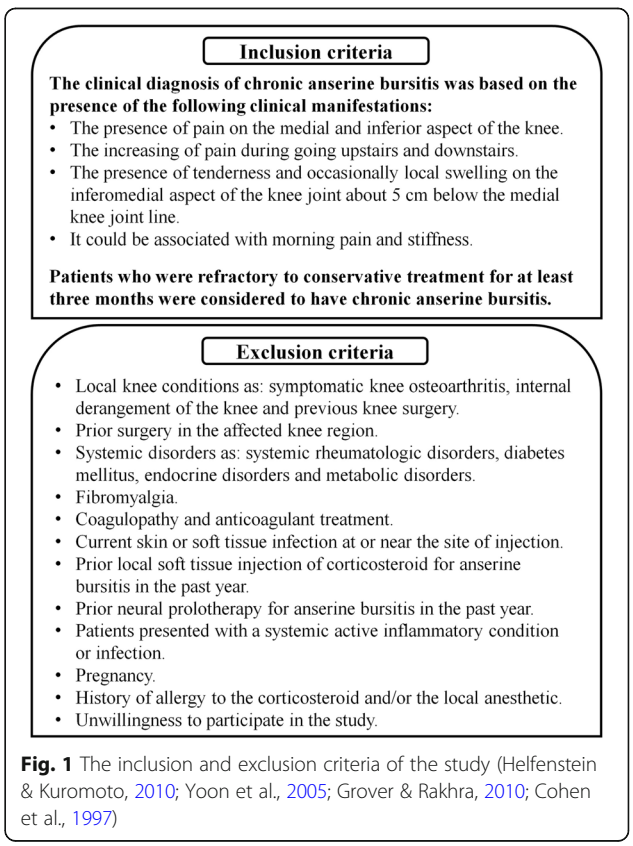

Fig. 1 The inclusion and exclusion criteria of the study (Helfenstein & Kuromoto, 2010; Yoon et al., 2005; Grover & Rakhra, 2010; Cohen et al., 1997)

improvement with the injection of the control drug were used. The following were used: study power of 80% (beta = 0.20) with a statistically significant difference of 5% (alpha = 0.05, two-sided significant level). On the bases of these data, the size of the sample was calculated using the following equation (Charan & Biswas, 2013; Malone et al., 2016):

$$\text{Sample size} = \left[2\left(Z_{\alpha/2} + Z_{\beta}\right)^2 P(1\text{-}P)\right] / (p_1\text{-}p_2)^2$$

in which:

$Z_{\alpha/2}$ = Standard normal variate for level of significance. $Z_{\alpha/2} = Z_{0.05/2} = Z_{0.025}$= 1.96 at type I error of 5% (alpha= 0.05, two-sided significant level).

Z_{β} = Standard normal variate for power. $Z_{\beta} = Z_{0.20}$ = 0.842 at power of 80% and type II error of 20% (beta = 0.20).

P = Pooled prevalence = [prevalence in case group (p_1) + prevalence in control group (p_2)]/2

$p_1 - p_2$ = It is the difference in the proportion of the events in the two groups.

The calculated sample size was 28 lower limbs per intervention group to confirm sufficient study power of 80% (beta = 0.20) with a statistically significant difference of 5% (alpha= 0.05, two-sided significant level). It was postulated that about 10% of the sample size might be lost for follow-up. Consequently, at least 31 lower limbs per intervention group had been recruited to confirm an adequate sample size to achieve a significant level.

Eighty patients were screened. Only 43 patients were selected for the study and the remaining patients were excluded. Twenty-one patients had symptomatic knee osteoarthritis, eleven patients had diabetes mellitus, one patient had internal derangement of the knee, one patient received anticoagulant treatment, one patient had previous local soft tissue injection of corticosteroid for AB, and two patients refused to participate in the study. A total of 67 lower limbs from 43 patients who had chronic AB were included in the study (Fig. 2).

Study assessment

Assessment of all patients in the study was done as follows: demographic data collection including age and sex were reported. Body mass index (BMI) was measured (weight (kg)/[height (m)]^2) (Agu et al., 2019). History taking was done regarding the duration of symptoms. Clinical musculoskeletal examination was done including assessment of tenderness on the inferomedial aspect of the knee joint about 5 cm below the medial knee joint line, as well as any other tender points in the region of the anserine bursa (Helfenstein & Kuromoto, 2010).

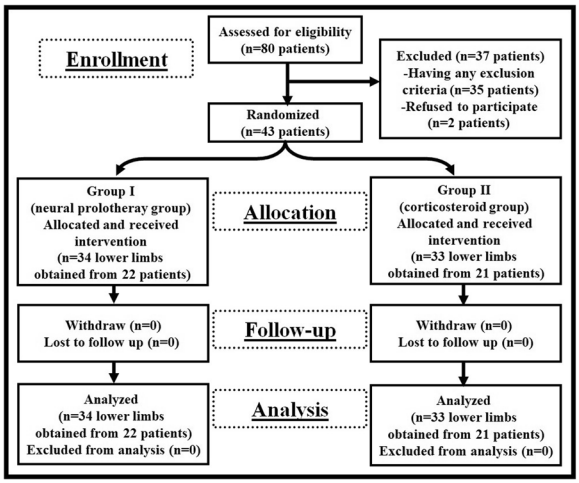

Fig. 2 Study profile. Patients were grouped according to the therapeutic intervention received. n, number

Study intervention

The enrolled patients were divided randomly into two treatment groups by a simple randomization method using the table of random number:

Group I (NP group): it constituted of 22 patients with 34 lower limbs with chronic AB. The patients received a single session of subcutaneous perineural injection of D5W solution.

Group II (corticosteroid group): it constituted of 21 patients with 33 lower limbs with chronic AB. The patients received a single local soft tissue injection of 40 mg of triamcinolone acetonide (40 mg/ml) mixed with 1.5 ml mepivacaine HCl 3% (local anesthetic).

The patients were instructed to stop any ongoing medical treatment or physiotherapy 48 h before the procedure and for a period of 4 weeks.

The injection area was disinfected by cleaning the area with three swipes of povidone-iodine then two swipes of 70% ethanol solution which was allowed to dry for about 2 min (Tan, 2006). Injection was done through an aseptic technique to minimize risk of infection. Injection was done using sterile and disposable needles and syringes.

For group I (NP group), before injection, clinical examination of the anserine bursa region was done to detect the maximal tender points at the cutaneous sensory nerves fascial exit points and any other tender points along the course of saphenous nerve branches that supply cutaneous sensory innervation for the medial and inferior knee region (Reeves & Lyftogt, 2011). The sites of fascial penetration points are: (i) at the depression on the lower border of the medial tibial condyle, and (ii) four finger breathes below the previous location in a line connecting the previous location with the medial malleolus (Reeves & Lyftogt, 2011; Alyan & El-Rouby, 2018). The tender points were marked.

The NP injection was done using D5W solution (trade name was "Glucose Intravenous Infusion (Dextrose 5%)®"; concentration was 5%; 500 ml solution per container; manufactured by "El Nasr Pharmaceutical Chemicals Company", Kalupia Governorate, Egypt). It was available as container of 500 ml. D5W injection was performed by the use of a 28-gauge needle (of 12.75 mm length) and an insulin syringe. The injection procedure was done while the patient lying supine and fully extending the knees. All tender points were injected subcutaneously. Injection was done with administration of 0.5 ml of the D5W solution at each tender point at 0.5 cm depth. A skin bleb was formed by the injected solution (Reeves & Lyftogt, 2011; Lyftogt, 2007a; Conaway & Browning, 2014). Up to six skin punctures were done, placing a minimal total volume of 3 ml of D5W solution. At the end of the NP injection, the patient was asked to point to any painful and tender points left without injection to be injected by the same procedure. The injection session was completed once all tender points were injected. Achievement of complete relief of AB pain was the aim of NP injection session (Reeves & Lyftogt, 2011; Conaway & Browning, 2014).

For group II (corticosteroid group), 40 mg of triamcinolone acetonide (40 mg/ml)(trade name was "Epirelefan®"; concentration was 40 mg/ml per vial; a vail of 1 ml; manufactured by "Egyptian International Pharmaceutical Industries Company", 10th of Ramadan City, Egypt) mixed with 1.5 ml mepivacaine HCl 3% (local anesthetic) (trade name was "Mepecaine 3%®"; concentration was 3%; a carpule (cartridge) of 1.8 ml; produced by "Alexandria Company for Pharmaceuticals", Alexandria, Egypt) were used for the injection. The corticosteroid injection was done using a 23-gauge needle (of 31.75 mm length). The steroid injection was done as the following. The patient lied supine and the leg was extended and slightly externally rotated. The point of maximal tenderness was localized by palpation. Injection was done at the point of maximal tenderness. It was done with the needle inserted perpendicular to the skin. The needle was advanced slowly till it contacted the periosteum of the medial surface of the tibia. Then the needle was slightly withdrawn for about 2-3 mm followed by injecting the steroid. Injection was done in a fan-like technique. No resistance should be found at injection (Ines & da Silva, 2005). Drawing back the plunger before injection was always done to make sure that the needle tip is not located within a blood vessel (Jacobs, 2009).

At the end of the injection procedure, the patient was asked to assess the injection procedure-induced pain by the visual analogue scale (VAS) (a 10-cm scale) (0 indicated no pain while 10 indicated intolerable pain) (Gould et al., 2001).

Rescue medication and post-injection care

After injection, instructions regarding resting the knees for 24 h were given. Cold pack application on the injected anserine bursa region was recommended in the first 48 h if pain increased following injection or the formation of bruises. Only acetaminophen is recommended occasionally as rescue analgesic medication to control intolerable pain (a dose up to 4 g daily was allowed) and discontinued 48 h prior to the follow-up assessment visit. Instruction was given for the patients who received NP that injection could be repeated at 1 week if their pain and symptoms recurred within a week after injection.

Study schedule and outcome measures

The patients were assessed twice using outcome measures. Patients were evaluated before injection (preinjection assessment) and after intervention by 4 weeks (postinjection assessment) (Fig. 2). Searching for side effects of injection procedure (as ecchymosis with pain at the injection site that was treated by the application of cold pack on the site of injection) and for side effects of injected medical solution (as post-injection flare of pain, injection site skin depigmentation, skin depression at the area of injection due to subcutaneous atrophy, facial flushing and hypersensitivity reaction to the injected medication) were done at the postinjection assessment visit (Jacobs, 2009). Also, inquiring about the recurrence of symptoms and patient's satisfaction to the procedure results were done at the postinjection assessment visit (Jacobs, 2009).

Outcome measures included the following: (A) Primary outcome measure: Western Ontario McMasters Universities osteoarthritis index (WOMAC). Total WOMAC score ranged from zero to 104 points. Lower scores meant better status (Bellamy et al., 2005). (B) Secondary outcome measures: (i) Assessment of overall AB pain severity using VAS (zero indicated no pain while ten indicated severe intolerable pain) (Gould et al., 2001). (ii) Patient's global assessment of AB severity using VAS (zero indicated negligible severity while ten indicated very severe disorder) in which the patient was asked to quantify the overall severity of AB regarding pain, tenderness, and effect on his/her quality of life on a scale of ten centimeters (VAS) (Gould et al., 2001). (iii) Clinical assessment for the presence of tenderness on the anserine bursa region was done. It was assessed as presence or absence of tenderness. The patient's degree of satisfaction to the procedure results was assessed at the postinjection assessment visit. It was assessed using a VAS (0 meant no satisfaction at all while 10 meant complete satisfaction) (Gould et al., 2001).

According to the results of the outcome measures at the 4-week postinjection assessment visit, the patients

were categorized as having the following (Saba & El-Sherif, 2016):

(I) Complete improvement: the patient had no symptoms and complete recovery of their function without the presence of tenderness on palpation.

(II) Partial improvement: the patient had improvement of more than 50% in all outcome measures especially WOMAC (the primary outcome measure) with or without the presence of tenderness on palpation.

(III) No improvement: the patient had no improvement of more than 50% in all outcome measures especially WOMAC (the primary outcome measure) with or without the presence of tenderness on palpation.

Statistical Package of Social Science (SPSS version 17) software was utilized for doing data analysis. Qualitative data were analyzed using Chi-square test or Fisher's exact test (if needed). Quantitative data were analyzed using Student's *t*-test and paired *t*-test. Significance was indicated for $P < 0.05$.

Results

The study included 67 lower limbs from 43 patients with chronic AB. Women constituted 35 participants (81.4%). The mean age of the patients was 39.76 ± 9.32 years (ranged from 24 to 62 years). There were 24 patients (55.8%) with bilateral AB. The participants had been divided randomly into two treatment groups. No statistically significant differences were found between the two groups regarding the basic characteristics of the patients (Table 1).

There were no significant differences between the two treatment groups as regards the WOMAC and its subscales, overall AB pain severity, and patient's global assessment of AB severity in the preinjection assessment and the postinjection assessment ($P > 0.05$) (Table 2). Tenderness at the anserine bursa region was present among all patients of both groups before injection. There were no significant differences between the two treatment groups regarding the presence of tenderness at the anserine bursa region in the postinjection assessment ($P > 0.05$) (Table 2).

There was a statistically significant improvement in the WOMAC and its subscales among the two treatment groups when the postinjection assessment was compared to the preinjection assessment ($P \leq 0.0001$). Also, there was a statistically significant decrease in the overall AB pain severity and patient's global assessment of AB severity among the two treatment groups when the postinjection assessment was compared to the preinjection assessment ($P \leq 0.0001$). At the postinjection assessment, the percentage of knees with tenderness at the anserine bursa region was significantly decreased in comparison to the preinjection assessment in both treatment groups (Table 2).

No patient withdrew during the study. No patients had been lost to follow-up. There were two lower limbs (5.9%) from two patients (9.1%) included in the NP

Table 1 Characteristics of the patients in the two treatment groups

Characteristics of the patient	Group I (NP) (*n* = 34 lower limbs obtained from 22 patients) mean ± SD	Group II (CS) (*n* = 33 lower limbs obtained from 21 patients) mean ± SD	Test of significance	*P*
Age (year)	41.61 ± 9.28	37.84 ± 9.11	(*t*) 1.676	0.098
Women†	19 (86.4)	16 (76.2)	(X^2) 0.734	0.457§
Weight (kg)	84.73 ± 17.73	81.30 ± 16.73	(*t*) 0.664	0.418
Height (cm)	163.11 ± 7.05	162.15 ± 5.62	(*t*) 0.619	0.538
BMI (kg/m^2)	31.89 ± 6.72	30.96 ± 6.40	(*t*) 0.582	0.562
BMI categories				
Normal weight†	3 (13.6)	4 (19.0)	(X^2) 1.323	0.724
Overweight†	9 (40.9)	7 (33.4)		
Obesity†	6 (27.3)	8 (38.1)		
Morbid obesity†	4 (18.2)	2 (9.5)		
Duration of the symptoms (months)	7.44 ± 4.34	8.39 ± 4.86	(*t*) − 0.847	0.400
Bilaterally†	12 (54.5)	12 (57.1)	(X^2) 0.029	0.864
Side (right/left)‡	19/15 (55.9/44.1)	16/17 (48.5/51.5)	(X^2) 0.367	0.628

kg kilogram, *cm* centimeter, *m* meter, *BMI* body mass index, *NP* neural prolotherapy group, *n* number, *SD* standard deviation, *CS* corticosteroid group, *t* value of Student's *t*-test, X^2 value of Chi-square test

**P* is significant at < 0.05

†Data are represented as number (percentage) of participants

‡Data are represented as number (percentage) of lower limbs

§*P* value of Fisher's exact test

Table 2 Comparison between the preinjection and postinjection assessments regarding outcome measures among the two treatment groups

Outcome measures	Group I (NP) (*n* = 34 lower limbs obtained from 22 patients) mean ± SD	Group II (CS) (*n* = 33 lower limbs obtained from 21 patients) mean ± SD	Test of significance[§]	*P*
WOMAC pain subscale				
Preinjection assessment	13.18 ± 3.78	10.95 ± 4.26	1.816	0.077
Postinjection assessment	2.31 ± 2.58	1.71 ± 2.02	0.849	0.401
Test of significance[†]	14.040	10.862		
P	≤ 0.0001*	≤ 0.0001*		
WOMAC stiffness subscale				
Preinjection assessment	1.36 ± 0.78	1.28 ± 0.71	0.338	0.737
Postinjection assessment	0.22 ± 0.42	0.19 ± 0.51	0.256	0.799
Test of significance[†]	6.884	6.532		
P	≤ 0.0001*	≤ 0.0001*		
WOMAC function subscale				
Preinjection assessment	25.13 ± 7.26	21.00 ± 7.94	1.783	0.082
Postinjection assessment	4.68 ± 5.83	3.14 ± 4.04	1.001	0.323
Test of significance[†]	13.838	11.971		
P	≤ 0.0001*	≤ 0.0001*		
WOMAC total				
Preinjection assessment	39.68 ± 10.20	33.23 ± 11.75	1.922	0.062
Postinjection assessment	7.09 ± 8.46	5.42 ± 7.54	0.679	0.501
Test of significance[†]	16.048	11.387		
P	≤0.0001*	≤0.0001*		
Overall AB pain severity (VAS)				
Preinjection assessment	8.76 ± 1.34	8.78 ± 1.45	− 0.068	0.946
Postinjection assessment	1.52 ± 1.82	0.96 ± 1.49	1.371	0.175
Test of significance[†]	20.773	23.105		
P	≤ 0.0001*	≤ 0.0001*		
Patient's global assessment of AB severity (VAS)				
Preinjection assessment	8.10 ± 1.38	8.54 ± 1.37	− 1.316	0.193
Postinjection assessment	1.00 ± 1.37	0.81 ± 1.23	0.570	0.571
Test of significance[†]	22.101	29.084		
P	≤ 0.0001*	≤ 0.0001*		
Tenderness at the anserine bursa region				
Preinjection assessment[‡]	34 (100)	33 (100)	NA	NA
Postinjection assessment[‡]	11 (32.4)	6 (18.2)	1.776[‖]	0.262

WOMAC Western Ontario McMasters Universities osteoarthritis index, *AB* anserine bursitis, *VAS* visual analogue scale, *NP* neural prolotherapy group, *n* number, *SD* standard deviation, *CS* corticosteroid group, *NA* not applicable
**P* is significant at < 0.05
[†]Value of paired *t*-test
[‡]Data are represented as number (percentage) of lower limbs
[§]Value of Student's *t*-test
[‖]Value of Chi-square test

group who had bruises at the injection sites that were resolved within few days after the procedure. Other than that, no drug nor injection technique side effects were reported during the postinjection assessment among any group.

All patients in both treatment groups tolerated the injection procedure. No significant difference was found between the two treatment groups regarding injection procedure-induced pain ($P > 0.05$) (Table 3). At the

Table 3 Comparison between the two treatment groups regarding procedure assessment

Procedure assessment	Group I (NP) (*n* = 34 lower limbs obtained from 22 patients) mean ± SD	Group II (CS) (*n* = 33 lower limbs obtained from 21 patients) mean ± SD	Test of significance	*P*
Injection procedure induced pain (VAS)	1.70 ± 0.81	1.39 ± 0.60	(t) 1.767	0.082
Patient's degree of satisfaction to the procedure results (VAS)	8.97 ± 1.64	9.06 ± 1.74	(*t*) − 0.217	0.829

VAS visual analogue scale, *NP* neural prolotherapy group, *n* number, *SD* standard deviation, *CS* corticosteroid group, *t* value of Student's *t*-test
**P* is significant at < 0.05

postinjection assessment visit, all patients were satisfied with the procedure. No significant difference was detected between the two groups regarding patients' satisfaction to the procedure results ($P > 0.05$) (Table 3).

No significant differences were found between both treatment groups regarding the occurrence of improvement, complete improvement, and partial improvement ($P > 0.05$) (Table 4).

Improvement was achieved in 86.4% of patients included in the NP group versus 95.2% of patients included in the corticosteroid group. Among the NP group, there were two patients (9.1%) with unilateral chronic AB who sought an extra injection upon their request due to the recurrence of their pain and symptoms within 1 week after injection. The same two patients (9.1%) were among the three patients (13.6%) [four lower limbs with chronic AB (11.8%)] who did not show any improvement at the postinjection assessment in the NP group.

Discussion

Chronic AB is a common etiology of inferomedial knee pain. It should be considered in the differential diagnosis of inferomedial knee pain (Morales et al., 2012). It could limit the patient's functional abilities and quality of life (Helfenstein & Kuromoto, 2010; Nemegyei & Canoso, 2004). Usually the AB symptoms are overlooked and attributed to knee osteoarthritis (Kang & Han, 2000).

The cause of AB could be attributed to bursitis and/or tendinitis (Nemegyei & Canoso, 2004). Risk factors for AB include obesity, knee osteoarthritis, and diabetes mellitus (Helfenstein & Kuromoto, 2010; Nemegyei & Canoso, 2004). AB is usually due to inflammation secondary to overuse of the knee joint and degenerative changes in the knee, as well as, strenuous physical exercise among athletes (Helfenstein & Kuromoto, 2010; Rennie & Saifuddin, 2005).

Statistically significant improvement was found in all outcome measures among the two treatment groups when comparing the postinjection assessment with the preinjection assessment. This was associated with significant improvement in tenderness in the region of the anserine bursa in both groups. There were no significant differences between both groups regarding different outcome measures, as well as the presence of tenderness at the anserine bursa region in the postinjection assessment. There were no significant differences between both treatment groups regarding the occurrence of improvement, complete improvement, and partial improvement. This was an indicator that NP injection had similar efficacy as local corticosteroid soft tissue injection in treating chronic AB. Both methods seem to be effective and valid options for the treatment of chronic AB.

Improvement was present in 88.2% of injected lower limbs with chronic AB (86.4% of patients) in group I (NP group). These data regarding the efficacy of NP for the treatment of chronic AB were not assessed previously in the literature. However, these were similar to previous studies that used NP for the treatment of a

Table 4 Comparison between the two treatment groups regarding the degree of improvement of chronic anserine bursitis at the postinjection assessment visit

Degree of improvement	Group I (NP) (*n* = 34 lower limbs obtained from 22 patients) *n*(%)	Group II (CS) (*n* = 33 lower limbs obtained from 21 patients) *n*(%)	Test of significance	*P*
Improvement	30(88.2)[†]	32(97.0)[‡]	(X^2) 1.850	0.356[§]
Complete improvement	13(38.2)	20(60.6)	(X^2) 3.353	0.089
Partial improvement	17(50.0)	12(36.4)	(X^2) 1.268	0.327

NP neural prolotherapy group, *n(%)* number (percentage) of lower limbs, *CS* corticosteroid group, X^2 value of Chi-square test
**P* is significant at < 0.05
[†]No improvement was present among three patients (13.6%) with four lower limbs with chronic anserine bursitis (11.8%)
[‡]No improvement was present among one patients (4.8%) with unilateral chronic anserine bursitis (3%)
[§]*P* value of Fisher's exact test

variety of chronic musculoskeletal painful conditions (Reeves & Lyftogt, 2011; Soliman et al., 2016; Lyftogt, 2007a; Lyftogt, 2007b; Lyftogt, 2008; Alyan & El-Rouby, 2018; Conaway & Browning, 2014; Weglein, 2011; El-Badawy et al., 2021; Elshoura et al., 2020).

Neural prolotherapy is the subcutaneous perineural injection of D5W solution at the fascial penetration point of the cutaneous sensory nerve where it reaches the subcutaneous plane and along its course (Reeves & Lyftogt, 2011; Conaway & Browning, 2014). NP is a type of prolotherapy (Lyftogt, 2005). Dextrose is normally present in the blood. It is safe, if it is injected in multiple areas, as well as in any quantity (Reeves & Lyftogt, 2011; Hauser et al., 2011). Determining the sites of NP injection is according to Hilton's law. This law stated that the cutaneous sensory nerve supply of the skin over a joint and its periarticular structures also supply deep sensation to the underlying joint and its periarticular structures including the anserine bursa region (Reeves & Lyftogt, 2011).

The mechanism of action of NP for treatment of AB could be the stimulation of the release of a group of growth factors that enhance soft tissue healing in response to D5W solution injection (Lyftogt, 2007a; Lyftogt, 2007b; Rezasoltani et al., 2017). Subcutaneous injection of D5W solution was found to stimulate human cells to start proliferation and increase cell protein and DNA synthesis. It enhances the release of growth factors such as transforming growth factor-β and other growth factors (Hauser et al., 2011).

Another mechanism of NP for the treatment of AB is the treatment of neurogenic inflammation. It was proposed that C-fibers transmit deep pain sensation signals from the anserine bursa. The antegrade nerve transmission to the brain ends with pain perception. The retrograde nerve transmission travel to the nociceptors with the release of substance P (sub P) and calcitonin gene-related peptide (CGRP) (Ji et al., 2018). In chronic AB, there is increased production of these neuropeptides (Ji et al., 2018). These lead to nerve swelling, pain, and inflammation at the site of the release of these neuropeptides. It is a sort of neurogenic inflammation (Reeves & Lyftogt, 2011; Weglein, 2011; McDougall, 2006). Subsequently, soft tissue inflammation occurs with the release of neuropeptides (Reeves & Lyftogt, 2011; Weglein, 2011). The fascial penetration point of the sensory nerve is the site where the nerve reaches the subcutaneous plane. When the nerve swelling reaches the fascial penetration points, chronic constriction injury (CCI) takes place. Inhibition of the normal neural axoplasmic flow of the nerve growth factors takes place at the CCI site. This neural axoplasmic flow is essential for nerve integrity and repair (Reeves & Lyftogt, 2011; Weglein, 2011). The NP aimed to suppress the release of these neuropeptides (Reeves & Lyftogt, 2011; Rezasoltani et al., 2017). It was postulated that dextrose 5% inhibits the transient receptor potential vanilloid-1 (TRPV1) receptor (a capsaicin-sensitive receptor) on glucose-responsive nerves. TRPV1 receptor has a role in pain response to stimuli as prostaglandins and low PH (Cui et al., 2006). Inhibition of TRPV1 receptors by dextrose 5% leads to a decrease in the release of proinflammatory neuropeptides as sub P and CGRP which are essential for induction of neurogenic inflammation (Conaway & Browning, 2014; Weglein, 2011). The inhibited TRPV1 receptor allows the decrease in nerve swelling. This leads to the normal flow of different nerve growth factors with nerve recovery and pain disappearance (Weglein, 2011).

In this research, it was found that all patients of the NP group experienced immediate post-injection relief of AB pain. This coincided with previous researches (Reeves & Lyftogt, 2011; Alyan & El-Rouby, 2018; Weglein, 2011; Soliman, 2017). This might be due to the inhibition of the TRPV1 receptor with a decrease in the release of sub P and CGRP (Conaway & Browning, 2014; Weglein, 2011).

In the current study, an extra NP injection was done in two patients (9.1%) with unilateral AB. This was done due to the recurrence of their pain and symptoms within 1 week after injection. A large number of NP sessions was reported in some patients to show complete improvement of symptoms (Lyftogt, 2005; Lyftogt, 2007a; Lyftogt, 2007b; Lyftogt, 2008). However, these two patients (9.1%) showed a lack of improvement at the post-injection assessment visit. Recurrence of pain and symptoms of AB within 1 week after injection with the need for an extra injection could be an indicator of inadequate efficacy of NP.

Improvement was present in 97% of injected lower limbs with chronic AB (95.2% of patients) in group II (corticosteroid group). This was similar to Kang et al. who reported complete remission of AB in 91.6% of their patients with local corticosteroid injection (Kang & Han, 2000). However, it did not coincide with other studies. Yoon et al. presented improvement in 53% (Yoon et al., 2005). Larsson and Baum mentioned improvement in 70% of their patients (Larsson & Baum, 1985). These differences could be due to differences in the study design and characteristics of the included patients; inclusion of patients with knee osteoarthritis and differences in the definition of improvement after injection.

Local corticosteroid injection is a therapy for refractory chronic AB. The mechanism of action of corticosteroid is the suppression of the inflammatory process associated with AB. Subsequently, improvement of AB takes place (Tan, 2006; Ines & da Silva, 2005).

All patients in both treatment groups tolerated the injection procedure. There was no significant difference

between the two groups as regards injection procedure-induced pain. There were only two lower limbs (5.9%) from two patients (9.1%) included in the NP group who had bruises at the injection site that were limited and resolved within few days after the procedure. Among the two groups, there were no other side effects that had been reported at the 4-week postinjection assessment. All patients were satisfied with the procedure results at the postinjection assessment visit. There was no statistically significant difference between the two groups as regards patients' satisfaction with the injection procedure. These were in agreement with previous studies (Reeves & Lyftogt, 2011; Soliman et al., 2016; Lyftogt, 2007a; Lyftogt, 2007b; Lyftogt, 2008; Alyan & El-Rouby, 2018; Conaway & Browning, 2014; Weglein, 2011; El-Badawy et al., 2021; Elshoura et al., 2020).

The NP is an easy, inexpensive, and effective method for the treatment of chronic musculoskeletal disorders including chronic AB. It could be used instead of local soft tissue injection of corticosteroid especially in compromised patients (Reeves & Lyftogt, 2011; Rezasoltani et al., 2017).

This is considered the first clinical study that assessed the efficacy and safety of NP by D5W solution in patients with chronic AB in comparison to corticosteroid local soft tissue injection. Corticosteroid is a well-established therapy for AB (Helfenstein & Kuromoto, 2010; Morales et al., 2012). Subsequently, NP could be an effective therapy for chronic AB. Chronic AB could be present alone or in association with other regional pain disorders as knee osteoarthritis; subsequently, its treatment in these situations could improve the regional pain in these conditions (Ibrahim et al., 2019; Ismail et al., 2020; Mohasseb et al., 2019).

Some limitations had been present: (i) The use of VAS and WOMAC which are subjective scales and are not objective measures. They are dependent on individual ideas and culture (Morales et al., 2012). However, these assessment methods have good validity and excellent reliability (Bellamy et al., 2005; De Boer et al., 2004). (ii) The lack of blinding of the type of therapy as it was not a blind study. It was not possible because of the difference in the techniques of injection between the two treatment groups. (iii) All the injections were done by the same investigator which can be influenced by the experience of the investigator regarding the injection accuracy. Subsequently, the generalization of the obtained results should be limited according to the experience of the researcher to local soft tissue injection (Finnoff et al., 2010). (iv) There is no standardized protocol for the number and schedule of NP sessions for chronic AB. Future researches are recommended to clarify this point. (v) The present study did not evaluate the mechanism of action of D5W. Further studies are recommended to assess this issue. (vi) The study did not assess the long-term effect of NP. Further studies with a longer follow-up period are needed to assess the long-term efficacy of NP for the treatment of chronic AB.

Conclusions

In conclusion, NP was effective in reliving pain, improving local tenderness, and improving function in patients with chronic AB similar to local corticosteroid injection. NP was an effective therapy for chronic AB. NP injection should be considered in the conservative treatment armamentarium of AB. Further randomized placebo-controlled studies with longer follow-up periods are recommended for verification of the effectiveness and the long-term efficacy of NP for the treatment of chronic AB.

Abbreviations

AB: Anserine bursitis; BMI: Body mass index; CCI: Chronic constriction injury; CGRP: Calcitonin gene-related peptide; D5W: Dextrose 5% in water; NP: Neural prolotherapy; sub P: Substance P; TRPV1: Transient receptor potential vanilloid-1; VAS: Visual analogue scale; WOMAC: Western Ontario McMasters Universities osteoarthritis index

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Author's contributions

The author (EKAS) contributed to the concepts, design, definition of intellectual content, literature search, clinical studies, data acquisition and analysis, manuscript preparation, editing, and revision. The author approved the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The local Ethics Committee of Faculty of Medicine, Alexandria University, Egypt (IRB NO:00007555-FWA NO: 00018699) approved the study. Date of approval: 12/4/2018. Serial number: 0303902. A written informed consent was given by participants. Trial registration: ClinicalTrials.gov, registration number: NCT04509440. Registered 12 August 2020 - Retrospectively registered.

Consent for publication

Consent for publication was taken from all participants in the study.

Competing interests

The author declares that there are no competing interests.

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References

Agu AU, Esom EE, Anyaeji PS, Nzekwe KC, Chime SC, Ikele II et al (2019) Obesity indices and academic performance of medical students of Igbo extraction at College of Medicine, University of Nigeria. World J Med Sci 16(4):191–195

Alyan II, El-Rouby MA (2018) Comparison of analgesic effect of perineural dextrose injection and low level laser therapy for osteoarthritis knee pain. Med J Cairo Univ 86(5):2727–2731

Bellamy N, Bell MJ, Goldsmith CH, Pericak D, Walker V, Raynauld JP, Torrance GW, Tugwell P, Polisson R (2005) Evaluation of WOMAC 20, 50, 70 response criteria in patients treated with Hylan G-F 20 for knee osteoarthritis. Ann Rheum Dis 64(6):881–885. https://doi.org/10.1136/ard.2004.026443

Charan J, Biswas T (2013) How to calculate sample size for different study designs in medical research? Indian J Psychol Med 35(2):121–126. https://doi.org/10.4103/0253-7176.116232

Cohen SE, Mahul O, Meir R, Rubinow A (1997) Anserine bursitis and non-insulin dependent diabetes mellitus. J Rheumatol 24(11):2162–2165

Conaway E, Browning B (2014) Neural prolotherapy for neuralgia. J Prolotherapy 6:e928–e931

Cui M, Honore P, Zhong C, Gouvin D, Mikusa J, Hernandez G et al (2006) TRPVA receptors in the CNS play a key role in broad-spectrum analgesia of TRPV1 antagonists. J Neurosci 26(37):9385–9395. https://doi.org/10.1523/JNEUROSCI.1246-06.2006

De Boer AG, van Lanschot JJ, Stalmeier PF, van Sandick JW, Hulscher JB, de Haes JC et al (2004) Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? Qual Life Res 13(2):311–320. https://doi.org/10.1023/B:QURE.0000018499.64574.1f

El-Badawy MA, El-Nagaar HA, Mohammed MM, Assaf NY, El-Mallah RME (2021) Musculoskeletal ultrasonographic evaluation of perineural injection therapy versus therapeutic ultrasound in chronic lateral epicondylitis. Egypt Rheumatol Rehabil 48(1):1. https://doi.org/10.1186/s43166-020-00050-1

Elshoura HM, Saber NZ, Elwy MA, Abdelhakim MM (2020) Therapeutic potential of perineural injection for temporomandibular joint pain, dysfunction and musculoskeletal ultrasound findings in rheumatoid arthritis patients. Egypt Rheumatologist 42(1):11–15. https://doi.org/10.1016/j.ejr.2019.08.004

Finnoff JT, Nutz DJ, Henning PT, Hollman JH, Smith J (2010) Accuracy of ultrasound-guided versus unguided pes anserinus bursa injections. Phys Med Rehabil 2(8):732–739. https://doi.org/10.1016/j.pmrj.2010.03.014

Gould D, Kelly D, Gammon J (2001) Visual analogue scale (VAS). J Clin Nurs 10(5):697–706. https://doi.org/10.1046/j.1365-2702.2001.00525.x

Grover RPS, Rakhra KS (2010) Pes anserine bursitis: an extra-articular manifestation of gout. Bull NYU Hosp Jt Dis 68(1):46–50

Hauser RA, Hauser MA, Baird NM (2011) Evidence-based use of dextrose prolotherapy for musculoskeletal pain: a scientific literature review. J Prolotherapy 3(4):765–789

Helfenstein M, Kuromoto J (2010) Anserine syndrome. Bras J Rheumatol 50(3):313–327

Ibrahim IK, Saba EKA, Saad NLM, Mohammed DYA (2019) Relation of interleukin-15 with the severity of primary knee osteoarthritis. Egypt Rheumatol Rehabil 46(4):313–320. https://doi.org/10.4103/err.err_42_19

Ines LPBS, da Silva JAP (2005) Soft tissue injections. Best Pract Res Clin Rheumatol 19(3):503–527. https://doi.org/10.1016/j.berh.2005.01.003

Ismail STE, Ibrahim IK, Saad NLM, Saba EKA (2020) Relation of interleukin-21 with primary knee osteoarthritis severity and functional disability. World J Med Sci 17(3):69–78

Jacobs JW (2009) How to perform local soft-tissue glucocorticoid injections. Best Practice Res Clin Rheumatol 23(2):193–219. https://doi.org/10.1016/j.berh.2008.11.002

Ji R, Nackley A, Huh Y, Terrando N, Maixner W (2018) Neuroinflammation and central sensitization in chronic and widespread pain. Anesthesiology 192(2):343–366. https://doi.org/10.1097/ALN.0000000000002130

Kang I, Han S (2000) Anserine bursitis in patients with osteoarthritis of the knee. South Med J 93(2):207–209. https://doi.org/10.1097/00007611-200093020-00011

Khosrawi S, Taheri P, Ketabi M (2017) Investigating the effect of extracorporeal shock wave therapy on reducing chronic pain in patients with pes anserine bursitis: a randomized, clinical-controlled trial. Adv Biomed Res 6:70. https://doi.org/10.4103/2277-9175.190999

Larsson LG, Baum J (1985) The syndrome of anserine bursitis: an overlooked diagnosis. Arthritis Rheum 28(9):1062–1065. https://doi.org/10.1002/art.1780280915

Lyftogt J (2005) Prolotherapy and Achilles tendinopathy: a prospective pilot study of an old treatment. Australas Musculoskelet Med 10:16–19

Lyftogt J (2007a) Subcutaneous prolotherapy treatment of refractory knee, shoulder and lateral elbow pain. Australas Musculoskelet Med 12:110–112

Lyftogt J (2007b) Subcutaneous prolotherapy for Achilles tendinopathy. Australas Musculoskelet Med 12:107–109

Lyftogt J (2008) Prolotherapy for recalcitrant lumbago. Australas Musculoskelet Med 13:18–20

Malone HE, Nicholl H, Coyne I (2016) Fundamentals of estimating sample size. Nurse Res 23(5):21–25. https://doi.org/10.7748/nr.23.5.21.s5

McDougall JJ (2006) Arthritis and pain: neurogenic origin of joint pain. Arthritis Res Ther 8(6):220. https://doi.org/10.1186/ar2069

Mohasseb DMF, Saba EKA, Saad NLM, Sarofeem ADH (2019) Genetic association between growth differentiation factor 5 single nucleotide polymorphism and primary knee osteoarthritis in a group of Egyptian patients: a pilot study. Mediterr J Rheumatol 30(2):114–122. https://doi.org/10.31138/mjr.30.2.114

Morales D, Valerio J, Lopez R, Delgado D, Elizondo M (2012) Safety and efficacy of methylprednisolone infiltration in anserine syndrome treatment. Reumatol Clin 8:63–67

Nemegyei JA, Canoso JJ (2004) Evidence-based soft tissue rheumatology IV. Anserine bursitis. J Clin Rheumatol 10(4):205–206. https://doi.org/10.1097/01.rhu.0000135561.41660.b0

Reeves KD, Lyftogt J (2011) Prolotherapy. In: Waldman SD (ed) Pain management, 2nd edn. Saunders (Elsevier), Philadelphia, pp 1027–1044. https://doi.org/10.1016/B978-1-4377-0721-2.00194-X

Rennie WJ, Saifuddin A (2005) Pes anserine bursitis: incidence in symptomatic knees and clinical presentation. Skelet Radiol 34(7):395–398. https://doi.org/10.1007/s00256-005-0918-7

Rezasoltani Z, Taheri M, Mofrad MK, Mohajerani SA (2017) Priarticular dextrose prolotherapy instead of intra-articular injection for pain and functional improvement in knee osteoarthritis. J Pain Res 10:1179–1187. https://doi.org/10.2147/JPR.S127633

Saba EKA, El-Sherif SM (2016) Ultrasound-guided versus palpation-guided local corticosteroid injection therapy for treatment of plantar fasciitis. Egypt Rheumatol 38(2):123–131. https://doi.org/10.1016/j.ejr.2015.06.005

Sarifakioglu B, Afsar SI, Yalbuzdag SA, Ustaömer K, Bayramoğlu M (2016) Comparison of the efficacy of physical therapy and corticosteroid injection in the treatment of pes anserine tendino-bursitis. J Phys Ther Sci 28(7):1993–1997. https://doi.org/10.1589/jpts.28.1993

Soliman DMI (2017) Advantages of dextrose, platelet rich plasma and stem cells over the traditional conventional methods in treatment of sports injuries and joint osteoarthritis. J Sports Sci 5:113–118

Soliman DMI, Sherif NM, Omar OH, El Zohiery AK (2016) Healing effects of prolotherapy in treatment of knee osteoarthritis. Egypt Rheumatol Rehabil 43(2):47–52. https://doi.org/10.4103/1110-161X.181858

Tan JC (2006) Practical manual of physical medicine and rehabilitation, 2nd edn. Elsevier Mosby, New York

Uysal F, Akbal A, Gökmen F, Adam G, Reşorlu M (2015) Prevalence of pes anserine bursitis in symptomatic osteoarthritis patients: an ultrasonographic prospective study. Clin Rheumatol 34(3):529–533. https://doi.org/10.1007/s10067-014-2653-8

Weglein AD (2011) Neural prolotherapy. J Prolotherapy 3(2):639–643

Yoon HS, Kim SE, Suh YR, Seo YI, Kim HA (2005) Correlation between ultrasonographic findings and the response to corticosteroid injection in pes anserinus tendinobursitis syndrome in knee osteoarthritis patients. J Korean Med Sci 20(1):109–112. https://doi.org/10.3346/jkms.2005.20.1.109

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