European Spine Journal (2019) 28:1610–1617
https://doi.org/10.1007/s00586-019-06011-3

ORIGINAL ARTICLE

Dextrose injections for failed back surgery syndrome: a consecutive case series

İlker Solmaz[1] · Serkan Akpancar[2] · Aydan Örsçelik[3] · Özlem Yener-Karasimav[3] · Deniz Gül[2]

Received: 2 January 2019 / Revised: 13 March 2019 / Accepted: 13 May 2019 / Published online: 21 May 2019

Abstract

Purpose Patients with chronic low back pain, who do not respond to conservative treatment methods, generally undergo surgical revision operations, and sometimes an undesirable condition called failed back surgery syndrome (FBSS) may be inevitable. Hereby, dextrose is one of the regenerative methods that has gained popularity in the treatment of many musculoskeletal problems, and we aimed to present and evaluate the outcomes of 5% dextrose for the treatment of FBSS.

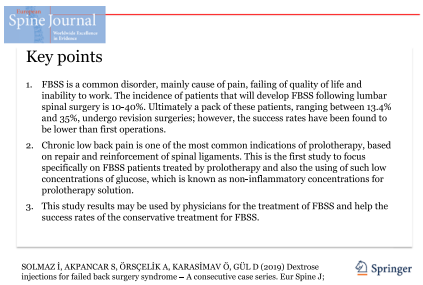
Methods It has been designed as a consecutive case series. A total of 79 patients with FBSS, who had minimum 6 months of symptoms and did not respond to 3 months of conservative methods between May 2014 and March 2016, participated in the study. Prolotherapy injections were applied in posterior and lateral approaches. Visual Analog Scale (VAS) and Oswestry Disability Index (ODI) were used for the pre- and post-treatment evaluations. Patient satisfaction was assessed with using a 5-point Likert scale by phone contacting.

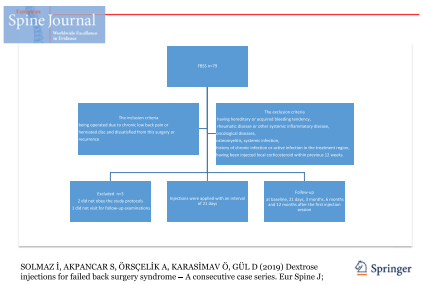
Results There was statistically significant difference between repeated VAS and ODI measurements.

Conclusions These results may be the first step giving a lead to an undiscovered field. This treatment method should be kept in mind for FBSS patients before giving a decision of revision surgery.

Graphical abstract

These slides can be retrieved under Electronic Supplementary Material.





Keywords Failed back surgery syndrome · FBSS · Prolotherapy · Dextrose · Injection

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00586-019-06011-3) contains supplementary material, which is available to authorized users.

✉ Özlem Yener-Karasimav
drozlemkarasimav@hotmail.com

[1] Gulhane Training and Research Hospital, Traditional and Complementary Medicine Practice Center, University of Health Sciences, Ankara, Turkey

[2] Orthopaedics and Traumatology Clinics, Tokat State Hospital, Tokat, Turkey

[3] Gulhane Training and Research Hospital, Department of Sports Medicine, University of Health Sciences, Ankara, Turkey

Introduction

Chronic back pain is one of the most common degenerative diseases and a major cause of disability in the population [1]. Surgery is inevitable in some patients resistant to conservative methods. Owing to rise of scientific knowledge, surgical techniques and feasibility, more satisfactory outcomes are obtained compared to the past. In spite of this progress, these surgeries failed to satisfy a considerable group of patients, and therefore, an undesirable condition failed back surgery syndrome (FBSS) is inevitable [2]. The incidence of patients that will develop FBSS following lumbar spinal surgery is 10–40% [3]. FBSS is a common disorder, mainly cause of pain, failing of quality of life and inability to work. Treatments for FBSS include medical treatment, physical therapy spinal cord stimulation, epidural adhesiolysis, intra-articular joint steroid injections, radiofrequency ablation, acupuncture; however, the success of some was lower, or some have lacking scientific evidence [4]. Ultimately, a pack of these patients, ranging between 13.4% and 35%, undergo revision surgeries; however, the success rates have been found to be lower than first operations [5–8]. A panel study has discussed convenient treatment methods of the persisting pain after spine surgery, and it might accepted a guide for physicians [9].

There is a growing interest to regenerative therapies. Positive effects of the most commonly preferred injection treatment—prolotherapy—have been shown in many randomized controlled studies [10, 11]. In this approach, regeneration aims to renew and restore the tissues that are resistant to normal healing process. Various concentrations of dextrose solutions have commonly been used as prolotherapy solution for many musculoskeletal injuries [12] and provided healing and strengthening of damaged or degenerated structures through inflammation and proliferation processes [13]. It has been shown that interaction of high-concentrated glucose with the extracellular matrix causes irritative effect on targeted tissue, and this initiates acute inflammation. This inflammatory response then enhances proliferation of fibroblasts and improves collagen synthesis, which provides healing and renewal of damaged tissues [14-17]. But 5% concentration of dextrose (low concentrated) is also known to target sensory peptidergic nerves that cause reduced pain perception, and also, repeated injections improve neural sensation and terminate neuropathic pain [18].

Randomized controlled trials have demonstrated Level I–III evidences for injection of dextrose concentrated between 10% and 25% into damaged ligament, tendon and cartilage regions in adults to manage finger osteoarthritis, knee osteoarthritis, lateral epicondylosis, sacroiliac joint pain [19]. Also, Maniquis-Smigel injected 5% dextrose solution without local anesthetics onto facet joints and positive results were obtained for a short-term-period [20]. This study showed glucose has a significantly greater effect than saline on pain.

Chronic low back pain is one of the most common indications of prolotherapy, based on repair and reinforcement of spinal ligaments. In the literature, there is a controversy about injection and exercise protocols for chronic low back pain, and the studies have conflicting results [21]. Dagenais al [22]. compared prolotherapy and normal saline in the treatment of low back pain and declared that two of the methods were revealed significant improvements when compared to baseline; however, there was no statistically significant difference between the two groups.

In one of our studies, we have shown that 5% dextrose solution increased gene expression in angiogenetic factors (vascular endothelial growth factor-A, platelet-derived growth factor-A and B, insulin-like growth factor-I) and in apoptotic factors (caspase-3 and caspase-8) in adult fibroblast culture [23]. We targeted to have a healing improvement as inducing less inflammation, so we planned to inject 5% dextrose solution to low back prolotherapy points of Hackett in the book [24]. Other methodological issue differentiating our study from various low back pain prolotherapy researches is the injection sites, which were determined based on tenderness decreasing injection number.

We hypothesized that deep perineural injection with 5% of dextrose is effective in FBSS as it is in chronic back pain.

This is the first study to focus specifically on FBSS patients treated by prolotherapy and also the use of such low concentrations of glucose, which is known as non-inflammatory concentrations for prolotherapy solution.

The aim of this consecutive case series study is to present the clinical outcomes of prolotherapy with 5% of dextrose for the treatment of FBSS.

Materials and methods

Study design and subjects

This is a clinical prospective consecutive case series study in which 79 patients with FBSS participated, who had minimum 6 months of symptoms and did not respond to 3 months of conservative methods, between May 2014 and March 2016. The population of this study consisted of patients who admitted to Traditional and Complementary Medicine, Orthopaedics and Traumatology, Neurosurgery and Physical Therapy and Rehabilitation departments for the treatment of FBSS. The local institutional ethics committee approval was obtained. All patients signed the informed consent. Among total 79 patients, 3 were excluded from the

study (2 did not obey the study protocols and 1 did not visit for follow-up examinations).

The inclusion criteria were as follows: being operated due to chronic low back pain or herniated disk and being dissatisfied from this surgery or recurrence. The exclusion criteria were as follows: having hereditary or acquired bleeding tendency, rheumatic disease or other systemic inflammatory disease, oncological diseases, osteomyelitis, systemic infection, history of chronic infection or active infection in the treatment region, having been injected local corticosteroid within previous 12 weeks.

Demographic data and clinical characteristics are shown in Table 1 and distribution of surgically operated regions in Table 2.

Table 2 Distribution of surgically operated regions

Surgically operated regions	Frequency	Percent
L4-L5	21	27.6
L3-L5	10	13.2
L4-S1	19	25.0
L3-S1	11	14.5
L5-S1	8	10.5
Others	7	9.2

Others: L1-S1, L5-T12, L3-T12, L2-S1, L3-L4

Two patients had been surgically operated on each of L1-S1 and L2-S1 regions and 1 patient on each of the other regions, so they were added to the distribution list in a mass

Intervention

The prolotherapy injections were performed under aseptic conditions and guided by ultrasonographic imaging. Twenty-three G × 3 1/8" needles were used for injections. The injected points were determined by physical examination, which were observed to be tender during palpation. Injections were performed while patient was lying in prone or lateral decubitus positions.

Posterior injections were applied while the patient was lying in prone position. A pillow was placed under the abdomen. The posterior injection points are shown in Fig. 1. Four milliliters of 5% dextrose was injected into each point. Also, 2 ml of 5% dextrose was injected to spinous processes of L1-L2-L3-L4-L5-S1 vertebrae in case of tenderness.

Lateral injections were applied while the patient was lying in lateral decubitus position and the hip in neutral position. The hip was brought in flexion position only while the piriformis muscle was injected. The lateral injection points are shown in Fig. 2. Two milliliters of 5% dextrose was injected into these points in case of tenderness.

After the injections, patients were instructed to rest and refrain from heavy lifting activity. Patients were allowed to take 500 mg of acetaminophen up to four times per day, if only the pain became untolerable. All other anti-inflammatory drugs were prohibited. Hot pack application onto the injection regions was suggested during the first 3 days after the treatment session three times a day. All of the patients received a standard home exercise program: passive range of motion exercises for lumbar, back and abdominal muscles during the first 7 days after the treatment session, and then stretching exercises for same body regions three times a day until the next injection session. Injections were applied with an interval of 21 days. The injection sessions were terminated when the Visual Analog Scale (VAS) scores decreased to at least 75% ratio of pre-treatment values, maximum 8

Table 1 Demographic data and clinical characteristics

	Mean ± SD	Min–Max
Age (year)	59.1 ± 12.9	26–96
Sex [*n* (%)]		
Male	24	31.6%
Female	52	68.4%
Duration of complaints	9.5 ± 6.4	3–40
Number of operations	1.2 ± 0.5	1–3
Number of sessions	3.4 ± 1.5	1–7

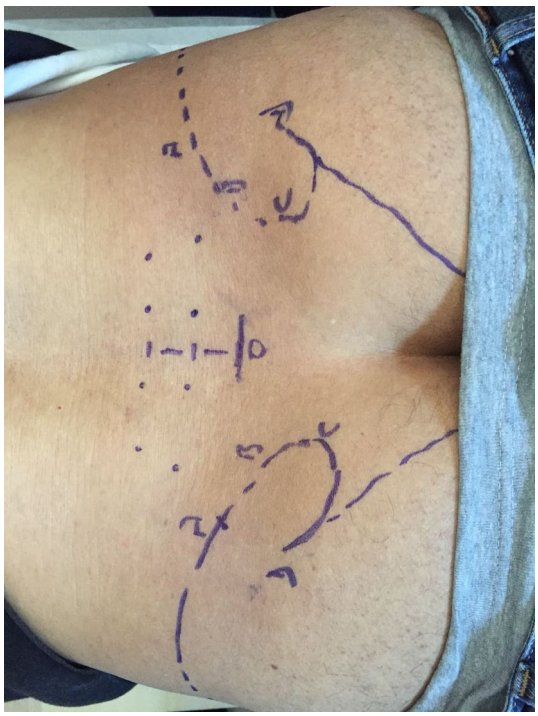


Fig. 1 The posterior injection points. A points: posterior sacroiliac ligament insertions bilaterally. B points: iliolumbar ligament insertions bilaterally. C points: transverse ligament insertions bilaterally. Facet joints bilaterally

Fig. 2 The lateral injection points. Anterolateral: Pubofemoral ligament insertion (PF). Superolateral: Piriformis muscle origin (PQ) and insertion (Pİ) points and iliofemoral ligament insertion (İF). Posterolateral: ischiofemoral ligament insertion (İsF)

sessions of injection were completed, or the patients withdrew from the treatment.

Assessment and outcomes

One of the coauthors (AO) carried out the follow-up assessments independently at baseline, 21 days, 3 months, 6 months and 12 months after the first injection session and was not involved in patients' treatments. We have designed the follow-up periods as defined in the literature [10]. VAS was used for assessment of pain intensity, showing 0 as indicator of painlessness and 10 as indicator of untolerable pain. Oswestry Disability Index (ODI) was used to evaluate patient's functional disability which is considered to be the gold standard evaluation tool for chronic low back pathologies [25]. Total score ranged between 0 and 100; also the higher the score was, the worse the function was. The clinical outcomes were defined by Seven's classification [10] in four categories as excellent, good, fair and poor. The patient's pain intensity during exercise, work or daily activities assessed the appropriate category; painlessness was qualified as 'excellent'; decrease of pain more than 50% in comparison with the pre-treatment level was qualified as 'good'; decrease between 25 and 50% as 'fair' and decrease below 25% as 'poor.' Patient satisfaction was assessed with using a 5-point Likert scale (extremely satisfied, satisfied, neutral, dissatisfied and extremely dissatisfied) based on the patient responses by phone at least 2 years after treatment [26].

Statistical analyses

The statistical analysis was made by Statistical Package for Social Sciences software version 22.0 for Windows. The clinical data were presented as numeral, percent (%), mean ± SD and minimum–maximum (min–max). The compatibility of normal distributions of continuous variables was assessed by the single sample Kolmogorov–Smirnov test. The data obtained in the study were found to be ineligible for normal distribution, and the Mann Whitney *U* test was used to investigate the difference between the groups. The difference between repeated measurements of VAS and ODI was analyzed by Friedman test. Wilcoxon test with Bonferroni adjustment was used for post hoc tests. $p < 0.05$ was considered to indicate a statistically significant difference.

Results

Following the exclusion of 3 patients from the study, 76 patients' results were evaluated.

Reductions in pain and disability scores were statistically and clinically significant from 21st day to the last follow-up examination through the trial. After 1 year of follow-up, VAS score decreased from 7.9 ± 1.6 to 2.3 ± 2.2, and Oswestry Disability Index (ODI) decreased from 36.1 ± 9.1 to 11.4 ± 11.1 (Table 3). There was statistically significant difference between repeated VAS measurements ($X2 = 238.935$; $p < 0.001$) and repeated ODI measurements ($X2 = 238.235$; $p < 0.001$). There was no statistically significant difference between the mean values of VAS and ODI scales of repeated measurements according to gender ($p = 0.059$, $p = 0.032$, $p = 0.878$, $p = 0.654$, $p = 0.646$, $p = 0.144$, $p = 0.654$, $p = 0.427$, $p = 0.201$, $p = 0.323$, respectively). There was no significant difference between VAS and ODI scales of baseline to 1-year follow-up according to gender ($p = 0.235$, $p = 0.266$ female and male, respectively) (Table 4). Sixty-five patients (85.5%) reported excellent or good outcomes (excellent: $n = 45$, good: $n = 20$), and 11 patients (14.5%) reported fair or poor outcomes (fair: $n = 2$, poor: $n = 9$) at the final follow-up. Five-point Likert scale resulted as extremely satisfied: $n = 24$ (31.5%), satisfied: $n = 30$ (39.4%), neutral: $n = 9$ (11.8%), dissatisfied: $n = 4$ (5.2%), extremely dissatisfied: $n = 9$ (11.8%). All of the binary comparisons of the VAS and ODI measurements were found to be similar according to post hoc comparisons (Table 5). None of the patients experienced any serious complication (e.g., bleeding, cellulitis, septic joint arthritis or

Table 3 Comparison of VAS and ODI data

Follow-up	VAS Mean ± SD (min–max)	ODI (%)Mean ± SD (min–max)
Baseline	7.9 ± 1.6 (4–10)	36.1 ± 9.1 (16–49)
21 days	5.8 ± 1.9 (1–9)	27.4 ± 10.1 (4–47)
3 months	4.7 ± 1.9 (0–9)	20.2 ± 9.9 (2–40)
6 months	3.3 ± 2.1 (0–8)	14.3 ± 11.4 (2–41)
12 months	2.3 ± 2.2 (0–8)	11.4 ± 11.1 (2–40)
Test statistics and *p* value	238,935[a] < 0.001*	238,235[a] < 0.001*

[a] Friedman test *$p < 0.05$

osteomyelitis). Only 5 patients had pain of the injected sites in severity of acetaminophen necessity four times a day, during 5–10 days after the injection sessions, the other patients had no or mild pain that they did not require any analgesic. One patient developed second-degree skin burn after the first injection because of incorrect application of hot pack. Two patients developed hypotension and vasovagal syncope while injecting the solution.

Table 4 Comparison of VAS and ODI between genders

	Female ($n = 52$)	Male ($n = 24$)	p*
VAS (0–12mo**)	5.76 ± 2.7	5.31 ± 2.2	0.235
ODI (0–12 mo**)	25.48 ± 12.27	23.58 ± 12.19	0.266

* Inter-group analysis (Student's t test)

** Improvement between baseline to 12 months

Discussion

FBSS remains to be a fearful dream of clinicians as one of the most frequent post-surgical complications. Unfortunately, there is limited evidence and are few methods available. In the treatment of FBSS, we used 5% dextrose combined with rehabilitation program, and this was observed to be efficient and safe.

In the treatment of this situation, epidural adhesiolysis and spinal cord stimulation were found to be most efficient methods, regarding long-term pain relief [27]. Some studies mentioned that these methods have advantages over revision surgeries [28-30]. Epidural steroid, hyaluronidase or local anesthetic injections are increasingly being used because of their simplicity and cheapness; however, there is limited evidence about them and some other studies declared that these injections do not present better clinical outcomes than percutaneous adhesiolysis [31-33]. Revision surgeries had been the most common used method with the rates ranging from 5 to 33% in the past [34]. However, conservative methods have gained popularity due to increasing rates of fibrosis and instability [35]. Some studies reported similar functional improvement and pain relief level when revision surgeries and conservative methods have been compared [36, 37]. So prolotherapy is considered to be an efficacious, cheap and accessible intervention. Although several methods have been defined, there is still need for clinical evidence and new cost-effective methods.

In our study, we used 5% dextrose injections for patients with FBSS. VAS score decreased from 7.9 ± 1.6 to 2.3 ± 2.2; ODI decreased from 36.1 ± 9.1 to 11.4 ± 11.1; these results were found to be statistically significant. We think that prolotherapy injections with 5% dextrose may be considered as a promising method in the treatment of FBSS, depending on its clinic efficacy, procedure simplicity, cheapness and safety.

Optimal concentrations of dextrose solution for prolotherapy remain unclear in clinical practice. Hypertonic dextrose solutions (10–20%) have been commonly used as prolotherapy solutions. In many studies, higher concentrations of dextrose than 10% have been used and they have declared successful results for different musculoskeletal problems. But the majority of these studies reported extreme pain, fatigue and discomfort as the leading complaints of patients after the injections, and therefore, patients who decided to discontinue the treatment were not in an ignorable ratio [12]. These complaints are thought to be the result of the inflammatory reaction due to high concentrations of dextrose [13]. Jensen et al. [38] stated that concentrations of dextrose below 10% provide proliferation without inflammatory reaction in their animal study. In our study, very few numbers of patients complained about excessive pain and fatigue after the injections and our results are similar with those in which higher concentrations of dextrose were used. The large number of injection sessions scared patients at the beginning, but patients decided to continue because of its benefit and they trusted their physician. We believe that 5%

Table 5 Comparison of VAS and ODI measurements between regions

	L3-L5 ($n=10$)	L3-S1 ($n=11$)	L4-L5 ($n=21$)	L4-S1 ($n=19$)	L5-S1 ($n=8$)	P*
VAS (0–12 mo**)	6.2 ± 1.8 a	4.6 ± 3.2 a	5.8 ± 1.8 b	5.5 ± 2.7 a	5.4 ± 3.0 a	> 0.05†
ODI (0–12 mo**)	27.8 ± 9.1	19.5 ± 14.3	25.9 ± 9.1	23.5 ± 12.5	21.8 ± 15.9	> 0.05†

* Inter-group analysis (Student's t test)

** Improvement between baseline to 12 months

† All of the binary comparisons of the measurements were found to be similar according to post hoc comparisons

dextrose provides a more comfortable and patient-compliant treatment opportunity with same clinical success.

FBSS is a condition in which many different causes come together and which occurs as a mix of persistent muscle spasm, persistent nerve pain and persistent tissue pain (often sourcing from the disk). Some authors state that an important cause of FBSS is postoperative extreme inflammatory reaction that causes fibrogenesis in the epidural space and compression of spinal nerve roots [3, 39]. Maniquis-Smigel showed that injection of 5% dextrose into the caudal cavity has an analgesic effect within 15 min that lasted at least 48 h. This result may be due to a pain-specific neurogenic effect at the dorsal root level [20]. 5% dextrose may also affect pain from ligaments. Therefore, lower concentrations of dextrose may be more suitable for this indication and we think it might be used for similar problems which have a chronical inflammatory process basically in the next future.

In the previous studies, combination of local anesthetics (lidocaine, sensorcaine and xylocaine) and hypertonic dextrose was used as prolotherapy solution [12]. Drucker et al. [40] showed that local anesthetics delay and disrupt wound healing by inhibiting collagen synthesis of fibroblast tissue. In another study, superficial 5% dextrose injections have been shown to be more effective than lidocaine in the trigger point-related pain [41, 42]. Also, 5% dextrose solution without local anesthetics addition was injected onto facet joints and positive results were obtained for a short-term-period [20]. In our study, we preferred to use 5% dextrose for similar effects.

In FBSS, not only the lumbar ligaments, but also the pelvic and sacroiliac ligaments are often disrupted or weakened, and therefore, insufficient autocontrol of lumbopelvic motion and muscular balance will result in pain and discomfort. Lumbar, pelvic and sacroiliac ligaments support posture, balance and walking abilities [43, 44]. In this study, we targeted sacroiliac, pelvis and lumbar injection points and obtained improvements in patient's posture, balance and walking ability. The most convenient treatment choice for FBSS patients with spinal instability accepted as re-operation in a panel study [9]. This study's patient selection criteria [9] were similar to our study, and however, our results supported prolotherapy for these patients.

Physical exercise occupies an important place in the treatment of FBSS [35]. Yelland [45] compared flexion exercises with no exercise as well as prolotherapy injection with saline injection for chronic low back pain in his 2 × 2 factorially designated study and obtained statistically significant results in pain and disability scores when compared to pre-treatment values. However, no attributable effect was found for prolotherapy injections over saline injections or for exercises over normal daily activities. In Dagenais' study [22], prolotherapy alone is not considered to be an effective treatment for chronic low back pain. He reported prolotherapy might improve chronic low back pain and disability if it only combines with exercise program. In our study, we recommended an exercise program after injections to improve functionality. VAS and ODI scores significantly decreased. Sixty-five patients (85.5%) declared excellent or good outcomes. Exercise was only a cointervention in our study, and analysis of the effect that can be attributed to exercise cannot be possible with this study design.

The limitations of this study are lack of placebo control group, only-exercise control group and high-concentrated dextrose solution (15%) group. Our study is a consecutive case series, so there absolutely is a risk of bias. The strength of this study is that the follow-up period could be completed. Higher-quality studies which are designed with addition of these groups might be a highlighter in this way. Our study may be the first step giving a lead to an undiscovered field. This treatment method should be kept in mind for FBSS patients before giving a decision of revision surgery.

Acknowledgements We all thank Michael Yelland, Associate Professor, MD, and John Lyftogt, MD, for their respected contributions to the designation of this paper.

Compliance with ethical standards

Conflict of interest İlker Solmaz, Serkan Akpancar, Aydan Örsçelik, Özlem Yener-Karasimav and Deniz Gül declare that they have no conflict of interest.

References

1. Dagenais S, Caro J, Haldeman S (2008) A systematic review of low back pain cost of illness studies in the United States and internationally. Spine J 8(1):8–20. https://doi.org/10.1016/j.spine.2007.10.005
2. Schofferman J, Reynolds J, Herzog R et al (2003) Failed back surgery: etiology and diagnostic evaluation. Spine J 3(5):400–403
3. Chan C-W, Peng P (2011) Failed back surgery syndrome. Pain Med 12:577–606
4. Hussain A, Erdek M (2014) Interventional pain management for failed back surgery syndrome. Pain Pract 14:64–78
5. Choi HS, Chi EH, Kim MR et al (2014) Demographic characteristics and medical service use of failed back surgery syndrome patients at an integrated treatment hospital focusing on complementary and alternative medicine: a retrospective review of electronic medical records. Evid Based Complement Altern Med 2014:714389
6. Shapiro C (2014) The failed back surgery syndrome: pitfalls surrounding evaluation and treatment. Phys Med Rehabil Clin N Am 25(2):319–340
7. Hazard RG (2006) Failed back surgery syndrome: surgical and nonsurgical approaches. Clin Orthop Relat Res 443:228–232
8. Weir S, Samnaliev M, Kuo TC et al (2017) The rate of persistent post-operative pain (FBSS) in revision lumbar spinal surgery. Spine J 17(3):S10
9. Tronnier VM, Eldabe S, Franke J, Huygen F, de Andres Rigoard P, Ares J et al (2018) The appropriate management of persisting pain after spine surgery: a European panel study with recommendations based on the RAND/UCLA method. Eur Spine J 28(1):31–45. https://doi.org/10.1007/s00586-018-5711-0
10. Seven MM, Ersen O, Akpancar S et al (2017) Effectiveness of prolotherapy in the treatment of chronic rotator cuff lesions. Orthop Traumatol Surg Res 103(3):427–433
11. Ersen O, Koca K, Akpancar S et al (2017) A randomized-controlled trial of prolotherapy injections in the treatment of plantar fasciitis. Turk J Phys Med Rehab 64(1):i–xi
12. Akpancar S, Seven MM, Tuzun HY et al (2017) Current concepts of prolotherapy in orthopedic surgery. Arch Trauma Res 6(2):e40447
13. Rabago D, Slattengren A, Zgierska A (2010) Prolotherapy in primary care practice. Prim Care 37(1):65–80
14. Reeves KD, Topol GA, Fullerton BD (2008) Evidence-based regenerative injection therapy (prolotherapy) in sports medicine. In: Seidelberg PH, Beutler PL (eds) The sports medicine resource manual. Saunders, Philadelphia, pp 611–619
15. Di Paolo S, Gesualdo L, Ranieri E, Grandaliano G, Schena FP (1996) High glucose concentration induces the overexpression of transforming growth factor-beta through the activation of a platelet-derived growth factor loop in human mesangial cells. Am J Pathol. 149(6):2095–2106
16. Murphy M, Godson C, Cannon S, Kato S, Mackenzie HS, Martin F et al (1999) Suppression subtractive hybridization identifies high glucose levels as a stimulus for expression of connective tissue growth factor and other genes in human mesangial cells. J Biol Chem. 274(9):5830–5834
17. Krump E, Nikitas K, Grinstein S (1997) Induction of tyrosine phosphorylation and Na+/H+ exchanger activation during shrinkage of human neutrophils. J Biol Chem 272(28):17303–17311
18. Lyftogt J (2008) Pain conundrums: which hypothesis? Central nervous system sensitization versus peripheral nervous system autonomy. Aust Musculoskelet Med 13(2):72
19. Sanderson LM, Bryant A (2015) Effectiveness and safety of prolotherapy injections for management of lower limb tendinopathy and fasciopathy: a systematic review. J Foot Ankle Res 8:57. https://doi.org/10.1186/s13047-015-0114-5
20. Maniquis-Smigel L, Dean Reeves K, Jeffrey Rosen H et al (2017) Short term analgesic effects of 5% dextrose epidural injections for chronic low back pain: a randomized controlled trial. Anesthesiol Pain Med 7(1):e42550. https://doi.org/10.5812/aapm.42550
21. Yelland MJ, Glasziou PP, Bogduk N, et al (2004) Prolotherapy injections, saline injections, and exercises for chronic low-back pain: a randomized trial. Spine (Phila Pa 1976) 29(1):9–16 **(discussion 16)**
22. Dagenais S, Yelland MJ, Del Mar C, Schoene ML (2007) Prolotherapy injections for chronic low-back pain. Cochrane Database Syst Rev. 18(2):CD004059.
23. Guran S, Coban ZD, Karasimav O et al (2018) Dextrose solution used for prolotherapy decreases cell viability and increases gene expressions of angiogenic and apopitotic factors. Gulhane Med J 60:42
24. Hackett GS, Hemwall GA, Montgomery GA (1993) Ligament and tendon relaxation treated by prolotherapy, 5th edn. Gustav A. Hemwall, Oak Park
25. Fairbank JCT, Pynsent PB (2000) The oswestry disability index. Spine 25(22):2940–2953
26. Jamieson S (2004) Likert scales: how to (ab)use them. Med Educ 38(12):1217–1218
27. Lee JH, Lee SH (2014) Clinical effectiveness of percutaneous adhesiolysis versus transforaminal epidural steroid injection in patients with postlumbar surgery syndrome. Reg Anesth Pain Med 39:214–218
28. Hollingworth W, Turner JA, Welton NJ et al (2011) Costs and cost effectiveness of spinal cord stimulation (SCS) for failed back surgery syndrome. Spine 36:2076–2083
29. Lad SP, Babu R, Bagley JH et al (2014) Utilization of spinal cord stimulation in patients with failed back surgery syndrome. Spine 39:E719–E727
30. North RB, Kidd D, Shipley J et al (2007) Spinal cord stimulation versus reoperation for failed back surgery syndrome: a cost effectiveness and cost utility analysis based on a randomized, controlled trial. Neurosurgery 61:361–368
31. Manchikanti L, Abdi S, Atluri S et al (2013) An update of comprehensive evidence-based guidelines for interventional techniques in chronic spinal pain. Part II: guidance and recommendations. Pain Physician 16:S49–283
32. Chun-jing J, Hao-xiong N, Jia-ziang N (2012) The application of percutaneous lysis of epidural adhesions in patients with failed back surgery syndrome. Acta Cir Bras 27:357–362
33. Manchikanti L, Boswell MV, Datta S et al (2009) Comprehensive review of therapeutic interventions in managing chronic spinal pain. Pain Physician 12:E123–E198
34. Fritsch EW, Heisel J, Rupp S (1996) The failed back surgery syndrome: reasons, intraoperative findings, and long-term results: a report of 182 operative treatments. Spine (Phila Pa 1976) 21:626–633
35. Amirdelfan K, Webster L, Poree L et al (2017) Treatment options for failed back surgery syndrome patients with refractory chronic pain: an evidence based approach. Spine 42:S41–S52
36. Louw A, Diener I, Landers MR et al (2014) Preoperative pain neuroscience education for lumbar radiculopathy: a multicenter randomized controlled trial with 1-year follow-up. Spine (Phila Pa 1976) 39:1449–1457
37. Brox JI, Reikeras O, Nygaard O et al (2006) Lumbar instrumented fusion compared with cognitive intervention and exercises in patients with chronic back pain after previous surgery for disc herniation: a prospective randomized controlled study. Pain 122:145–155

38. Jensen KT, Rabago DP, Best TM et al (2008) Early inflammatory response of knee ligaments to prolotherapy in a rat model. J Orthop Res 26(6):816–823. https://doi.org/10.1002/jor.20600
39. Thomson S, Jacques L (2009) Demographic characteristics of patients with severe neuropathic pain secondary to failed back surgery syndrome (PROCESS study). Pain Pract 9:206–214
40. Drucker M, Cardenas E, Arizti P et al (1998) Experimental studies on the effect of lidocaine on wound healing. World J Surg. 22(4):394–397 **(discussion 397–8)**
41. Kim MY, Na YM, Moon JH (1997) Comparison on treatment effects of dextrose water, saline, and lidocaine for trigger point injection. J Korean Acad Rehabil Med 21(5):967–973
42. Rabago D, Kijowski R, Woods M et al (2013) Association between disease-specific quality of life and magnetic resonance imaging outcomes in a clinical trial of prolotherapy for knee osteoarthritis. Arch Phys Med Rehabil 94(11):2075–2082
43. Panjabi M, Abumi K, Duranceau J et al (1989) Spinal stability and intersegmental muscle forces. A biomechanical model. Spine 14(2):194–200
44. Clemente CD (1985) Gray's Anatomy, 30th edn. Lea & Febiger, Philadelphia
45. Yelland M, Glasziou P, Bogduk N, Schluter P, McKernon M (2004) Prolotherapy injections, saline injections, and exercises for chronic low back pain: a randomized trial. Spine 29(1):9–16