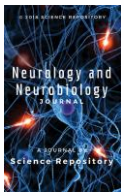

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Is Saline Injection a True Sham/Placebo Treatment in Randomized Controlled Trials? A Systematic Review

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ABSTRACT

Objective: To explore whether saline is a real sham/placebo agent, or it has potential therapeutic effects when used as control treatment in randomized controlled trials for the management of discogenic low back pain.

Methods: A comprehensive literature search was conducted investigating the effects of saline as a placebo in the treatment of chronic pain when administered into the intervertebral disc. Following stepwise filtering, selected articles were assessed for their levels of evidence, followed by a discussion of their contribution to the understanding of the role of saline in chronic pain management.

Results: Out of 95 articles that described the administration of intradiscal saline solution used as a placebo for chronic pain management, 8 articles met all of the inclusion criteria. Their levels of evidence ranged from 1a to 4 (Oxford Centre CEBM). Intradiscal administration of saline solution was found to have measurable therapeutic benefits. In some studies, the pain relief was similar to that provided by local anaesthetics and steroids.

Conclusion: Although the exact mechanism of the analgesic effects of saline is not clear, yet the use of intradiscal saline appears to have some analgesic benefits like local anaesthetics and steroids when used individually. Researchers should practice caution when designing RCTs using intradiscal saline injection as a sham/placebo treatment for the control arm or maybe, when possible, avoid the use of intradiscal saline injection as a sham treatment.

Introduction

Randomized controlled trials (RCTs) are considered the gold standard methodology in clinical research. It is commonly used to evaluate the therapeutic effects of a new treatment or intervention [1]. In order to eliminate or minimize the placebo effect, research subjects need to be blinded to which treatment arm they were randomized to. By doing so, the quality and reliability of the research outcomes improve significantly [2]. To further minimize the potential bias, researchers expand blinding to include the study evaluation team and sometimes the investigator(s) administering the therapy and biostatisticians analysing the data to further increase the reliability and validity of the results. When evaluating the safety and efficacy of an interventional procedure, the only way to blind participants is to randomize subjects to receive either the study intervention or a sham treatment that is administered in a way that simulates the study intervention. For example, the sham treatment is performed using the same or at least a very similar technique to the active treatment with the exception of substituting the active agent/treatment with an inactive agent. Saline solution is used in many clinical trials as the inactive or sham treatment agent without clear data to support the notion that it is, in reality, an inactive agent. One cannot ignore or underestimate the importance of the placebo/sham treatment arm in RCT and how it significantly strengthens the level of evidence a specific clinical trial provides. Although the positive results in the control arm could be explained by the placebo effect, we should not ignore the unknown potential therapeutic effect of injecting saline or other inactive formulation at the treatment target.

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In a well-designed RCT published in New England Journal of Medicine (NEJM), Friedly *et al.* compared epidural injections of glucocorticoids plus lidocaine or lidocaine alone for symptom control in patients with spinal canal stenosis. At 6 weeks, there was no statistically significant difference in Roland-Morris Disability Questionnaire (RMDQ) scores between the 2 groups, albeit both groups showed some improvement in their pain scores. On the Swiss Spinal Stenosis Questionnaire (SSSQ) satisfaction scale, 67% of patients who received glucocorticoids plus lidocaine reported being very or somewhat satisfied with their treatment, as compared with 54% of those who received only lidocaine (P=0.01) [3]. The authors did not provide an explanation for the long-term improvement in the lidocaine group. It is well-established, that lidocaine is a short-acting local anaesthetic; therefore, the prolonged pain relief and improved disability at 6 weeks must have a different mechanism than local anaesthesia. In another literature review conducted by Bar-Or *et al.*, it was assumed that intra-articular saline injection that is used as placebo for knee osteoarthritis clinical trial has some analgesic effect since its effects were always better than no treatment [4]. The fundamental question became; is it all placebo effects? Or is there a long-term benefit of lidocaine beyond its duration of action as a local anaesthetic? Or is it possible that control treatment agent (lidocaine or saline) has potential unknown therapeutic effects [5]?

To our knowledge, there are no available systematic reviews to elucidate whether the saline solution is a really inactive agent, or it might have some therapeutic effects when used to evaluate interventional treatment of discogenic pain. Therefore, our goal is to review the world literature of the published randomized controlled trials to treat discogenic pain involving the use of intradiscal injection of saline as a sham treatment arm. The hope is to clarify if saline is a real inactive/sham treatment, or does it have some therapeutic benefits that investigators should be aware of or even not to use saline as a sham treatment arm.

Methods

I Research Question

"Is intradiscal saline injection a real sham treatment?" A literature review was performed using Ovid EMBASE MEDLINE INFO from 1974 to July 17, 2020.

II Data Collection

Inclusion criteria: Intradiscal electrothermal therapy, intradiscal drug administration, saline, and sodium chloride. All study designs limited to the English language were included. These studies were reviewed with regard to clinical application, dosage and route of administration, efficacy and potential side effects and complications. The level of evidence for each article selected for inclusion was determined based on the concept outlined by the Oxford Centre for Evidence-Based Medicine (CEBM) (Appendix 1). Results were filtered using the stepwise approach, as shown in the flowchart in (Figure 1).

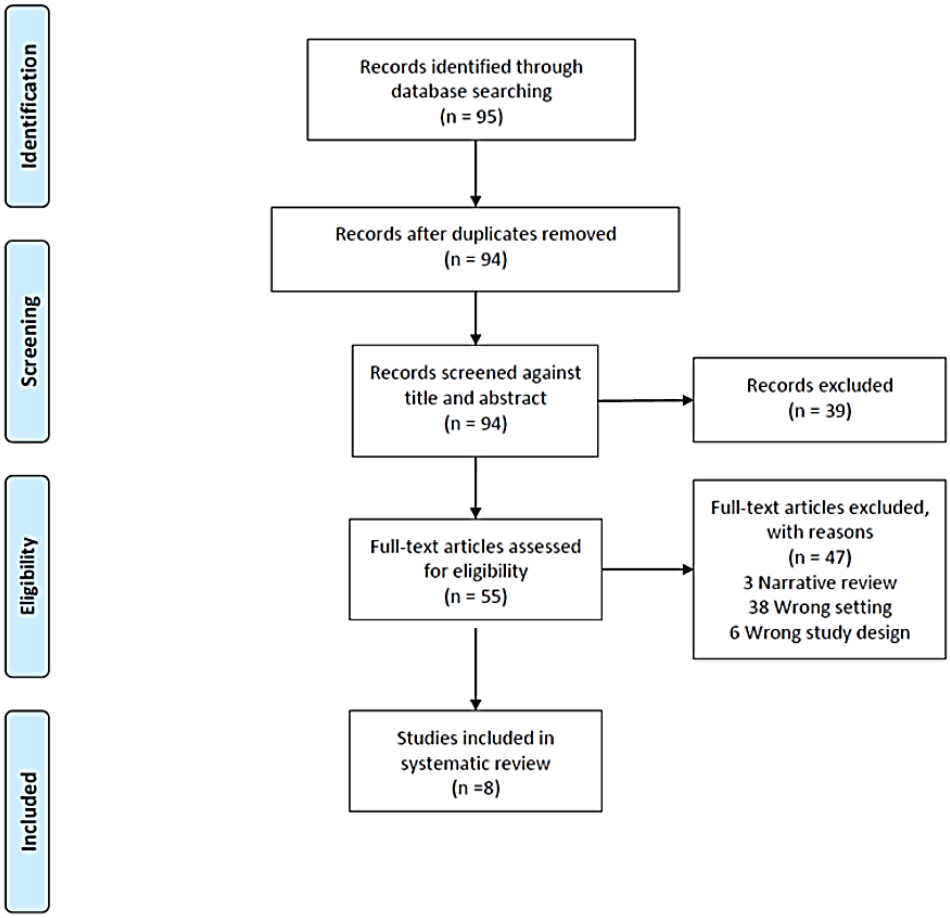

Figure 1: PRISMA flowchart for study inclusion.

Results

We obtained 95 results after selecting the following keywords: intradiscal electrothermal therapy, intradiscal drug administration, saline, and sodium chloride. After title and abstract review, 39 studies were excluded. The remaining 55 studies were reviewed by two investigators. In case of disagreement, a third reviewer was used to break the tie. After full review, only 8 studies were included (see Figure 1 for inclusion and exclusion details). The level of evidence for each article selected for inclusion was determined based on the concept outlined by the Oxford Centre for Evidence-Based Medicine (CEBM), as shown in the (Appendix 1). Table 1 summarizes each of the studies meeting the inclusion criteria and the related level of evidence for each study according to Oxford CEBM.

Table 1: Summary of each of the studies meeting the inclusion criteria and the related level of evidence for each study according to Oxford CEBM.

Authors	Study name	Study design	Patient population	No. of patients	Treatment groups	Outcomes	Level of evidence**
Cao *et al.* 2011 [13]	Intradiscal injection therapy for degenerative chronic discogenic low back pain with end plate Modic changes	RCT	Discogenic LBP and end plate Modic changes (MRI) + discography.	120	Intradiscal injection of saline, diprospan, and diprospan+songmeile.	No significant pain relief within the groups receiving intradiscal saline. The groups that received either diprospan or diprospan + songmeile injections significantly improved their VAS and ODI scores.	1b
Peng *et al.* 2010 [6]	A randomized placebo-controlled trial of intradiscal methylene blue injection for the treatment of chronic discogenic low back pain	RCT	Discogenic LBP longer than 6 months with no previous lumbar surgery	72	Intradiscal injection of methylene blue and isotonic saline	Mean reduction in NRS-101 of 52.50, and ODI of 35.58. As well as 91.6% patient satisfaction in the MB group vs 0.70%, 1.68%, and 14.3% in the placebo group.	1b
Khot *et al.* 2004 [8]	The Use of Intradiscal Steroid Therapy for Lumbar Spinal Discogenic Pain	RCT	Chronic discogenic LBP	120	Intradiscal injection of methylprednisolone and saline	No difference in outcomes measures (disability and pain scores) at 12 months	1b
Beall *et al.* 2020 [9]	VAST Clinical Trial: Safely Supplementing Tissue Lost to Degenerative Disc Disease	RCT	Disc degeneration at 1 or 2 vertebral levels from L1 to S1 with chronic low back pain for a minimum of 6 months	220	Allograft, saline or continue nonsurgical management (NSM)	VAS improved at 6 months from 54.81 to 16.0 on the allograft group and from 55.25 to 41 in the saline group. At 12 months the allograft decreased to 12.27 and in the saline group decreased to 19.67. ODI from 53.73 and 49.25 in the allograft and saline respectively to 18.47 at 6 months and 28.75 at 12 months in the allograft group. Saline group: 15.67 and 9.33 at 6 and 12 months, respectively.	1b
Kallewaard *et al.* 2019 [7]	A multicenter randomized controlled trial on the efficacy of intradiscal methylene blue injection for chronic discogenic low back pain: the IMBI study	Double-blinded RCT	Chronic discogenic low back pain for at least 6 months with poor response to conservative therapy	84	Intradiscal injection of methylene blue and isotonic saline	NRS between the groups was statistically insignificant after 6 months with no change in the PGIC	1b
Nguyen *et al.* 2017 [26]	Intradiscal glucocorticoid injection for patients with chronic low back pain (LBP) associated with active discopathy	Double-blinded RCT	Chronic lower back pain for at least 3 months with discopathy on MRI	135	glucocorticoids and iodixanol contrast vs iodixanol contrast alone	At 1 month 11-point NRS was higher in the GC IDI (55.4%) vs control (33.3%), the improvement of LBP-related limitation improved in the GC IDI group (84.6% VS 54.0%). At 3 months pain scores in the GC IDI were higher than in the control and by 12 months, there were not differences between the 2 groups	1b

Schwetschenau *et al.* 1976 [10]	Double-blinded evaluation of intradiscal chymopapain for herniated lumbar disc	Double-blinded RCT	LBP with radiculopathy and no improvement after 3 months of conservative treatment	66	Chymopapain vs placebo	The successful rate for the chymopapain group was 58% and for the placebo group was 49%, with a p value of 0.14	1b
Bae *et al.* 2014 [12]	Is there clinical improvement associated with saline injection for discogenic low back pain: comparison of RCTs	Post-hoc comparison of RCT	N/A	N/A	Intervertebral disc injection of saline vs investigational drug	At 12 months: saline patients had a 58.5% decreased in VAS vs 36.6% decreased for the investigational group	1a

** level of evidence key. According to Oxford Centre for Evidence-Based Medicine (CEBM).

Peng and collaborators evaluated the treatment of chronic discogenic low back pain with intradiscal methylene blue (MB) injection in a double-blinded RCT [6]. 72 patients were confirmed with discogenic pain through a positive discography. Of those 72 patients, 36 patients received one ml of 1% MB injection; the remaining 36 patients received 1 ml of saline. The main outcome was pain alleviation and physical function improvement, assessed with 0-100 point's numerical rating scale and ODI at 6, 12, and 24 months. There was a statistically significant difference between the MB and placebo (saline) groups when comparing NRS and ODI, with long-lasting results up to 24 months that favoured the MB group.

Kallewaard and collaborators replicated Peng *et al.* study in 2019 with a bigger sample size. 81 patients were enrolled in the study, 40 patients in the interventional group and 41 in the placebo (saline) group [6, 7]. The results did not support the findings of Peng *et al.* [6]. NRS between the groups was statistically insignificant after 6 months. Responders rate at 3 months, defined as >30% reduction in pain score, was 24.4% and 25% in placebo (saline) and treatment group, respectively. Patients' global impression of change was also evaluated. In the placebo group, 26.8 and 24.4% reported improved PGIC at 3 and 6 months, respectively compared to 20 and 25% in the treatment group.

In a prospective, blinded RCT by Khot *et al.*, 120 patients with chronic low back pain of discogenic origin, confirmed by discography, were randomized to receive an intradiscal injection of either saline (1 mL) or methylprednisolone (40 mg in 1 mL) after a positive discography [8]. The primary outcome was a change in disability scores at 1 year follow-up. Interestingly, there was no significant difference in disability scores between the groups. Patients in the steroid group reported a mean change of 2.28 in percentage disability compared to 3.42 with intradiscal saline injection. Moreover, there was no difference in changes of VAS among the groups even though the patients reported achieving pain relief with the administration of saline and steroids, indicating that no superiority was demonstrated between the two.

In a recent prospective, multicenter RCT, Beall and collaborators analysed the results of 220 patients with discogenic pain due to disc degeneration using MRI scoring, physical examination and pain evaluation [9]. Patients were randomized to receive intradiscal active allograft, non-surgical management (NSM) or saline as a placebo. Interim analysis of the first 24 patients was examined and clinical improvement was achieved at 6 months. VAS for back pain improved from 54.81 to 16.0 (70% improvement) for the allograft group and from 55.25 to 41.0 (26% improvement) for the saline group. At 12 months, VAS continued to decrease to 12.27 (78% improvement) and 19.67 (64% improvement) in allograft and saline group, respectively. More interestingly, average pain score and percentage reduction in VAS at 3 months were lower in the intradiscal saline group compared to intradiscal allograft, while in NSM average VAS score increased at 3 months. The ODI at 6 and 12 months improved by 66 and 76% for the allograft group, respectively and improved by 42 and 81% in placebo group at 6 and 12 months, respectively. Similarly, at 3 months, ODI increased from baseline for the NSM group. All NSM patients elected to cross over to the allograft group at 3 months.

In another double-blinded RCT, Nguyen *et al.* randomized 135 patients with low back pain (LBP) secondary to disc pathology to receive a single injection of either 1 mL of iodixanol contrast plus 1 mL (25 mg) of prednisolone acetate (2 mL total) versus 1 mL of iodixanol contrast only. Although the percentage of responders "defined to have LBP <40 on 0-100 NRS at 1 month" were statistically significant between the treatment and placebo group, 55% and 33%, respectively. 54% of the placebo group reported improvement in LBP-related limitations in activities at 1 month. This is, in addition to 33% of the placebo group achieving primary endpoint. After 3 months, the pain score started to increase in the treatment group, even higher than in the control group and at 12 months, no differences were seen between the two groups.

Schwetschenau and collaborators in 1976 studied chymopapain to treat lumbar herniated disc [10, 11]. 66 patients were enrolled in the double-blinded RCT. 35 patients received placebo (contrast diluted in water only) and 31 patients received contrast diluted in water plus chymopapain. The subjects were followed in 6 weeks, 3 months, 6 months and 12 months. The outcome of the study was classified as failure and successful response ['success' (if symptoms improved significantly)] or as ['failure' (if symptoms remained essentially unchanged or became worse)]. No statistically significant difference was found between the 2 groups. While chymopapain was successful in 53% of patients, intradiscal placebo injection showed 49% success rate. The authors conclude that there was no statistical significance and there was no advantage in using chymopapain.

Bae and collaborators performed a post hoc comparison using data from the results of four clinical trials assessing intervertebral disc injections. All trials were randomized, controlled trials utilizing intradiscal saline as a placebo. At 12 months, patients injected with intradiscal saline experienced a 58% reduction in their VAS score compared to only 36.6% VAS reduction in the treatment group. There was a statistically significant decrease in VAS for both groups across the four studies. The authors concluded that an intervertebral injection of saline could offer patients pain relief, decreased disability, diminish substance reaction and injection trauma [12].

On the other hand, there are some studies that contradict the possible therapeutic mechanism of action of intradiscal saline injection. In a double-blinded RCT, Cao and collaborators assessed the outcomes of intradiscal steroid therapy in patients with chronic discogenic pain [13]. They compared the effect of intradiscal saline, diprospan and diprospan+songmeile in patients with type I or type II Modic changes. In his RCT, there was no improvement in outcome measures with intradiscal normal saline injection while diprospan either alone or with songmeile resulted in statistically significant improvement in VAS and ODI at 3 and 6 months.

Discussion

Discogenic pain refers to pain originating from within the intervertebral disc due to derangement of the disc structure and the development of nociceptors as part of the degeneration that occurs with the aging process. Although it is an aging process, it is mistakenly called degenerative disc disease (DDD). Discogenic pain is a major cause of chronic low back pain in the United States. Degenerative changes of the disc include loss of water and proteoglycans and structural changes leading to imbalances between synthesis and degenerations favouring catabolism and disc degradation. Based on the degenerative process, one could conclude that the addition of an isotonic fluid e.g., normal saline solution, would aid the homeostasis maintenance of the structure hence decreasing the pain of such origin. If so, should we continue to use intradiscal saline injection as a sham treatment?

The potential therapeutic effect of saline injection has been studied previously in different interventions. In 1980, Frost and his colleagues randomized patients with myofascial trigger point pain into 2 groups to receive trigger point injections with local anaesthetics versus saline. It was surprising when they found that the group who received saline injection tended to have better pain relief in an experimental animal study, where authors injected rabbits with intradiscal hypertonic saline for the purpose of decreasing intradiscal pressure and relieving the pain generated by lumbar disc herniation through chemonucleolysis [14]. Intradiscal injections were administered in rabbits at 1, 4, 8, and 12 months. The authors concluded that 0.02 ml 10% hypertonic saline has the potential for reducing intradiscal pressure. Furthermore, an injection of a higher amount and concentration could be effective clinically [15].

An interesting, randomized control study conducted by Karppinen and his colleagues comparing transforaminal epidural methylprednisolone bupivacaine combination or saline found significant leg pain relief in favour of the steroid group but there was statistically significant more improvement in back pain in the saline group at 3 and 6 months [16]. Similarly, the use of intradiscal saline injection was found to have a positive effect in 6 out of 8 studies, demonstrating some improvement in pain and disability scores with sham treatment or at least no significant difference between sham and investigational treatment. One study showed no significant improvement in pain scores or functionality with intradiscal saline injection compared to methylene blue, while subjects who received intradiscal methylene blue reported statistically significant improvement in pain scores. Nonetheless, when the study was replicated by Kallewaard in 2019, it did not show a significant difference between intradiscal saline injections and intradiscal methylene blue [7]. Among subjects who received intradiscal saline injection, the responder rates were 17, 24.4 and 26.7 at 6 weeks, 3 and 6 months, respectively.

In animal models, the expression of pro-inflammatory mediators has been studied and compared between healthy versus degenerated intervertebral discs. It was found that induction of degenerative disc changes increases expression of Interleukin (IL) 1, 8 10 and Tumor necrosis factor α (TNF-α), with a more exaggerated response with repeated and prolonged injury [17, 18]. Similarly, in humans, IL-1β and TNF-α were elevated in degenerated and herniated intervertebral discs [19, 20]. Although the exact etiology for intervertebral disks (IVDs) degeneration is unclear, there are multiple hypotheses explaining potential mechanisms of IVDs degenerations. It includes up-regulation of proteolytic enzymes e.g., aggrecanases, alkaline phosphatase and inflammatory cytokines e.g., interleukin 1β (IL-1β) [21]. In another interesting study that was published in nature, Gilbert *et al.* found that acidic intervertebral disc media promotes disc degeneration. Another possible explanation of the therapeutic effect of intradiscal saline is neutralizing IVD acidic media which will slow down disc degeneration [22].

Although the mechanism of pain and disability improvement with intradiscal saline injection is yet unclear, there is some speculation that saline injection can potentially dilute/wash out inflammatory mediators, proteolytic enzymes and cytokines that in turn ameliorate nerve endings irritations or by neutralizing IVD acidic media [5]. A study investigating the effects of local anaesthetics in degenerated rabbit IVDs showed interesting results [23]. During the *in vivo* analysis, the number of cells in the nucleus pulposus was significantly decreased among the saline and local anaesthetics groups compared with the control and puncture-only groups. The results were confirmed with histologic analysis with no difference between the saline, puncture-only, bupivacaine, and lidocaine groups. In a prospective study, 20 out of 25 patients with low back pain due to disk herniation achieved tearing of the thinned posterior longitudinal ligament after undergoing a high-pressure injection of saline. These patients received a single high-pressure injection of 5-10 mL of normal saline into the nucleus of the disk. Even though patients experience immediate pain relief, long-term follow-up is pending [24]. In a double-blinded RCT comparing biacuplasty to sham treatment, there was no statistical significance in VAS scores and ODI at 8 weeks between the 2 groups. Nonetheless, VAS and ODI showed similarities and even showed slightly more improvement in the sham group. However, it might be a placebo effect. One cannot exclude a possible mechanical mechanism or similar mechanism of action to trigger point injection (TPI) which, in addition to local anaesthetic effect, could be secondary to mechanical disruption of muscle pain and release of local mediators [25]. On the other hand, there are some studies that contradict

the possible therapeutic mechanical mechanism of action of intradiscal saline injection.

Conclusion

The use of saline possibly represents the result of a type II statistical error when used as in the control group vs active treatment for the management of chronic pain. Having pain relief in a control group is detrimental to the objectivity of the study and this error could pass unnoticed by investigators. On the other hand, the use of saline could be useful, pending further trials, as a treatment in the management of chronic pain.

Appendix 1: Level of evidence by the Oxford Centre for Evidence-Based Medicine (CEBM).

Level	Therapy/Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	SR of RCTs	SR of inception cohort studies; CDR" validated in different populations	SR of Level 1 diagnostic studies; CDR" with 1b studies from different clinical centers	SR of prospective cohort studies	SR of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval)	Individual inception cohort study with > 80% follow-up; CDR" validated in a single population	Validating** cohort study with good" reference standards; or CDR" tested within one clinical center	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts" "	All or none case-series	Absolute better-value or worse-value analyses
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT, e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR" or validated on split-sample§§§ only	Exploratory** cohort study with good" reference standards; CDR" after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor-quality cohort and case-control studies§§)	Case-series (and poor-quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

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REFERENCES

1. Kabisch M, Ruckes C, Seibert Grafe M, Blettner M (2011) Randomized controlled trials: part 17 of a series on evaluation of scientific publications. *Dtsch Arztebl Int* 108: 663-668. [Crossref]
2. Probst P, Grummich K, Heger P, Zaschke S, Knebel P et al. (2016) Blinding in randomized controlled trials in general and abdominal surgery: protocol for a systematic review and empirical study. *Syst Rev* 5: 48. [Crossref]
3. Friedly JL, Comstock BA, Turner JA, Heagerty PJ, Deyo RA et al. (2014) A randomized trial of epidural glucocorticoid injections for spinal stenosis. *N Engl J Med* 371: 11-21. [Crossref]
4. Bar Or D, Rael LT, Brody EN (2017) Use of Saline as a Placebo in Intra-articular Injections in Osteoarthritis: Potential Contributions to Nociceptive Pain Relief. *Open Rheumatol J* 11: 16-22. [Crossref]
5. Fukusaki M, Kobayashi I, Hara T, Sumikawa K (1998) Symptoms of spinal stenosis do not improve after epidural steroid injection. *Clin J Pain* 14: 148-151. [Crossref]
6. Peng B, Pang X, Wu Y, Zhao C, Song X (2010) A randomized placebo-controlled trial of intradiscal methylene blue injection for the treatment of chronic discogenic low back pain. *Pain* 149: 124-129. [Crossref]
7. Kallewaard JW, Wintraecken VM, Geurts JW, Willems PC, van Santbrink H et al. (2019) A multicenter randomized controlled trial on the efficacy of intradiscal methylene blue injection for chronic discogenic low back pain: the IMBI study. *Pain* 160: 945-953. [Crossref]
8. Khot A, Bowditch M, Powell J, Sharp D (2004) The use of intradiscal steroid therapy for lumbar spinal discogenic pain: a randomized controlled trial. *Spine (Phila Pa 1976)* 29: 833-836. [Crossref]
9. Beall DP, Wilson GL, Bishop R, Tally W (2020) VAST Clinical Trial: Safely Supplementing Tissue Lost to Degenerative Disc Disease. *Int J Spine Surg* 14: 239-253. [Crossref]
10. Schwetschenau PR, Ramirez A, Johnston J, Wiggs C, Martins AN (1976) Double-blind evaluation of intradiscal chymopapain for herniated lumbar discs. Early results. *J Neurosurg* 45: 622-627. [Crossref]
11. Martins AN, Ramirez A, Johnston J, Schwetschenau PR (1978) Double-blind evaluation of chemonucleolysis for herniated lumbar discs. Late results. *J Neurosurg* 49: 816-827. [Crossref]
12. Bae HW, Kanim L, Kim J, Provenzano NJ, Thordarson SR (2014) Is There Clinical Improvement Associated with Saline Injection for Discogenic Low Back Pain: Comparison of RCTs. *Spine J* 14: S32.
13. Cao P, Jiang L, Zhuang C, Yang Y, Zhang Z et al. (2011) Intradiscal injection therapy for degenerative chronic discogenic low back pain with end plate Modic changes. *Spine J* 11: 100-106. [Crossref]
14. Frost FA, Jessen B, Siggaard Andersen J (1980) A control, double-blind comparison of mepivacaine injection versus saline injection for myofascial pain. *Lancet* 1: 499-500. [Crossref]
15. Sato K, Nagata K, Hirohashi T (2002) Intradiscal pressure after repeat intradiscal injection of hypertonic saline: an experimental study. *Eur Spine J* 11: 52-56. [Crossref]
16. Manchikanti L, Nampiaparampil DE, Manchikanti KN, Falco FJE, Singh V et al. (2015) Comparison of the efficacy of saline, local anesthetics, and steroids in epidural and facet joint injections for the management of spinal pain: A systematic review of randomized controlled trials. *Surg Neurol Int* 6: S194-S235. [Crossref]
17. Rousseau MAA, Ulrich JA, Bass EC, Rodriguez AG, Liu JJ et al. (2007) Stab incision for inducing intervertebral disc degeneration in the rat. *Spine (Phila Pa 1976)* 32: 17-24. [Crossref]
18. Holm S, Mackiewicz Z, Holm AK, Konttinen YT, Kouri VP et al. (2009) Pro-inflammatory, pleiotropic, and anti-inflammatory TNF-alpha, IL-6, and IL-10 in experimental porcine intervertebral disk degeneration. *Vet Pathol* 46: 1292-1300. [Crossref]
19. Le Maitre CL, Freemont AJ, Hoyland JA (2005) The role of interleukin-1 in the pathogenesis of human intervertebral disc degeneration. *Arthritis Res Ther* 7: R732-R745. [Crossref]
20. Kokubo Y, Uchida K, Kobayashi S, Yayama T, Sato R et al. (2008) Herniated and spondylotic intervertebral discs of the human cervical spine: histological and immunohistological findings in 500 en bloc surgical samples. Laboratory investigation. *J Neurosurg Spine* 9: 285-295. [Crossref]
21. Risbud MV, Shapiro IM (2014) Role of cytokines in intervertebral disc degeneration: pain and disc content. *Nat Rev Rheumatol* 10: 44-56. [Crossref]
22. Gilbert HTJ, Hodson N, Baird P, Richardson SM, Hoyland JA (2016) Acidic pH promotes intervertebral disc degeneration: Acid-sensing ion channel -3 as a potential therapeutic target. *Sci Rep* 6: 37360. [Crossref]
23. Ura K, Sudo H, Iwasaki K, Tsujimoto T, Ukeba D et al. (2019) Effects of Intradiscal Injection of Local Anesthetics on Intervertebral Disc Degeneration in Rabbit Degenerated Intervertebral Disc. *J Orthop Res* 37: 1963-1971. [Crossref]
24. Kanai A (2009) Treatment of lumbar disk herniation by percutaneous intradiscal high-pressure injection of saline. *Pain Med* 10: 76-84. [Crossref]
25. Wong CSM, Wong SHS (2012) A new look at trigger point injections. *Anesthesiol Res Pract* 2012: 492452. [Crossref]
26. Nguyen C, Boutron I, Baron G, Sanchez K, Palazzo C et al. (2017) Intradiscal Glucocorticoid Injection for Patients With Chronic Low Back Pain Associated With Active Discopathy: A Randomized Trial. *Ann Intern Med* 166: 547-556. [Crossref]