Systematic Review

Efficacy of Botulinum Toxin, Local Anesthetics, and Corticosteroids in Patients With Piriformis Syndrome: A Systematic Review and Meta-analysis

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Background: Piriformis syndrome (PS) is a painful condition caused by entrapment of the sciatic nerve within the piriformis muscle. PS is typically unilateral and mainly occurs related to entrapment of the sciatic nerve. Treatments include physiotherapy, analgesics, anti-inflammatory drugs, behavioral modifications, injection therapy with local anesthetics (LAs) and steroids, epidural injection, botulinum toxin (BT) injection, and surgery.

Objectives: To investigate the efficacy of BT, LA, and corticosteroid (CS) injections in relieving pain in patients affected by PS.

Study Design: This systematic review and meta-analysis was conducted according to the "Cochrane Handbook for Systematic Reviews of Interventions" and the "Preferred Reporting Items for Systematic Reviews and Metaanalyses (PRISMA)" guidelines.

Methods: A systematic search was conducted through PubMed, Cochrane, Web of Science, and Scopus through April 2021 for studies investigating the efficacy of BT, LA, or CS injection in improving pain in patients with PS. After screening retrieved studies, data were extracted from included studies and pooled. Overall results were reported as standardized mean difference (SMD) and 95% confidence interval (CI). Analysis was performed using RevMan software version 5.4.

Results: Sixteen studies were included in this systematic review, and 12 of them were included in the quantitative synthesis. The pain scores decreased significantly after treatment with BT (SMD = -2.00; 95% CI [-2.84, -1.16], $P < 0.001$), LA and CS (SMD = -4.34; 95% CI [-5.77, 2.90], $P < 0.001$), LA (SMD = -3.73; 95% CI [-6.47, -0.99], $P = 0.008$), CS (SMD = -2.78; 95% CI [-3.56, -2.00], $P < 0.001$), and placebo injection (SMD = -0.04; 95% CI [-0.07, -0.01], $P = 0.002$). BT injection was less effective than LA and CS together ($P = 0.006$), more effective than placebo ($P = 0.001$), and similar to LA ($P = 0.24$) and CS ($P = 0.18$), when injected alone.

Limitations: A wide variety of study designs were utilized to obtain the largest sample size available. Many of the included studies lack randomization, and some are retrospective in nature. These limitations may introduce bias into the analyzed data and affect the results. Many studies had a low sample size and are of moderate quality, limiting the generalizability of the results. Also, we could not conduct a direct meta-analysis due to the lack of sufficient double-arm studies comparing different types of injection therapies.

Conclusions: In patients with PS, satisfactory pain improvement can be obtained by BT, LA plus CS, LA, or CS injection therapy. Injection of LA plus CS showed the best efficacy.

Key words: Botulinum toxin, corticosteroids, local anesthetics, meta-analysis, piriformis syndrome, systematic review

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Piriformis syndrome (PS) is a painful condition affecting the back and may extend to the leg (1,2). PS mainly occurs related to entrapment of the sciatic nerve within the piriformis muscle, while the nerve exits the pelvis through the greater sciatic notch, or due to spasm or hypertrophy of the piriformis muscle (3,4). PS causes sciatica-like symptoms and represents about 6% to 8% of sciatica-like painful conditions (3-5).

PS pain typically is unilateral and affects the buttock area. It worsens by prolonged sitting (1,6). It also limits straight leg raising, determines tenderness near the external sciatic notch, and is associated with positive PS tests. These physical tests (e.g., Freiburg, Pace, tonic external rotation, flexion, abduction internal rotation of the hip, Beatty, heel contralateral knee, active piriformis, and seated piriformis tests) help to differentiate PS from radiculopathy. However, none of them can accurately diagnose PS, which still is a diagnosis of exclusion (1). These tests increase the tension of the piriformis and the pressure on the sciatic nerve, so reproducing the pain (1).

Besides clinical characteristics, PS diagnosis is suggested by magnetic resonance neurography showing any of the following: hypertrophied or atrophied piriformis, splitting of the sciatic nerve, additional slips of the muscle, and prominence, flattening, or increased signal of the sciatic nerve at the sciatic notch that may be associated with increased signal at the L5 or S1 nerve root (7). PS is managed initially by physiotherapy, analgesics, anti-inflammatory drugs, and behavioral modifications. But if the pain is still persistent, injection therapy with local anesthetics (LAs) and steroids, epidural injection, botulinum toxin (BT) injection, and even surgery may have a role (8-10).

BTs are used in disorders, such as cervical dystonia, blepharospasm, axillary hyperhidrosis, glabellar lines (11), spasticity (12), and hyperactive bladder (13). BTs also have a useful role in pain disorders as myofascial pain, neck pain, back pain (14,15), and spasticity disorders (17) and are also used in masseteric and facial wrinkle therapy (16-18). BT has 2 known serotypes, A (BT-A) and B (BT-B). BT-A is helpful in painful spastic conditions like dystonia, myofascial pain, and sacroiliac joint injections (19,20)

The role of BT injection in treating pain conditions is promising, but for PS, the evidence is still lacking. Previous studies investigating the role of BT treatment and summarized in Tables 1 and 2 are controversial, and no previous research has reviewed all the available evidence regarding BT's role in this condition. Additionally, there is no systematic comparison of BT's pain-relieving efficacy with commonly used therapies, such as LAs and corticosteroids (CSs) in patients with PS. In this study, therefore, we aim to summarize the evidence regarding the efficacy of BT injection, LA, and CS injection in patients with PS and compare BT with each of these active treatments and with placebo.

Methods

This systematic review and meta-analysis was conducted according to the "Cochrane Handbook for Systematic Reviews of Interventions" and the "Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)" guidelines (21,22).

Literature Search and Data Collection

A systematic search through PubMed, Scopus, Web of Science, and Cochrane Library databases was conducted using the key words "Pyriformis syndrome" and "botulinum toxin." The search was updated through April 2021. Retrieved records were imported to Endnote software for removing duplicates. Titles and abstracts were screened according to inclusion and exclusion criteria, then full texts of the remaining studies were retrieved and reviewed to confirm their eligibility to the synthesis. Reference lists of the

Table 1. *Baseline characteristics of the included studies.*

Study	Arms	Number	Gender M/F (n)	Age, years	Pain score	Duration of pain (months)	Site of injection		FAIR test (+/-)
							Left	Right	
Al-Al-Shaikh 2015	BT	12	-	46.5 (26-63)	7.5 (1.61)	-	-	-	-
	Control	8	-	48 (24-77)	-	-	-	-	-
Albayrak 2015	LA & CS	28	14/14	46.1 (19-71)	8.3	-	-	-	-
Childers 2002	BT	10	-	42.1 (5.7)	-	38.7	-	-	-
	Placebo								
Fanucci 2001	BT	30	16/14	41 (29-54)	-	-	-	-	-
Fishman 2002	BT	26	17/9	53.69 (13.3)	-	-	-	-	-
	LA & CS	37	25/12	55.5 (13.6)	-	-	-	-	-
	Placebo	24	16/7	60.75 (11.53)	-	-	-	-	-
Fishman 2004	BT	27	-	53	-	-	-	-	-
Fishman 2017	BT	26	-	-	-	-	-	-	-
	Placebo	28	-	-	-	-	-	-	-
Fowler 2014	LA & CS (FL)	12	-	-	5.13 (2.09)	-	-	-	-
	LA & CS (US)	15	-	-	4.83 (1.77)	-	-	-	-
Jeong 2015	CS	37	14/13	60.6 (0.6)	6.89 (1.08)	-	-	-	-
Lang 2004	BT	20	5/15	54.3 (9.96)	-	-	-	-	-
Masala 2012	LA & CS	13	5/8	37 (8)	9 (0.8)	-	-	-	13/0
Misirlioglu 2015	LA & CS	25	2/23	47.2 (13.4)	7.4 (2.4)	17.4 (28.6)	15	10	25/0
	LA	22	5/17	45.5 (14.1)	7.2 (2.0)	23.6 (30.5)	13	9	22/0
Mullin 1990	CS	12	0/12	32 (16-49)	-	24	-	-	-
Naja 2009	LA	40	13/27	52.1 (17.4)	-	-	21	20	-
Yan 2021	BT	70*	26/44	53 (41–65)[a]	8 (7–9)[a]	2 y (1.5–3)[a]	-	-	11/59
	LA	41*	15/26	54 (44–63)[a]	8 (7–9)[a]	2.5 y (1–4)[a]	-	-	3/38
Yoon 2007	BT	20	8/12	45.65 (14.28)	7.06 (1.48)	17.2 (19.65)	10	10	-

BT: botulinum toxin; LA: local anesthesia; CS: corticosteroids; FL: fluoroscopy; US: ultrasound; M/F: male/female; y: years; *: number per injection; [a]: interquartile range; FAIR: flexion, adduction, and internal rotation; n: number.

Data are presented as mean (standard deviation or minimum-maximum).

included articles were also screened for potentially eligible articles.

Inclusion and Exclusion Criteria

The present investigation included articles reporting data obtained on patients with PS and treated with injections of BT (whether BT-A or BT-B), LAs, and/or CSs. We included studies reporting pain score change at any time point after injection, with no study design restrictions, including randomized controlled trials (RCTs), case series, cohort, and retrospective studies. We excluded abstracts, theses, editorials, reviews, non-English publications, and case series or arms including < 10 patients.

Data Extraction

Extracted data included: 1) baseline characteristics of the included studies' population, including the number in each arm, age, gender, pain score, duration of pain, 2) summary of the included studies, including study design, duration, sample size, pain scale used, follow-up period, and doses of each drug, 3) pain score as reported in each trial, either by the Visual Analog Scale (VAS) or Numeric Rating Scale (NRS-11).

Quality Assessment

The present investigation assessed the quality of included RCTs using the Cochrane tool for risk of bias

Table 2. *Summary of the included studies*.

Study	Design	Duration	Sample size	Pain scale	Follow-up	Doses
Al-Al-Shaikh 2015	Case control	12/2009-06/2012	20	VAS	6.1 M	100 IU
Albayrak 2015	Case series	08/2012-09/2013	28	VAS	6 W	-
Childers 2002	RCT	-	10	VAS	10 W	100 IU
Fanucci 2001	Cohort	4/1997-12/1999	30	-	12 M	100 IU
Fishman 2002	RCT	-	87	VAS	12 W	200 U
Fishman 2004	Non-randomized CT	-	27	VAS	12 W	5000, 7500, 10000, 12500 U
Fishman 2017	RCT	10/2014-10/2015	28	VAS	12 W	300 IU
Fowler 2014	RCT	-	27	NRS	3 M	-
Jeong 2015	Cohort	01/2010-10/2012	63	VAS	36 M	-
Lang 2004	Case series	-	20	VAS	16 W	6000 U
Masala 2012	Non-randomized CT	01/2008-10/2009	23	VAS	12 M	-
Misirlioglu 2015	RCT	09/2010-05/2011	50	NRS	3 M	-
Mullin 1990	Cohort	1980-1989	12	-	12 M	-
Naja 2009	RCT	01/2005-1/2007	80	VAS	6 M	-
Yan 2021	Cohort	01/2014-10/2018	97	VAS	6 M	100 IU
Yoon 2007	RCT	04/2003-02/2004	20	NRS	12 W	150 U

RCT: randomized controlled trial; CT: clinical trial; M: months; W: weeks; VAS: visual analogue scale; NRS: numeric rating scale.

(RoB) assessment in randomized trials (23). The tool consists of judging the risk of selection, performance, detection, attrition, reporting, and other biases. Other included studies' quality was assessed using the suitable National Institute of Health (NIH) tool for each study, according to their study design (observational cohort studies, case-control studies, and case series) (24).

Statistical Analysis

The present investigation pooled change in pain score data as a standardized mean difference (SMD) and standard error using the inverse-variance method under the random-effects model. The overall results were reported as SMD and 95% confidence interval (CI). We pooled the results of BT, LA, and CS, LA alone, CS alone, and placebo at all available time points. We compared the pooled estimate for BT with LA and CS, LA only, CS only, and placebo by the test for subgroup difference. Also, we pooled the data from included RCTs at all time points and as a subgroup analysis at 0-4 weeks, 5-9 weeks, and 10-14 weeks after injection. Heterogeneity among pooled data was assessed by the chi-square and I-square tests and was considered significant at chi-square $P < 0.1$. Whenever heterogeneity was significant, we tried to solve the heterogeneity by performing a sensitivity analysis using the leave-one-out test. Analysis was conducted using RevMan software version 5.3.

Results

Literature Search

Databases search yielded 1,408 records, of which 483 were duplicates, and the remaining 925 records were screened. Nine hundred and two were excluded just screening the titles and abstracts and 7 articles were excluded after the full-text screening. The remaining 16 articles were included in the qualitative synthesis (2,25-39). Of these, 12 articles were included in the quantitative synthesis (25-27,30-37,39). Figure 1 shows the flow chart of the study inclusion and exclusion process.

Summary of the Included Studies

The present investigation included different studies, including RCTs, nonrandomized trials, case series, cohort studies, and case-control studies. Studies used the VAS or NRS-11 to evaluate the intensity of pain. Sample size ranged from 10 cases to 97 cases, and the follow-up period ranged from 6 weeks to 36 months across studies. The mean age of included patients ranged from 32 years to 60.75 years, and the mean pain score ranged from 4.83 to 9 across study arms. Tables 1 and 2 show more details about the characters of included studies and their population. The commonly used doses of BT injection were 100 IU for BT-A and 5,000 units for BT-B.

Quality of the Included Studies

According to Cochrane's RoB tool, included studies were of moderate to high quality, except one study (39) that was of low quality. Most included RCTs had a low risk of selection, performance, detection, attrition, and reporting biases. However, 3 studies (27,37,39) had an unclear risk of selection bias because they did not demonstrate the random sequence generation and treatment allocation. Two studies (32,39) had a high risk of performance and detection biases related to lack of blinding. One study (39) had a high risk of attrition bias due to incomplete outcome data. Other sources of bias were high in Fishman et al (29) and unclear in other 5 trials (27,31,32,37,39). Figure 2 shows the summary of each study judgment, and Supplementary Fig. 1 shows the RoB graph.

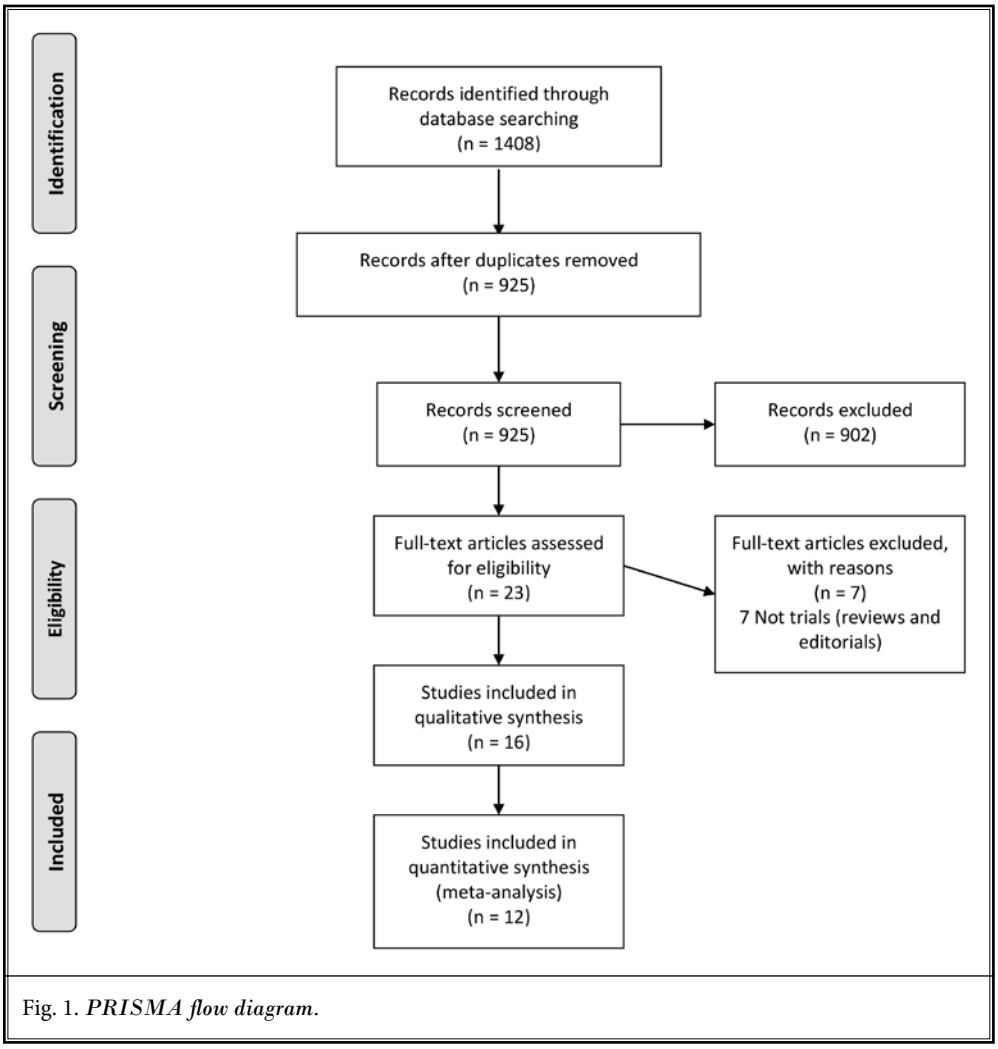

Fig. 1. *PRISMA flow diagram.*

Regarding other studies' quality as assessed by the NIH tools, included cohort studies were of fair to high quality, scoring 11 to 12.5 out of 14 quality assessment points (2,28,30,33,35,38). The included case series and the case-control studies were of fair quality (25,26,34).

Pain Score Change

Botulinum Toxin vs Local Anesthetic and Corticosteroid Injection

Pooled Results for All Included Studies (Fig. 3)

The pain score change showed a significant reduction in both BT (SMD = -2.00; 95% CI [-2.84, -1.16], $P < 0.001$), and LA and CS subgroups (SMD = -4.34; 95% CI [-5.77, 2.90], $P < 0.001$). The test for subgroup difference showed that LA and CS have better pain score reduction than BT ($P = 0.006$). Both subgroups were heterogenous ($P < 0.001$, $I^2 > 90\%$) and the heterogeneity could not be solved.

Pooled Results for Included RCTs only (Fig. 4)

The pain score change showed a significant reduction in both BT (SMD = -2.35; 95% CI [-3.96, -0.73], $P = 0.004$) and LA and CS subgroups (SMD = -2.34; 95% CI [-3.38, -1.30], $P < 0.001$). The test for subgroup difference showed similar pain score change for both subgroups ($P = 1.00$). The results for BT were heterogenous ($P < 0.001$, $I^2 = 93\%$), but the heterogeneity was solved after excluding Fishman et al (31)

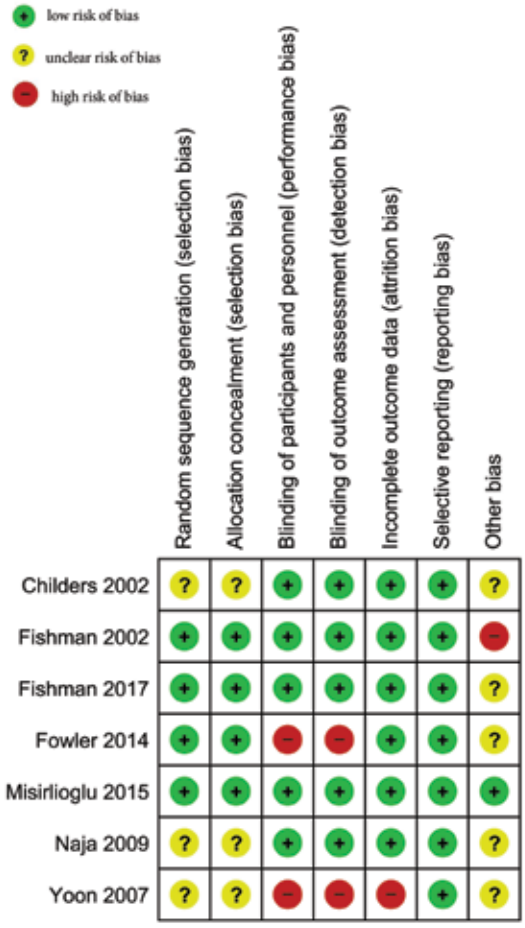

Fig. 2. *Risk of bias (RoB) summary of included RCTs.*

(12 weeks) and the results remained significant (Fig. 5). The results for LA and CS were heterogenous (P = 0.007, I^2 = 66%), but the heterogeneity was solved after excluding Misirlioglu et al (36) (3 months) and the results remained significant. The test for subgroup difference remained not significant after solving heterogeneity (Fig. 5).

Pooled Results for Included RCTs at 0-4 Weeks (Fig. 6)

The pain score change showed a significant reduction in both BT (SMD = -2.00; 95% CI [-3.09, -0.92], P = 0.0003), and LA and CS subgroups (SMD = -2.62; 95% CI [-4.52, -0.72], P = 0.007). The test for subgroup difference showed comparable results for both BT, and LA and CS (P = 0.58). The results for BT were homogenous (P = 0.1, I^2 = 62%). The results for LA and CS were heterogenous (P = 0.001, I^2 = 81%), but heterogeneity was solved after excluding Masala et al (35) and the results remained significant. The test for subgroup difference remained not significant after solving heterogeneity (Fig. 7).

Pooled Results for Included RCTs at 5-9 Weeks (Fig. 8)

The pain score change showed a significant reduction in both BT (SMD = -2,41; 95% CI [-4,48, - 0.34], P = 0.02), and LA and CS subgroups (SMD = - 5.30; 95% CI [-8.72, -1.87], P = 0.002). The test for subgroup difference showed comparable results for both subgroups (P = 0.16). The results were heterogenous for both BT (P = 0.007, I^2 = 86%), and LA and CS subgroups (P = 0.001, I^2 = 93%), and the heterogeneity could not be solved.

Pooled Results for Included RCTs at 10-14 Weeks (Fig. 9)

The pain score decreased significantly with LA and CS (SMD = -3.70; 95% CI [-6.74, -0.65], P = 0.02), but not with BT injection (SMD = -0.93; 95% CI [-2.62, 0.75], P = 0.28). The difference between both subgroups was not significant (P = 0.12). The results for both subgroups were heterogenous (P < 0.001, I^2 > 90%) and the heterogeneity could not be solved.

Botulinum Toxin vs Local Anesthetic Injection

Pooled Results for All Included Studies (Supplementary Fig. 2)

The pain score change showed a significant reduction in both BT (SMD = -2.00; 95% CI [-2.84, -1.16], P < 0.001) and LA subgroups (SMD = -3.73; 95% CI [-6.47, -0.99], P = 0.008). The difference between both subgroups was not significant (P = 0.24). The results for BT was heterogenous and could not be solved. The results for LA were heterogenous (P < 0.001, I^2 = 96%), but heterogeneity was solved after excluding Naja et al. (37) (6 months). The results for LA remained significant, and the difference between subgroups favored LA over BT (P < 0.001) after solving heterogeneity (Supplementary Fig. 3).

Botulinum Toxin vs Corticosteroid Injection

Pooled Results for All Included Studies (Supplementary Fig. 4)

The pain score change showed a significant reduction in both BT (SMD = -2.00; 95% CI [-2.84, -1.16], P < 0.001), and CS subgroups (SMD = -2.78; 95% CI [-3.56, -2.00], P < 0.001). The difference between BT and CS was not significant (P = 0.18).

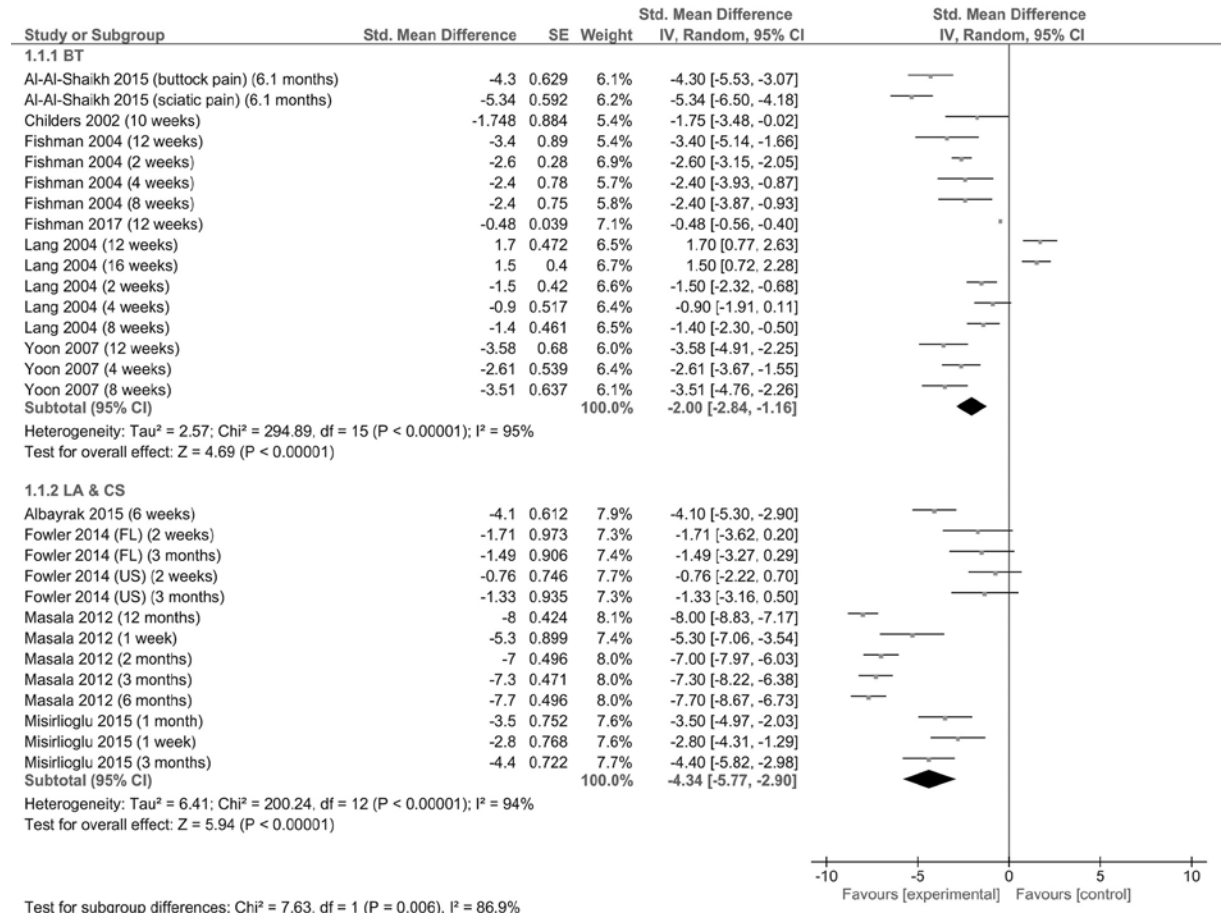

Fig. 3. *Results of botulinum toxin vs local anesthetic and corticosteroid injection (all included studies).*

Botulinum Toxin vs Placebo

Pooled Results for All Included Studies (Supplementary Fig. 5)

The pain score change showed a significant reduction in both BT (SMD = -2.00; 95% CI [-2.84, -1.16], $P < 0.001$) and placebo subgroups (SMD = - 0.04; 95% CI [-0.07, -0.01], $P = 0.002$). The test for subgroup difference favored BT over placebo ($P = 0.001$). The results for placebo were homogenous ($P = 0.77$, $I^2 = 0\%$).

Qualitative Synthesis

In a retrospective cohort study, Yan et al (38) analyzed data of 97 PS patients who received 111 computed tomography (CT)-guided injections to the piriformis muscle (some patients had bilateral injections), and they had perineural injections to the sciatic nerve. The Botox cohort received LA and 100 IU Botox to the piriformis muscle and received LA and CS around the nerve. The non-Botox group received the same medications except Botox. The Botox group had a significantly better 48-hour pain relief ($P < 0.001$) and a not significantly more prolonged pain-free time (median of 30 days vs one day, $P = 0.059$).

Fishman et al (29), in a RCT including 67 PS patients receiving 72 injections, investigated the role of Botox added to twice weekly physical therapy in reducing PS-associated pain. They reported better pain relief in patients who had BT injection (n = 21) compared with LA and CS (n = 31, $P < 0.05$) and placebo (n = 15, $P = 0.001$) based on the percentage of patients who had 50% or more improvement of their pain score (65% for Botox, 32% for LA and CS, and 6% for placebo).

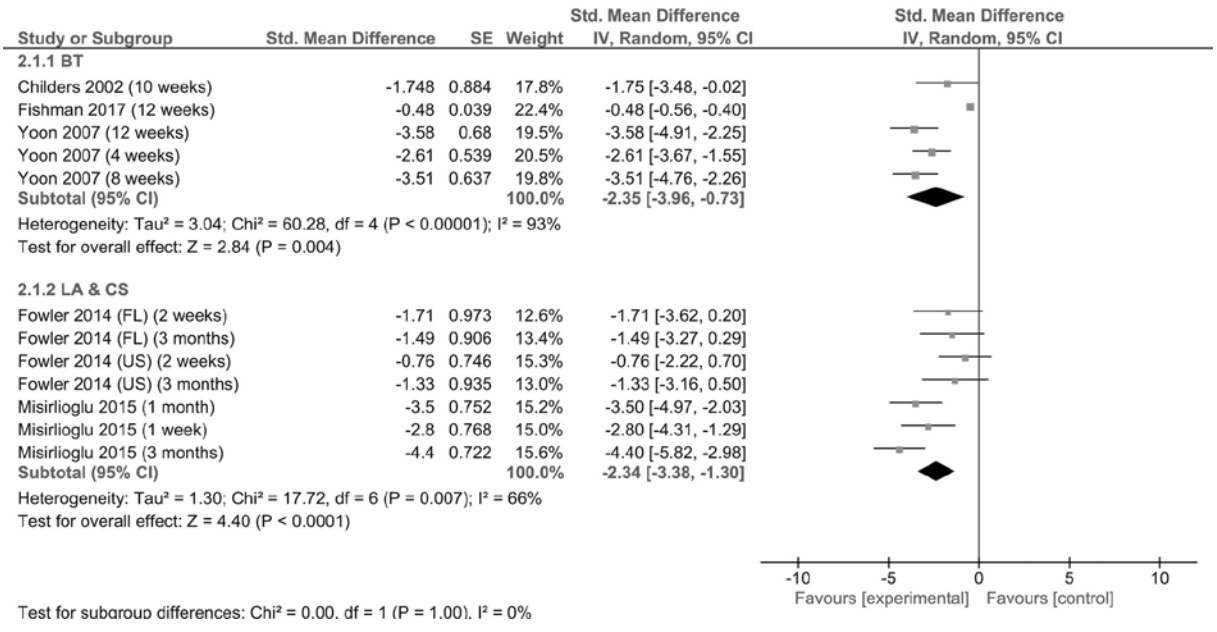

Fig. 4. *Results of botulinum toxin vs local anesthetic and corticosteroid injection (RCTs only).*

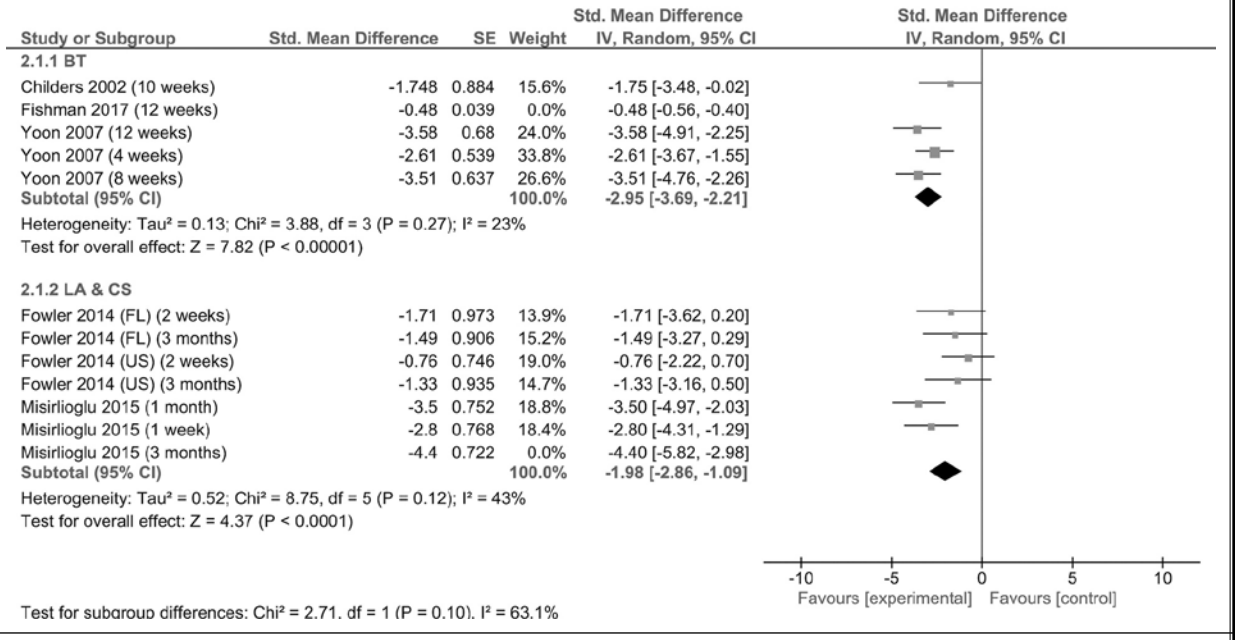

Fig. 5. *Results of botulinum toxin vs local anesthetic and corticosteroid injection after sensitivity analysis (RCTs only).*

Fanucci et al (28) included 30 PS patients who received CT-guided BT-A injections. Pain relief occurred in 26 cases out of 30, 5-7 days after the injection. In the remaining 4 patients, insufficient pain relief was attributed to BT dose insufficient, and the pain was relieved within a week following a second BT injection 2 months after the first injection (28).

Mullin et al (2) included 12 PS patients who received CS and LA injections (single injection in 7 patients, 2 injections in 3 patients, and 3 injections in

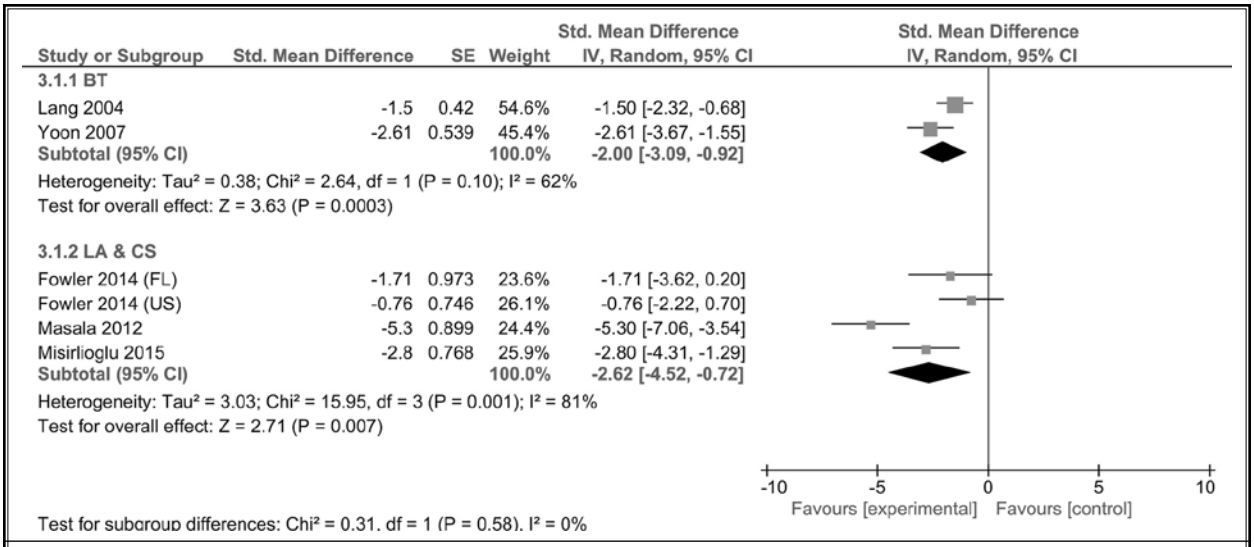

Fig. 6. *Results of botulinum toxin vs local anesthetic and corticosteroid injection (RCTs at 0-4 weeks).*

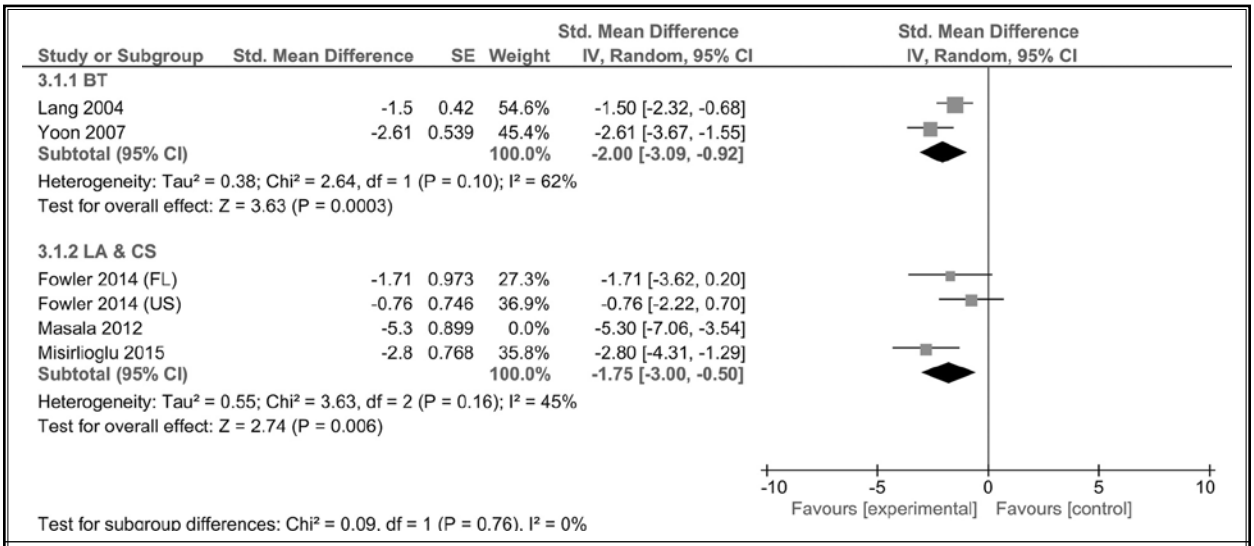

Fig. 7. *Results of botulinum toxin vs local anesthetic and corticosteroid injection after sensitivity analysis (RCTs at 0-4 weeks).*

2 patients). All patients reported pain relief during the 1-year follow-up duration. Pain relief lasted for 9-24 months (2). Pain relief was based on the subjective report (patients rating the pain as none, mild, moderate, or severe) and objective criteria (reducing or discontinuing analgesic use and improving functional capacity).

Discussion

In patients with PS, significant pain relief occurred after injection with either BT, LA. and CS, LA alone, or CS alone. Combined LA and CS injection had better results than BT, and BT injection was better than placebo. LA injection alone and CS injection alone showed a similar efficacy as the BT injection. The results of BT were similar to combined LA, and CS injection after pooling RCTs results only.

Previous studies (40,41) supported the advantage of BT injection over placebo in treating chronic low back pain (40). Also, it showed better efficacy than acupuncture therapy in patients with third lumbar transverse process syndrome (41).

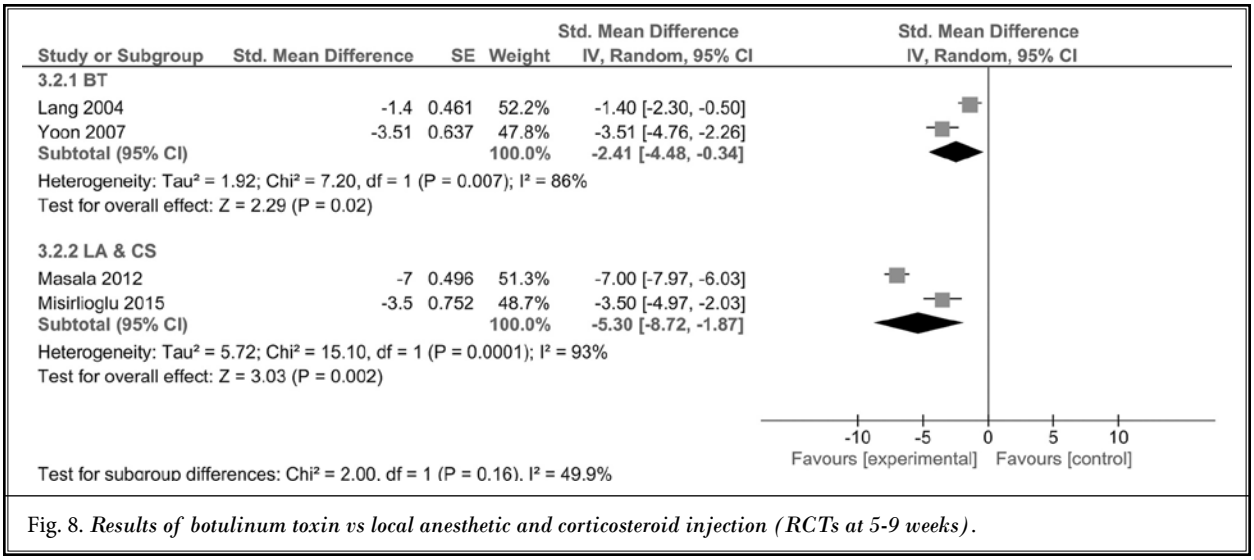

Fig. 8. *Results of botulinum toxin vs local anesthetic and corticosteroid injection (RCTs at 5-9 weeks).*

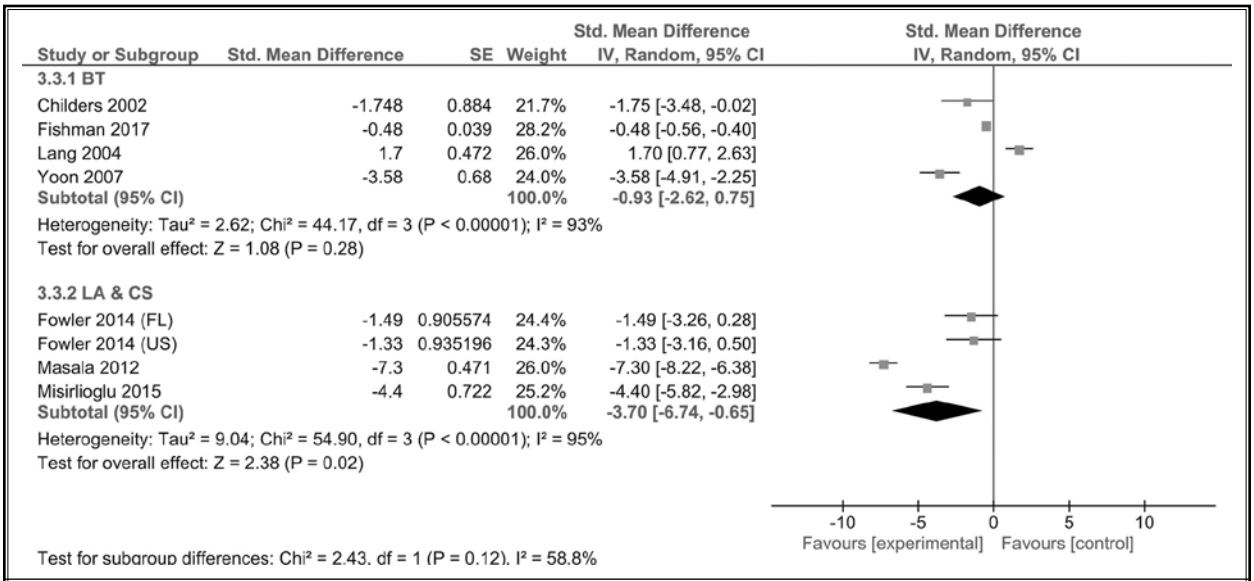

Fig. 9. *Results of botulinum toxin vs local anesthetic and corticosteroid injection (RCTs at 10-14 weeks).*

Muscle spasm contributes to the pain directly, but also causing local ischemia (11). BTs lessen pain by blocking impulse transmission from the nerve to the muscle at the neuromuscular junction, causing muscle relaxation or even paralysis (11). In addition, BT injection was associated with lowering the levels of inflammatory mediators in previous animal studies (42,43). Their effect starts after 2-4 days after injection and lasts for 3-6 months; then injection can be repeated if necessary (11). Due to their potent toxicity, BTs are prepared in minimal doses (11).

A previous systematic review (11) reported that BT injection has potential mild adverse events, including irritation and pain at the site of injection, rash, and muscle weakness. Some other rare but serious side effects included muscle paralysis, anaphylaxis, arrhythmia, and fainting (11). Also, there is a risk of BT spread from the site of injection, causing botulism-like symptoms (muscle weakness and difficulties in swallowing, speaking, and maybe in breathing) (11).

Adverse events of BT injection reported by the

articles included in this study (28,31,32,39) are mostly mild, transient, and not requiring medical intervention. Fishman et al (31) reported mild adverse events in 5 patients (out of 26 patients); these included injection-site pain (2 events), flu-like symptoms, neck stiffness, and wobbly neck. These adverse events happened 4 weeks following BT injection (31). Fowler et al (32) reported 2 events of injection-site pain lasting for < 2 weeks, 3 events of mild leg weakness lasting for less than a week, and one event of pain at the inner thigh that resolved after a week. Among the 20 patients treated, Yoon et al (39) reported mild, transient adverse events following BT-A injection. These included flu-like symptoms for 2 days, worsening muscle pain for 2-3 days, transient numbness for 3 days, lower limb ecchymosis for 2 days (1 case each), and piriformis muscle atrophy (2 cases) (39). Fanucci et al (28) reported a mild adverse event of limb paresthesia that occurred late after BT injection. No significant adverse events were reported by other authors (27, 28, 32, 38).

Lang (34) reported that, after BT-B injection in 20 patients, dry mouth was the most frequent adverse event (6 events), followed by flu-like symptoms (2 events), visual disturbances (2 events), dizziness, nausea, and gastroesophageal reflux (1 event each). Fishman et al (30) reported adverse events in patients receiving BT-B injection, including dry mouth and dysphagia that affected about 50% of patients at 2-4 weeks after injection in a dose-related manner. Interestingly, they also reported that repeated injections were associated with fewer and less severe adverse events. Other rare adverse events reported at a high dose (12,500 units) included blurred vision, severe heartburn, severe constipation, and difficult swallowing. None of these events required medical intervention (30,34).

Pain improvement, defined as pain relief by ≥ 50%, was reported in some of the included studies (29,30,33,38,39). It occurred in 25 patients (61%) patients treated with BT-A injection within 24 hours (38), and in 31 patients (65%) at 8-12 weeks (29). Yoon et al (39) reported pain improvement in 7 patients (35%) after 4 weeks, in 13 patients (65%) after 8 weeks, and in 12 patients (60%) after 12 weeks. In patients treated with BT-B (12,500 units) followed by regular physiotherapy, pain improvement was achieved in 24 patients (88.9%) within 2-4 weeks after injection (30). It was also reported in 15 patients (40.5%) treated with CS injection (33), and in 10 patients (32%) treated with LA and CS injection at 8-12 weeks (29).

Limitations

We included a wide variety of study designs to obtain the largest sample size available. Many of the included studies lack randomization, and some are retrospective in nature. These limitations may introduce bias into the analyzed data and affect the results. Many studies had a low sample size and are of moderate quality, limiting the generalizability of the results. Also, we could not conduct a direct meta-analysis due to the lack of sufficient double-arm studies comparing different types of injection therapies. Moreover, considering the results obtained with pharmacological therapies (44) and nonpharmacological managements (45), it would have been interesting a direct confrontation between invasive approaches and a simple oral administration of analgesics or noninvasive and nonpharmacological managements.

Conclusions

To our knowledge, this is the first meta-analysis assessing the efficacy of BT injection in patients with PS. It addressed the efficacy of BT, LA, and CS in reducing pain in PS patients. The present investigation included studies of patients diagnosed with PS only, avoiding confounding data like low back pain conditions. Thus, our results give a comprehensive overview of the value of different injection therapies in PS management. Each of BT, LA and CS, LA, or CS injection improve pain in patients with PS. Injection with LA and CS has better efficacy than BT injection.

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Authorship

All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions

The first 2 authors had the study idea, collected and analysed the data, and prepared the initial draft. All the authors have contributed to review and ameliorate the quality of the manuscript, and have reviewed and approved the final draft.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human patients or animal performed by the authors without a previous Ethics Committee approval.

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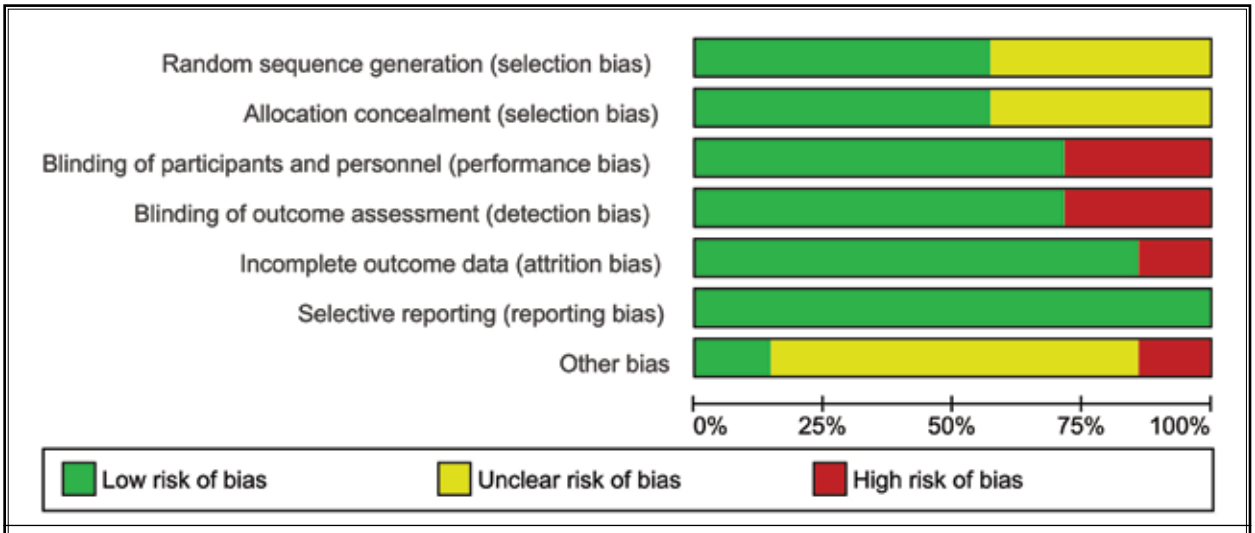
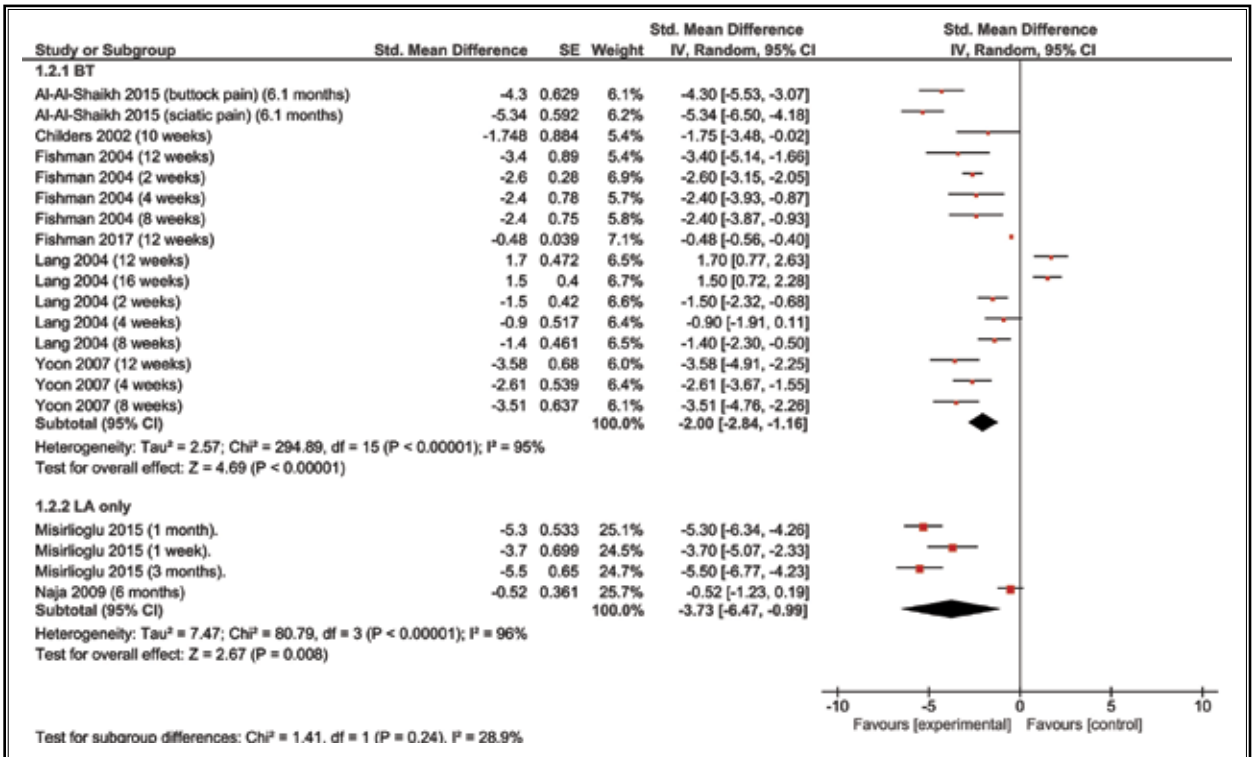
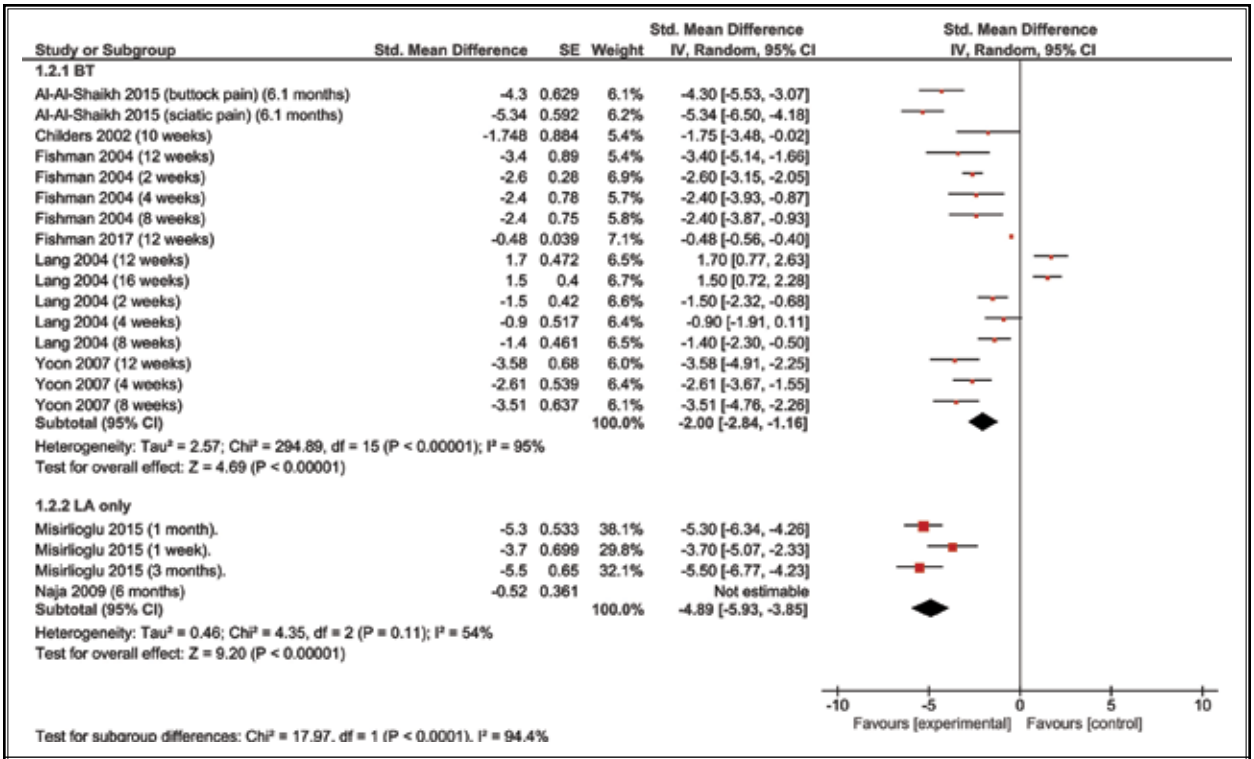


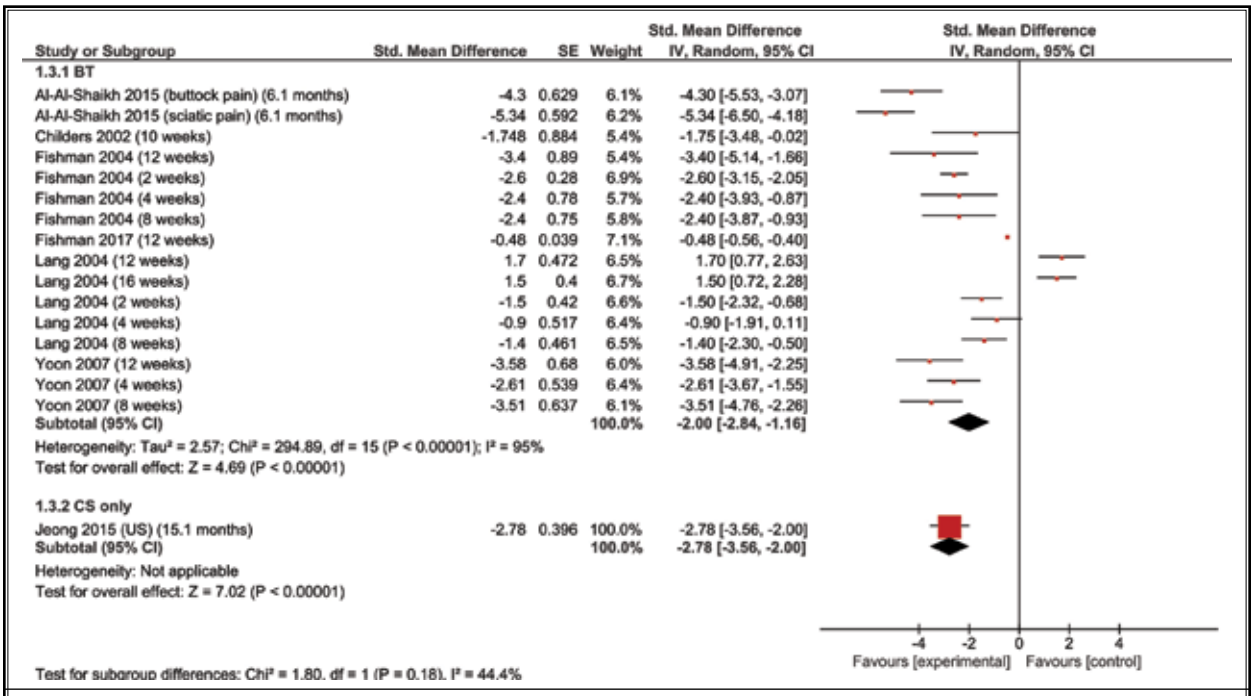
Supplemental Fig. 1. *Risk of bias (RoB) graph of included RCTs.*



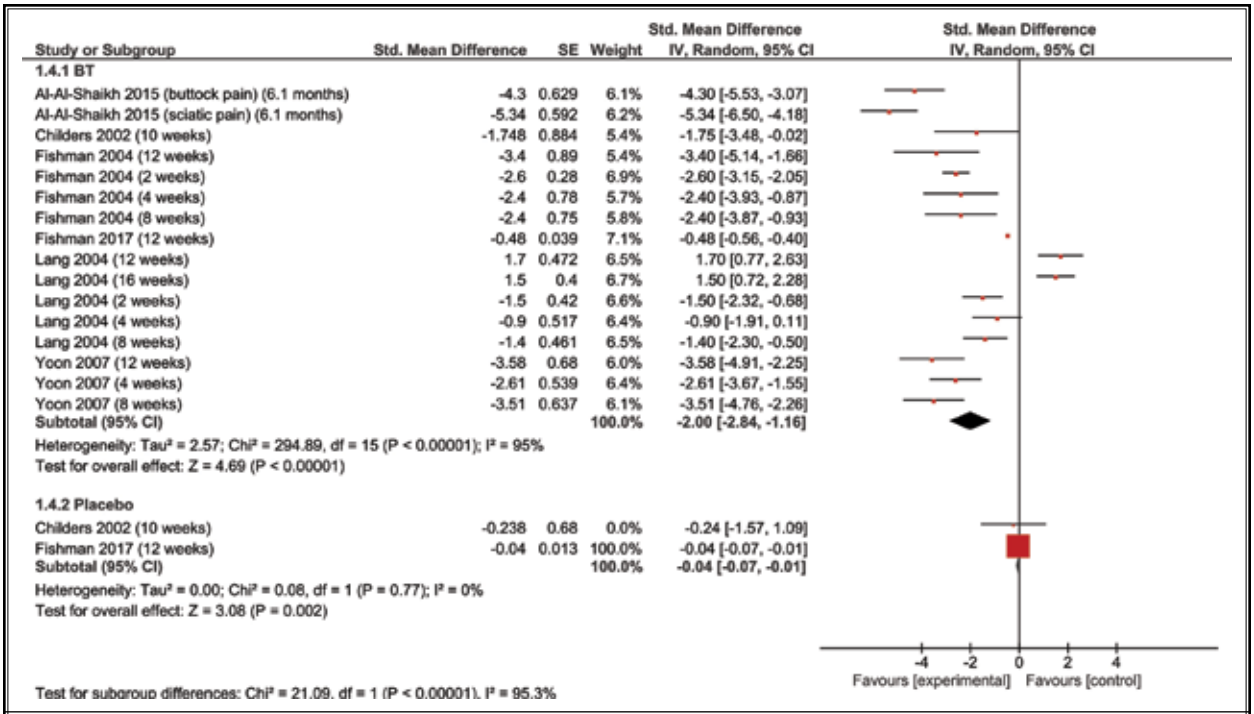
Supplemental Fig. 2. *Results of botulinum toxin vs local anesthetic injection (all included studies).*



Supplemental Fig. 3. *Results of botulinum toxin vs local anesthetic injection after sensitivity analysis (all included studies).*



Supplemental Fig. 4. *Results of botulinum toxin vs corticosteroid injection (all included studies).*



Supplemental Fig. 5. *Results of botulinum toxin vs placebo (all included studies).*