Systematic Review

Safety and Effectiveness of Different Approaches for Epidural Steroid Injections in Lumbar Spinal Stenosis: A Systematic Review and Meta-Analysis

Igor Wilderman, MD[1,2], Francesca Sarzetto, MD[1], Tina Didari, PhD[1], Rotem Frish Manor[1], and Seyed Kourosh Ghavami Riabi, BSc[1]

From: [1]Canadian Centre for Clinical Trials, ON, Canada; [2]Wilderman Medical Clinic, ON, Canada

Address Correspondence:
Igor Wilderman, MD
Wilderman Medical Clinic
8054 Yonge Street
Thornhill, ON, L4J 1W3 Canada
E-mail: iw@drwilderman.com

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Background: Lumbar canal stenosis is a common degenerative disorder that causes pain and functional alterations. Epidural steroid injections (ESIs) are often used to treat the symptoms of this condition; however, treatment protocols can vary significantly, and no standardized practice for the management of lumbar canal stenosis has been established.

Objectives: To identify the optimal method of administration for maximizing the effectiveness and duration of pain relief and functionality improvements provided by ESIs.

Study Design: Systematic review and meta-analysis.

Methods: We searched PubMed, Google Scholar, ScienceDirect, CINAHL, EMBASE, and OVID for clinical trials published from January 2000 to December 2025 that examined the effectiveness of different ESI protocols to ameliorate pain and functionality in spinal stenosis patients. The search terms included ("lumbar spinal stenosis" OR "lumbar canal stenosis" or "lumbar foraminal stenosis") AND "epidural steroid/corticosteroid injection(s)" AND ("interlaminar" OR "caudal" OR "transforaminal" OR "route"). Studies that met exclusion criteria were those that did not use human patients, that were not focused on lumbar stenosis, that had no consistent protocol, or did not express their outcomes as decreases in pain intensity. The risk of bias was assessed with the Cochrane RoB2 tool. We conducted a meta-analysis on the data from individual groups extracted from different studies, including sub-group and meta-regression analyses, to identify variables with significant effects.

Results: In total, 33 groups (comprising 1,350 patients) were extracted from 24 studies, with results from one week to 12 months after the injection. Most studies reported significant pain relief up to 3 months from the injections, and some reported that such pain relief persisted even after a year. Of all the factors that influenced the results, the type of steroid used had the greatest effect, with betamethasone providing the greatest and more prolonged relief. Triamcinolone and methylprednisolone offered similar initial levels of pain relief, though it decreased more rapidly, whereas dexamethasone showed the lowest level of benefits. Moreover, the pain relief effect was significantly weaker in patients with severe stenosis, and functionality improvements were also limited in patients with moderate/severe stenosis. In contrast, route of administration (transforaminal, interlaminar, or caudal), dose size, and other parameters showed no significant differences.

Limitations: Most groups included in the analysis were small, with 22 of the 33 (66.7%) having fewer than 50 patients, and only one group including more than 100. Furthermore, the results overall were significantly heterogeneous, and the follow-up times varied, meaning that some subgroups had only one result or none whatsoever at certain time points and limiting the subgroup analysis.

Conclusion: ESIs are an effective treatment for the pain caused by spinal stenosis; betamethasone, even at a low dose, appears to provide the greatest benefits, whereas dexamethasone seems the least effective. Patients with mild or moderate stenosis are more likely to experience positive results from ESIs, and the administration route can be chosen depending on the patient's status, offering

similar effects. The transforaminal route is likely more beneficial in single-level stenosis, while interlaminar (at the level of maximal stenosis or one caudad) and caudal injections are more appropriate for multilevel pathologies.

Key words: Spinal stenosis, injections, epidural, steroids, corticosteroids, interlaminar, transforaminal, caudal, severity, safety, effectiveness, systematic review

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Lumbar canal stenosis and neuroforaminal stenosis, collectively known as lumbar spinal stenosis (LSS), are degenerative disorders characterized by the narrowing of the spinal canal spaces (1), as shown by radiographic or anatomic evidence (2,3), and neurogenic claudication or radicular pain. Neurogenic claudication manifests as pain or discomfort during walking or prolonged standing; the pain commonly radiates into one or both lower limbs, possibly including the buttocks, thighs, lower legs, or feet, and can be relieved by rest or lumbar flexion and worsened by lumbar extension (2,3). Radicular pain is defined as activity-independent pain that can radiate uni- or bilaterally to one or more dermatomes (3). Furthermore, radiographic LSS refers to imaging evidence of stenosis of the central canal, lateral recesses, and/or neural foramina, whereas anatomic LSS indicates the corresponding findings that are noted intraoperatively (3).

LLS occurs at an annual incidence of 103 million persons (1.41%) worldwide (4). The condition affects approximately 11% of the asymptomatic population, based on diagnostic imaging studies (5), and its presence is commonly due to degenerative changes such as disk protrusion, bone hypertrophy, or spondylolisthesis (6).

Most mild to moderate cases are managed without surgery, and available treatments for the condition include epidural steroid injections (ESIs), exercise, and physical, thermal, or traction therapy (5). The possible surgical procedures, which are more limited than nonsurgical options, are performed when the latter prove to be ineffective, i.e., if after 2 or 3 months of treatments the patient begins exhibiting severe reductions in their quality of life (5).

ESIs have been used extensively by physicians and scientists; however, the procedure is not standardized, and the protocols for its administration vary considerably, with different routes of injection, types and doses of steroids, local anesthetics, frequency, and post-intervention follow-ups. The primary ESI routes are interlaminar (IL), transforaminal (TF), and caudal (C). In the IL approach, the injectant is released into the space between the laminae of 2 adjacent vertebrae, in near proximity to the potential pathological location (7). In CESIs, the needle is inserted through the sacral hiatus, giving physicians access to the sacral epidural space, where the injectant is released (8). This approach is the safest and simplest to use, though it requires large volumes of injectant and cannot target the specific pathological location (9). In contrast, TFESIs can be administered to specific nerve roots (9,10) and typically require a lower injectant volume than either ILESIs or CESIs (9).

The corticosteroids used in ESIs to treat LSS are triamcinolone acetonide, dexamethasone, betamethasone, and methylprednisolone (11-14), though the doses and injection protocols vary. Consequently, previous studies report inconsistent results, showing a general benefit in the short term (3 to 6 weeks), though long-term studies are lacking (5,6), or that the effectiveness of combinations of steroids and local anesthetics is similar to that of local anesthetics alone (15-17). Furthermore, although ESIs pose less risk than do other, more invasive procedures, rare adverse events in association with ESIs have been reported, mainly due to injections that are inadvertently delivered intrathecally or into a spinal artery (10,18). The latter event may cause spinal infarctions that lead to paraplegia, an issue more likely to occur with particulate corticosteroids (in descending order of particle size: methylprednisolone, triamcinolone, and betamethasone, the last of which is also available in water-soluble or mixed formulations) (18). The nonparticulate, water-soluble dexamethasone is generally considered safer (19).

The purpose of this review was to determine the safest, most effective approach for ESIs in LSS treatment, comparing the short- and long-term results of different ESI protocols, based on injection route, steroid type, dose size, and patients' characteristics, in terms of pain relief and functionality improvements.

Methods

Study Design and Search Strategy

A comprehensive search for clinical trials was

conducted on PubMed, Google Scholar, ScienceDirect, CINAHL, and EMBASE to identify relevant studies that were published between January 2000 and December 2025. The search terms used were ("lumbar spinal stenosis" OR "lumbar canal stenosis" OR "lumbar foraminal stenosis") AND "epidural steroid/corticosteroid injection(s)" AND ("interlaminar" OR "caudal" OR "transforaminal" OR "route") and similar combinations. The review was registered in PROSPERO (CRD420251237435) and followed the PRISMA guidelines (20).

Inclusion Criteria

We considered trials involving patients with symptomatic LSS (foraminal and/or central) that was confirmed by clinical imaging and who underwent ESIs. We included studies with group comparisons, such as between patients at different stages of LSS (mild, moderate, severe), or treatment and placebo/control groups, different treatment protocols, or single cohorts with before-and-after treatment data.

We included prospective and retrospective studies, such as randomized controlled trials (RCTs) and other randomized or clinical trials, that were published in English, compared the ESIs' effect on pain (and functionality, if available) to baseline values, and showed the results as overall group differences from baseline. Moreover, we included only studies that used imaging guidance techniques during the procedures to ensure safe and accurate needle placement and delivery of the steroid injections, such as fluoroscopy, ultrasonography (US), or computed tomography (CT).

The primary outcome measures considered concerned effectiveness (pain relief and functional improvement) and safety (adverse events and complications associated with the injection techniques). We included studies that recorded their outcome at one or more follow-up points between one week and one year after the injection(s).

Exclusion Criteria

We excluded studies based on in vitro or animal experiments, or studies in which LSS and related pain relief were not the main topics of interest. Moreover, we excluded studies that examined only nonsteroidal pharmaceuticals, that did not specify the exact steroid, dose size, or route of injection used, or that employed mixed protocols. We also eliminated studies without a clear explanation of methodology, results, or outcomes, or in which the outcome was expressed only as the percentage of patients whose interventions succeeded. Review articles, experimental designs, case reports, editorials, letters to the editor, conference abstracts, and commentaries were not included.

Data Extraction

The studies identified with the search were screened by title and then by abstract. The screening was done by 2 independent investigators (RFM and SKGR) to minimize bias and ensure consistency, with any discrepancies resolved through discussion or consultation with a third reviewer (FS). The final selection was based on the full text; study selection and data extraction were performed using the CADIMA tool (www.cadima.info) (21).

From each study included in the analysis, the same researchers independently extracted data on the study design (randomized, controlled, observational, prospective, or retrospective) and, separately, on the sample size and protocol used for each group treated with ESIs as well as their respective clinical data and outcomes. We considered the groups individually, excluding control groups and those treated with different methods or other medications, such as physical therapy, local anesthetics alone, or combinations of steroids and other substances. In particular, we collected the patients' demographic and clinical parameters (mean age, male-to-female [M/F] ratio, stenosis severity, baseline pain and functionality values, and duration of symptoms); route of injection (TF, IL, or C); steroid (betamethasone, dexamethasone, triamcinolone, or methylprednisolone); and injection protocol (steroid dose, single-injection volume, number of injections, and total dose and injection volume). The doses of each steroid were converted into hydrocortisone anti-inflammatory equivalent potency doses (HCAIDs) for uniform comparisons, based on the equipotency of each steroid with 20 mg of hydrocortisone: 4 mg for both triamcinolone and methylprednisolone, 0.75 mg for dexamethasone, and 0.6 mg for betamethasone (Table 1).

Moreover, we collected the baseline and follow-up measures for pain relief (assessed using the visual analog scale [VAS] or numeric rating scale [NRS]) and functional improvement (based on the Oswestry Disability Index [ODI], Roland-Morris Disability Questionnaire [RMDQ], or other scales), timing of follow-up assessments, and side effects or complications. Finally, the quality of each study was evaluated independently by 2 investigators (FS and NA), based on the criteria

described by Manchikanti et al for randomized and nonrandomized studies of interventional techniques (22,23), and the risk of bias was evaluated using the Cochrane RoB2 tool for the randomized studies (24) and ROBINS-I for the nonrandomized ones (25). Disagreements were solved by discussion and consultation with the senior author (IW).

Statistical Analysis

To ensure that the data were consistent for the analyses, the raw differences from baseline on the various scales were converted to percentages of pain relief and functionality improvement. Each difference was divided by the corresponding baseline value (e.g., for a group with a mean baseline pain of 8 in the NRS and 2 at follow-up, the difference was indicated as 75% pain relief). Effect sizes and standard errors of the continuous outcomes for each group included in the meta-analysis were calculated as unstandardized mean differences with unequal group variances in a random-effects model, at the various time points available. The Hartung-Knapp adjustment was used for confidence intervals. Sensitivity analyses for robustness were performed with subgroup analyses based on the injection route, type of steroid used, and stenosis severity. Meta-regressions were also used to assess the influence of continuous variables, such as age, M/F ratio, single dosage, number of injections, total steroid dosage, single and total injection volume. Publication bias was assessed with Egger's regression-based tests. The analysis was conducted with JASP version 0.95.3 (JASP Team), and *P*-values < 0.05 were considered statistically significant.

Results

The initial literature search retrieved 235 unique results. Among these studies, 47 were selected for abstract review based on their titles, and 40 underwent full-text revision; finally, 24 were included in the analysis (11 randomized controlled trials and 13 other studies), for a total of 33 individual groups (1350 patients, mean: 40.9 per group; Fig. 1). The 9 studies that involved more than one group suitable for the meta-analysis consisted of the following: 3 that compared patients with moderate stenosis to those with severe stenosis (26-28), 3 that compared the IL approach to the TF approach (29-31), one that compared C injections to TF injections (14), and 2 that examined different vertebral levels for ILESIs (at the maximal stenotic level and 2 levels cephalad or caudad) (13,32).

Triamcinolone was used in 13 groups from 11 studies (12,26,30,33-40), methylprednisolone in 9 groups from 5 studies (13,29,31,32,41), dexamethasone in 6 groups from 4 studies (27,28,42,43), and betamethasone in 5 groups from 4 studies (14,44-46). The IL approach was used in 15 groups (mostly at the level of maximal stenosis, or one or 2 levels cephalad or caudad), the TF approach in 10 (mono- or bilaterally), and the C approach in 8 groups. As for the level of stenosis severity, the groups were divided into 4 categories: 1) mild or mild/moderate (n = 3); 2) moderate or moderate/severe (n = 5); 3) severe (n = 8); and 4) all or unspecified severities (n = 17). All the studies and subgroups analyzed are summarized in Table 2.

The results of the methodological quality and risk of bias assessments for each study showed that all studies were of high or intermediate quality, though some of them presented a moderate or high risk of bias, due mostly to missing data (patients lost to follow-up or undergoing surgery) and deviations from the protocol, particularly repeated injections administered to some patients in cases of insufficient relief (Table 3). The evidence in this review, which included results from several high-quality RCTs, is of Level I, according to the criteria of the United States Preventive Services Task Force (USPSTF), and low/fair certainty, due to the high heterogeneity of results (47).

The outcomes for pain relief were reported for each of the 33 groups, whereas functionality was assessed in 23 groups. The evidence concerning functionality is thus less robust. Follow-up times varied widely, with one to 4 results per study at variable times; therefore, we grouped them in categories labeled one to 4 weeks (22 results for pain and 15 for functionality), one to 2 months (23 and 13 for pain and functionality, respectively), 2 to 3 months (20 and 16), 4 to 6 months (11 and 9), and 12 months (4 and 3).

Table 1. *Hydrocortisone anti-inflammatory equivalent potency dosages of each corticosteroid.*

	Hydrocortisone	Triamcinolone	Methylprednisolone	Dexamethasone	Betamethasone
Equivalent dose	20 mg	4 mg	4 mg	0.75 mg	0.6 mg
Multiplication factor	1×	5×	5×	25×	30×

Effectiveness

The overall difference between post-ESI pain scores and their baseline counterparts was significant at each time point, with the mean effect sizes for pain relief consistently between 40% and 50% (all $P < 0.001$ up to 6 months, and $P = 0.001$ at 12 months). All studies reported significant differences in pain intensity from baseline at one or more time points for all 33 groups (Figs. 2, 3). The functionality improvements were slightly lower, between 33% and 38%, but consistent and significant for up to 6 months (all $P < 0.001$; at 12 months, $P = 0.06$, Figs. 4, 5). However, significant heterogeneity among studies was also noted ($P < 0.001$ and $I^2 > 84\%$ at each time point for pain relief; $P < 0.001$ and $I^2 > 87\%$ for functionality improvements). Publication bias was likely low, as shown by nonsignificant results of Egger's tests at each time point.

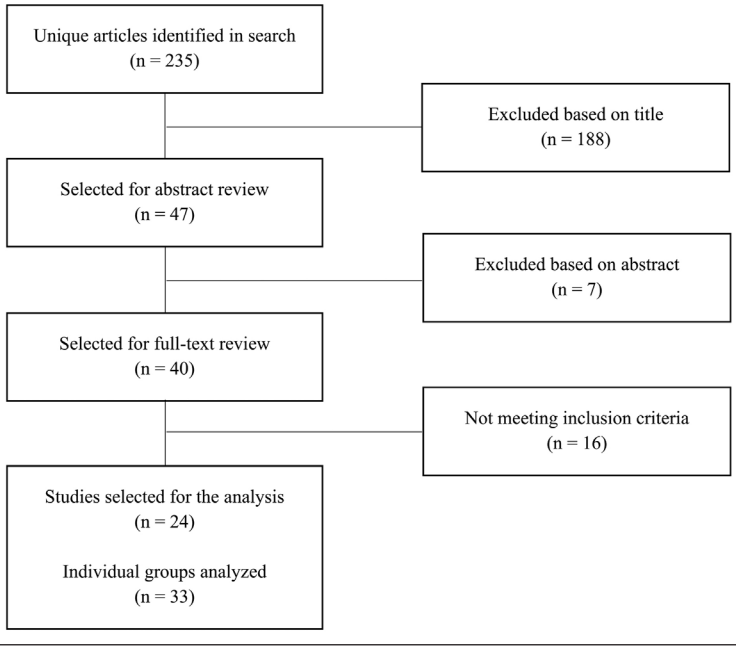


Fig. 1. *Flow diagram of the study selection and decision process.*

Corticosteroid Type

The subgroup analysis comparing different types of corticosteroids showed significant differences in pain relief at one to 4 weeks and 2 to 3 months ($P < 0.001$ and $P = 0.03$, respectively; Figs. 6, 7). At one to 2 months, the single result for betamethasone was not included in the analysis and made the differences nonsignificant ($P > 0.4$; Fig. 8); at 6 months, the differences approached significance again ($P = 0.08$), with a dexamethasone result appearing in one group and methylprednisolone results appearing in none (Fig. 9). At 12 months, the data were insufficient for subgroup analysis (3 results for betamethasone and one for triamcinolone, with the lowest effect size at 40%; Fig. 3C). Betamethasone appeared to be the most effective drug, consistently providing percentages of pain relief > 50% for up to 12 months, though with large 95% confidence intervals (CIs) at 2 to 3 and 4 to 6 months: 38.4-75.0% and 38.7-66.7%, respectively. Dexamethasone overall had the lowest effectiveness, with pain relief of approximately 30% for up to 3 months and 35% in the only result at 6 months (43). Methylprednisolone also had a strong initial effect, with 53.2% relief at one to 4 weeks (95% CI: 42.9-63.5%), though it decreased markedly at the 2 subsequent time points (42.2% and 35.2%) and had no data after 3 months; meanwhile, triamcinolone had a similar initial effect at 49.4% (95% CI: 36.9-62.1%), and then sustained pain relief ≥ 40% for up to 12 months.

The differences were also significant for the functionality improvements, even with fewer data ($P = 0.006$, $P = 0.016$, $P = 0.005$, $P = 0.002$ in the first 4 time points; Figs. 10-13). Betamethasone had effect sizes > 45% for up to 12 months (no data at one-2 months). Triamcinolone provided a consistent 27-29% improvement for up to 6 months and 16% at one year, whereas methylprednisolone showed initial improvements (31-42%) but no data after 3 months. Finally, dexamethasone showed only a mean 15% improvement in 2 groups at one to 4 weeks but 58%, 51%, and 33% improvements in the single group that included data at one, 3, and 6 months, respectively (43).

Notably, dexamethasone was administered at significantly lower doses than the other steroids were, even after converting to comparable potency (mean total HCAID ± standard deviation: dexamethasone 200 ± 69, betamethasone 592 ± 180, methylprednisolone 538 ± 274, and triamcinolone 425 ± 238; $P = 0.023$) and accounting for the different routes of injection. However, dexamethasone had similar effect sizes at doses of 5 (28), 7.5 (27), and 10 mg (42), all administered through the IL route. The first 2 studies compared patients with moderate stenosis to those with severe stenosis; the results were significantly worse in the latter group, and

Table 2. *Summary of the studies and individual groups included in the analysis.*

Study	Study Type	Group Size	Mean or Median Age (Years)	M/F Ratio	Stenosis Severity*	Injection Type	Steroid	Dosage (mg) (HCAID)	Number of Injections	Volume (mL)	Imaging Guidance	Pain scale	Functionality scale	Follow-ups
Koc et al, 2009 (12)	RCT	10	61.1 ± 9.8	2/8 (0.25)	4	IL	Triamcinolone	60.0 (300)	1	13.0	FL	VAS	RMDI	2 weeks, 1, 3, and 6 months
Kim HJ et al, 2014 (33)	Cohort trial	77	62.7 ± 13.5	32/45 (0.71)	4	TF	Triamcinolone	40.0 (200)	2.4 ± 1.9	2.5	FL	VAS	ODI	2 months
Milburn et al, 2014 (13)	Randomized trial	30	65.3 (range 32-88)	20/37 (0.54)	3	IL	Methyl-prednisolone	80.0 (400)	1	6.0	FL	NRS**	RMDQ	1, 4, 12 weeks
		27				IL 2 levels cephalad								
Ploumis et al, 2014 (14)	Prospective study	11	67.2 ± 3.0	7/4 (1.75)	1	C	Betamethasone	18.0 (600)	1.2 ± 0.4	20.0	FL	VAS	ODI	2 weeks, 3 and 6 months
		20	64.7 ± 1.8	12/8 (1.50)		TF		9.0 (300)	1	4.0				
Chang and Lee, 2018 (26)	Prospective study	31	66.0 ± 7.8	12/19 (0.63)	2§	TF	Triamcinolone	20.0 (100)	1	1.5	FL	NRS	-	1, 2, and 3 months
		26	69.0 ± 6.3	10/16 (0.62)	3§									
Bajpai and Yelavarthi, 2020 (32)	Randomized trial	30	50.0 ± 8.4	13/17 (0.76)	4	IL	Methyl-prednisolone	80.0 (400)	1	8.0	FL	NRS	ODI	2, 6, and 12 weeks
		30	52.0 ± 6.5	14/16 (0.87)		IL two levels cephalad or caudad								
Do et al, 2020 (27)	Prospective study	30	65.2 ± 10.2	18/12 (1.50)	2	IL	Dexamethasone	7.5 (200)	1	4.0	FL	NRS	-	1, 2, and 3 months
		28	67.6 ± 7.7	12/16 (0.75)	3									
Sencan et al, 2020 (29)	Randomized trial	34	63 (range 62-65)	8/26 (0.31)	2	IL one level caudad	Methyl-prednisolone	80.0 (400)	1	7.0	FL	NRS	ODI	3 weeks, 3 months
		33	62 (range 54-65)	10/23 (0.43)		TF bilateral								
Shamov et al, 2020 (42)	Prospective study	63	58.0 (range 38-76)	45/18 (2.50)	4	IL one level cephalad	Dexamethasone	10.0 (250)	1	3.0	FL	VAS	-	2 and 4 weeks
Srivastava et al, 2021 (34)	RCT	32	60.7 ± 7.3	19/13 (1.46)	1	C	Triamcinolone	80.0 (400)	1	12.0	FL	NRS	ODI	3, 6, 12, and 24 weeks

Table 2. cont *Summary of the studies and individual groups included in the analysis.*

Study	Study Type	Group Size	Mean or Median Age (Years)	M/F Ratio	Stenosis Severity*	Injection Type	Steroid	Dosage (mg) (HCAID)	Number of Injections	Volume (mL)	Imaging Guidance	Pain scale	Functionality scale	Follow-ups
Parvin et al, 2024 (41)	Randomized trial	15	60.4 ± 8.2	7/8 (0.87)	4	C	Methyl-prednisolone	80.0 (400)	1	10.0	FL	VAS	ODI	2, 4, 8 weeks
Kim M et al, 2022 (28)	Retrospective	64	69.2 ± 9.3	36/28 (1.29)	2	IL	Dexamethasone	5.0 (125)	1	8.0	FL	NRS	Walking distance†	2 weeks
		64	69.6 ± 8.2	31/33 (0.94)	3									
Rayegani et al, 2023 (35)	Randomized trial	23	64.5 ± 7.1	14/9 (1.56)	4	C	Triamcinolone	80.0 (400)	1	10.0	US	VAS	ODI	1 and 6 months
Gagliardi et al, 2024 (36)	Retrospective	42	70.7 ± 10.9	30/12 (2.50)	4	C	Triamcinolone	40.0 (200)	4.0 ± 2.0	10.0	US with Doppler	NRS	ODI	3 months
Lee JH et al, 2009 (30)	Randomized trial	42	62.0 ± 11.6	11/31 (0.35)	4	IL at level matching symptoms	Triamcinolone	40.0 (200)	1.6 ± 0.6	10.0	FL	NRS	-	2 weeks, 2 and 4 months
		57	62.2 ± 10.1	20/37 (0.54)		TF bilateral			1.5 ± 0.7	11.0				
Manakul et al, 2023 (37)	Retrospective	99	64.3 ± 9.2	21/78 (0.27)	4	TF	Triamcinolone	40.0 (200)	1.8 ± 0.8	3.0	FL	VAS	ODI	2 weeks
Botwin et al, 2002 (44)	Cohort trial	34	77.4 (range 62-87)	17/17 (1.00)	4	TF	Betamethasone	12.0 (400)	1.9	2.5	FL	VAS	-	2 and 12 months
Botwin et al, 2007 (38)	Cohort trial	34	74.6 ± 5.7	15/19 (0.79)	4	C	Triamcinolone	80.0 (400)	2.2	14.0	FL	VAS	ODI	6 weeks, 6 and 12 months
Smith et al, 2010 (31)	Retrospective	19	67.1	-	4	IL or IL one level caudad	Methyl-prednisolone	80.0 (400)	3.5 ± 2.6	4.0	FL	VAS	-	4-6 weeks
		19	67.7			TF mono or bilateral in pts. with bilateral symptoms			3.6 ± 3.0	3.0				
Manchikanti et al, 2015 (46)	RCT	60	50.0 ± 15.3	33/27 (1.22)	4	IL at L5/S1 or one level caudad of stenosis	Betamethasone	6.0 (200)	3.6 ± 1.2	6.0	FL	NRS	ODI	3, 6, and 12 months

Table 2. cont *Summary of the studies and individual groups included in the analysis.*

Study	Study Type	Group Size	Mean or Median Age (Years)	M/F Ratio	Stenosis Severity*	Injection Type	Steroid	Dosage (mg) (HCAID)	Number of Injections	Volume (mL)	Imaging Guidance	Pain scale	Functionality scale	Follow-ups
Lee S et al, 2022 (39)	Randomized trial	50	69.2 ± 7.1	21/29 (0.72)	3	TF bilateral	Triamcinolone	60.0 (300)	2.3 ± 0.6	10.0	FL	NRS	MODI	4, 8, and 12 weeks
Manchikanti et al, 2012 (45)	RCT	50	55.7 ± 15.9	25/25 (1.00)	4	C	Betamethasone	6.0 (200)	2.9 ± 1.4	10.0	FL	NRS	ODI	3, 6, and 12 months
Sabbaghan et al, 2020 (40)	Cohort study	111	61.0 ± 13.4	32/79 (0.40)	3	IL (level not specified)	Triamcinolone	80.0 (400)	1	10.0	FL	VAS	ODI	4 weeks
Aktan and Aktan, 2025 (43)	Retrospective	55	63.2 ± 10.8	31/24 (1.29)	3	C	Dexamethasone	12.0 (300)	1	8.0	US	VAS	ODI	1, 3, and 6 months

*: Stenosis severity (1: mild-moderate; 2: moderate-severe; 3: severe; 4: all levels or unspecified). **: Pain with ambulation score.
§: Foraminal stenosis.
†: For walking distance, the improvement was indicated by an increase of the parameter, rather than a decrease as in all other cases, and the percentage of difference was calculated accordingly.
C: caudal; FL: fluoroscopy; HCAID: hydrocortisone anti-inflammatory equivalent potency dosage; IL: interlaminar (at maximal stenosis level, unless specified otherwise); M/F: male-to-female; MODI: modified Oswestry Disability Index; N/A: not available; NRS: numerical rating scale; ODI: Oswestry Disability Index; RCT: randomized controlled trial; RMDI: Roland Morris Disability Index; RMDQ: Roland-Morris Disability Questionnaire; TF: transforaminal; US: ultrasonography; VAS: visual analog scale.

the third had a cohort of patients who experienced various levels of severity. The dexamethasone-based study that reported the strongest effect used 12 mg of the steroid, all administered through CESIs to patients with severe stenosis (43). For betamethasone, the few studies available were inconsistent in dose size, injection route, stenosis severity, and follow-up times, making comparisons challenging; however, 12-month results showed pain relief > 50% with 6 mg administered through C and IL injections (45,46) and 12 mg (TFESI) (44) per dose, though the injections were repeated (mean: 2.9, 3.6, and 1.9 per patient, respectively). Methylprednisolone was administered at 80 mg in each study and triamcinolone between 20 mg for foraminal stenosis and TF injections (26) and 80 mg (34,35,38,40), with results unrelated to the dose. A meta-regression analysis, in all results and in subgroups categorized by steroid type, showed no correlation between the effect sizes and the total HCAIDs; a nonsignificant negative trend was present, due to repeated injections given to patients who showed lesser responses.

Stenosis Severity

The degree of stenosis was also a relevant factor, exerting significant influence on the pain relief at one to 4 weeks (P = 0.001, Fig. 14) and 2 to 3 months (P = 0.038, Fig. 15). As with the steroid type, at one to 2 and at 6 months, the group distribution was unbalanced and the data inadequate for subgroup analysis, and the intergroup differences were not significant (data not shown). Overall, Group 3 (severe stenosis) experienced markedly lower pain relief than did the other groups at all available time points (30-35%). At the first time point, Group 2 (moderate/severe stenosis) had effect sizes similar to those of Group 1 (mild/moderate stenosis): 53.8% vs. 56.9%. The effect size was lower at 3 months (49.3 vs. 58.9%). Group 4 (various severities) showed size effects between 40 and 50%, in line with the overall mean, for up to 6 months. This group also had the only data available at the twelfth-month mark, which showed that the patients were experiencing almost 50% pain relief.

As for the functionality improvements, the differences were significant only at one to 4 weeks (P = 0.025, Fig. 16). However, Group 4 had size effects similar to those of Group 1—consistently between 37% and 42% for up to 12 months—though Group 1

Table 3. Assessment of methodological quality and risk of bias of the 24 studies included in this review.

Study	Q Quality Grading (RTCs: IPM-QRB criteria; other studies: IPM-QRBNR criteria)	Overall Quality Grading	Risk of Bias (RCTs: Cochrane RoB2 tool; other studies: Cochrane ROBIN-I)								
			Randomization	Confounding Factors	Selection of Patients	Classification of Interventions	Deviations	Missing Data	Measurement	Selection of results	Overall
RCTs											
Koc et al., 2009 (12)	30/48	Intermediate	?				+	+	+	?	?
Bajpai and Yelavarthi, 2020 (31)	33/48	High	+				+	?	+	+	+
Milburn et al., 2014 (13)	31/48	Intermediate	?				+	-	+	-	-
Sencan et al., 2020 (28)	36/48	High	+				+	+	+	+	+
Srivastava et al., 2021 (33)	32/48	High	+				+	+	+	+	+
Parvin et al., 2024 (40)	33/48	High	+				+	-	+	+	-
Rayegani et al., 2023 (34)	32/48	High	+				+	+	+	+	+
Lee JH et al., 2009 (29)	27/48	Intermediate	?				?	+	+	+	?
Manchikanti et al., 2015 (45)	44/48	High	+				?	+	+	+	+
Lee S et al., 2022 (38)	34/48	High	+				?	+	+	+	+
Manchikanti et al., 2012 (44)	46/48	High	+				?	+	+	+	?
Other studies											
Kim HJ et al., 2014 (32)	29/48	Intermediate		?	+	+	?	?	+	+	-
Ploumis et al., 2014 (14)	33/48	High		+	?	+	?	+	+	+	?

Table 3 cont. Assessment of methodological quality and risk of bias of the 24 studies included in this review.

Study	Q Quality Grading (RTCs: IPM-QRB criteria; other studies: IPM-QRBNR criteria)	Overall Quality Grading	Risk of Bias (RCTs: Cochrane RoB2 tool; other studies: Cochrane ROBIN-I)							
			Randomization	Confounding Factors	Selection of Patients	Classification of Interventions	Deviations	Missing Data	Measurement	Selection of results	Overall
Chang and Lee, 2018 (25)	38/48	High		+	+	+	+	+	+	+	+
Do et al., 2020 (26)	35/48	High		+	+	+	+	+	+	+	+
Shamov et al., 2020 (41)	29/48	Intermediate		+	+	+	+	+	+	+	+
Kim M et al., 2022 (27)	30/48	Intermediate		+	?	+	+	+	+	?	?
Gagliardi et al., 2024 (35)	24/48	Intermediate		?	+	+	?	+	+	+	?
Manakul et al., 2023 (36)	25/48	Intermediate		?	+	+	?	+	+	+	?
Botwin et al., 2002 (43)	32/48	High		+	+	+	?	?	+	+	?
Botwin et al., 2007 (37)	34/48	High		?	+	+	?	+	+	+	?
Smith et al., 2010 (30)	29/48	Intermediate		?	?	+	?	+	+	+	+
Sabbaghan et al., 2020 (39)	28/48	Intermediate		+	+	+	+	+	+	+	+
Aktan and Aktan, 2025 (42)	27/48	Intermediate		+	?	+	+	+	+	+	?

RCTs: randomized controlled trials; IPM-QRB: Interventional Pain Management Techniques - Quality Appraisal of Reliability and Risk of Bias Assessment; IPM-QRBNR: Interventional Pain Management Techniques - Quality Appraisal of Reliability and Risk of Bias Assessment for Non-Randomized Studies; RoB2: Risk of Bias 2 tool; ROBINS-I: Risk Of Bias In Non-randomized Studies - of Interventions.

had only 3 data and large 95% CIs (35-42% effect sizes for up to 6 months). The effect sizes in Groups 2 and 3 were lower, between 20% and 30% (up to 3 months, no data afterward).

Injection Route

In the subgroup analysis for the injection route, significant differences for pain relief emerged only in the follow-ups at 1-2 months ($P = 0.02$, Fig. 17), when the other predictors mentioned above had data underpowered to show significance. At that time point, the CESIs provided the strongest relief (47.5%, 95% CI: 36.0-59.5%), followed by TFESIs (43.5%, 95% CI: 27.7-59.4%), and, finally, ILESIs (33.0%, 95% CI: 25.3-40.6%). However, at all other time points, CESIs and TFESIs showed similar effect sizes, whereas ILESIs generally had slightly weaker effects. Overall, the mean effect size of the ILESIs was influenced negatively by

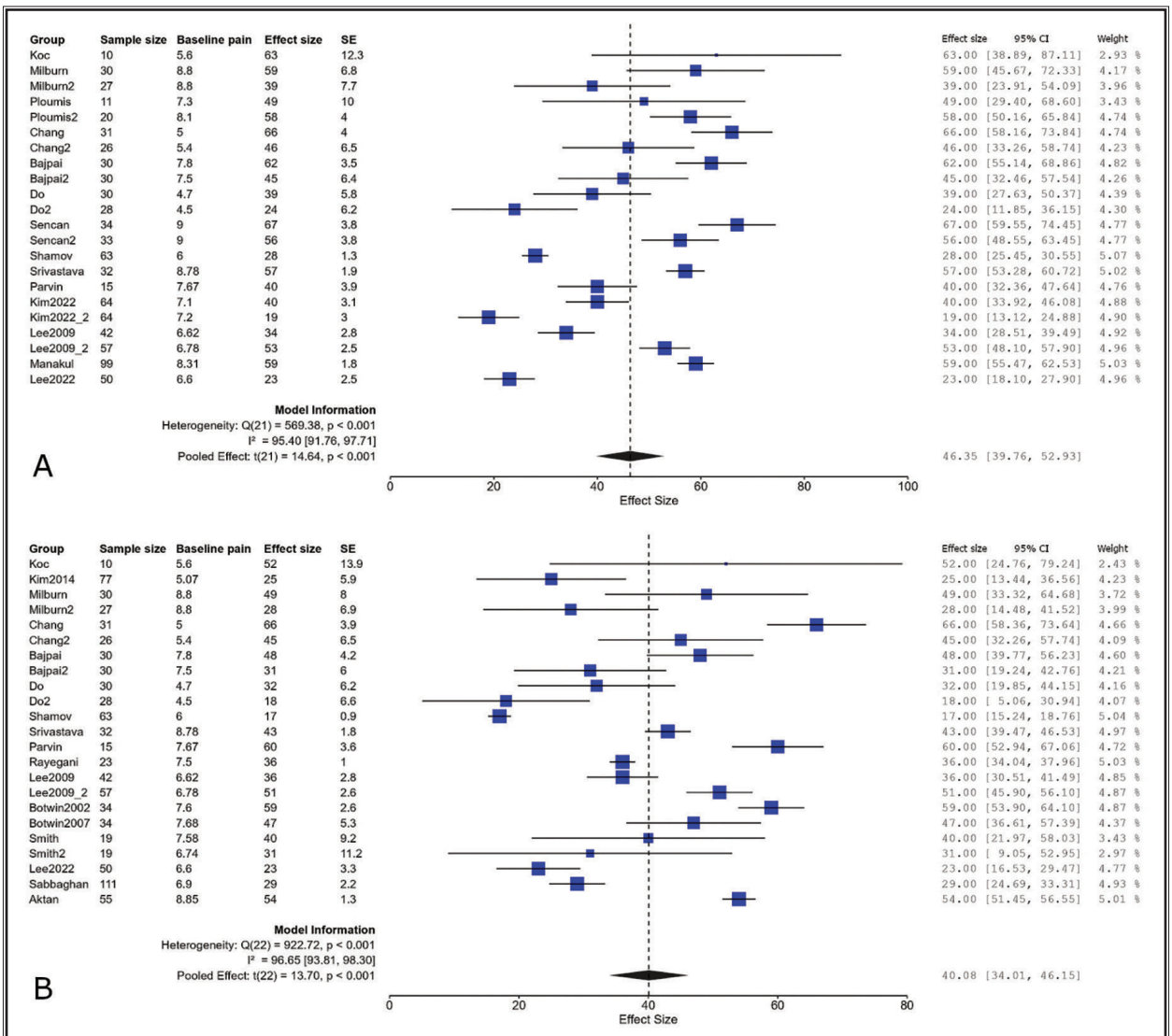


Fig. 2. *Forest plot of the pain relief effect sizes, as percentages, in the various groups, one or 2 per study. A: Effect at follow-ups between one and 4 weeks. B: Effect at follow-ups between one and 2 months. The heterogeneity of results was significant at each time point.*
SE: standard error; CI: confidence interval.

the 4 groups that underwent the treatment at spinal levels different than those affected by maximal stenosis (13,31,32,42), though the groups that received injections at one level caudad of the most stenotic one (29,46) experienced higher effectiveness. Meanwhile, the studies that performed TFESIs with a bilateral approach (29,30,39) had no advantage over those that used monolateral injections.

The differences in functionality improvements between injection routes were all nonsignificant.

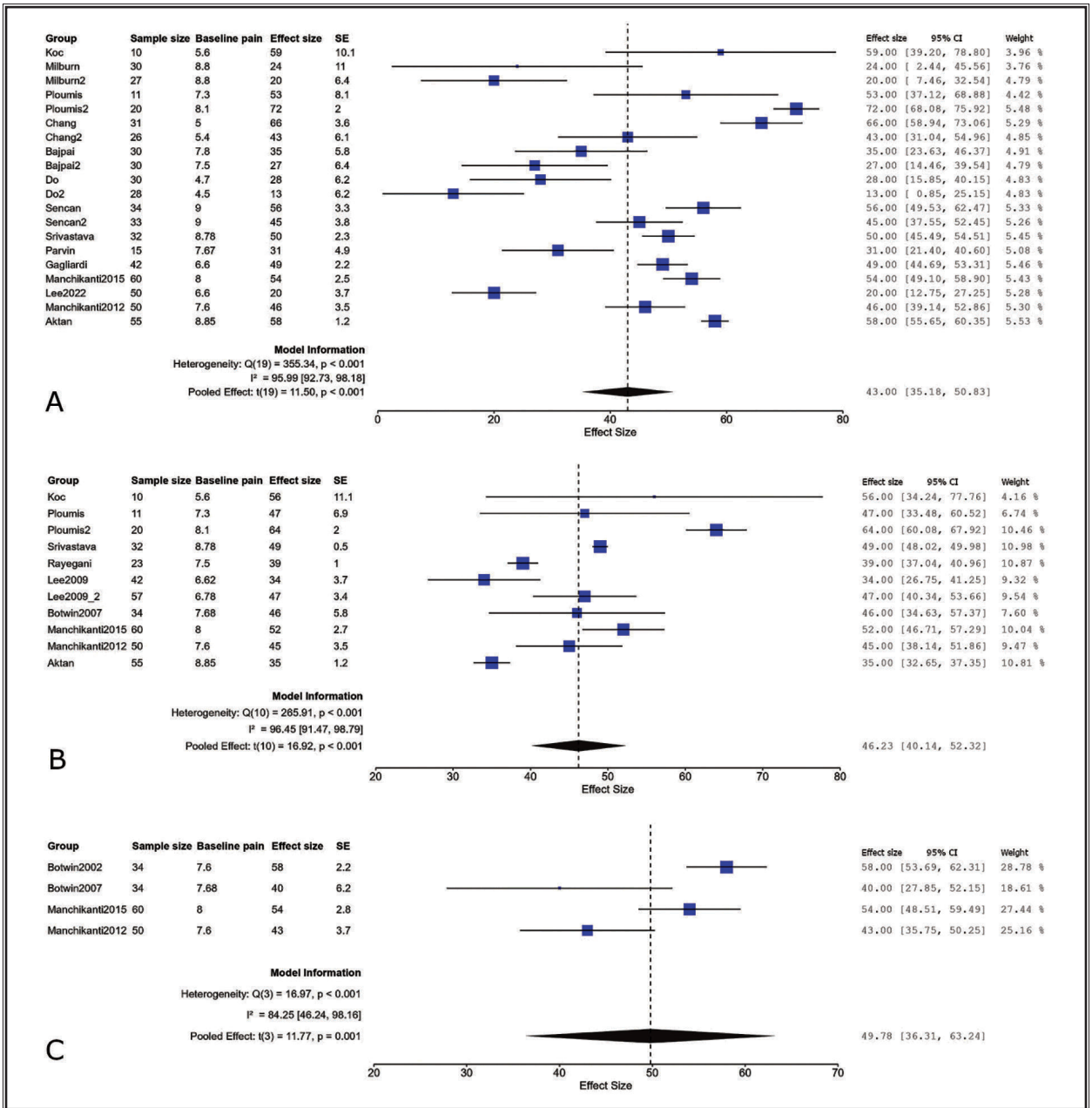


Fig. 3. *Forest plot of the pain relief effect sizes, as percentages, in the various groups, one or 2 per study. A: Effect at follow-ups between 2 and 3 months. B: Effect at follow-ups at 6 months. C: Effect after 12 months.*
SE: standard error; CI: confidence interval.

Overall Model

A pain-relief–predicting model, including both steroid type and stenosis severity, produced significant results only at the first time point, explaining more than half of the heterogeneity (moderation: $P = 0.005$, $R^2 = 58.0\%$, $I^2 = 86.5\%$ [95% CI: 73.0-94.3%]). Both steroid type and stenosis severity were still significant predictors ($P = 0.010$ and $P = 0.027$, respectively). At 2 to 3 months, these factors had a counterproductive interaction, despite being individually significant (moderation: $P = 0.11$, $R^2 = 25.3\%$, $I^2 = 91.6\%$ [95% CI: 83.1-96.6%]); adding the injection route to the model worsened its performance. At the other time points and for the functionality assessment, the data were insufficient for this analysis. The addition of other categorical (local anesthetic) or continuous parameters (mean age, M/F ratio, baseline pain, pain duration, HCAID, injected volume, number of injections, total dose, and total injected volume) to these models had only minimal effects, and no significant correlation was identified.

Safety

Among the 24 studies examined in this review, 8 reported no side effects or adverse events following ESIs, for a total of 416 patients (12,13,26,27,36,39,40,45); in addition, 2 studies, comprising 68 patients, mentioned no major complications (38,44). Nine studies, involving 745 patients, made no explicit mention of whether side effects or adverse events were occurred or not (28,30-34,37,41,43).

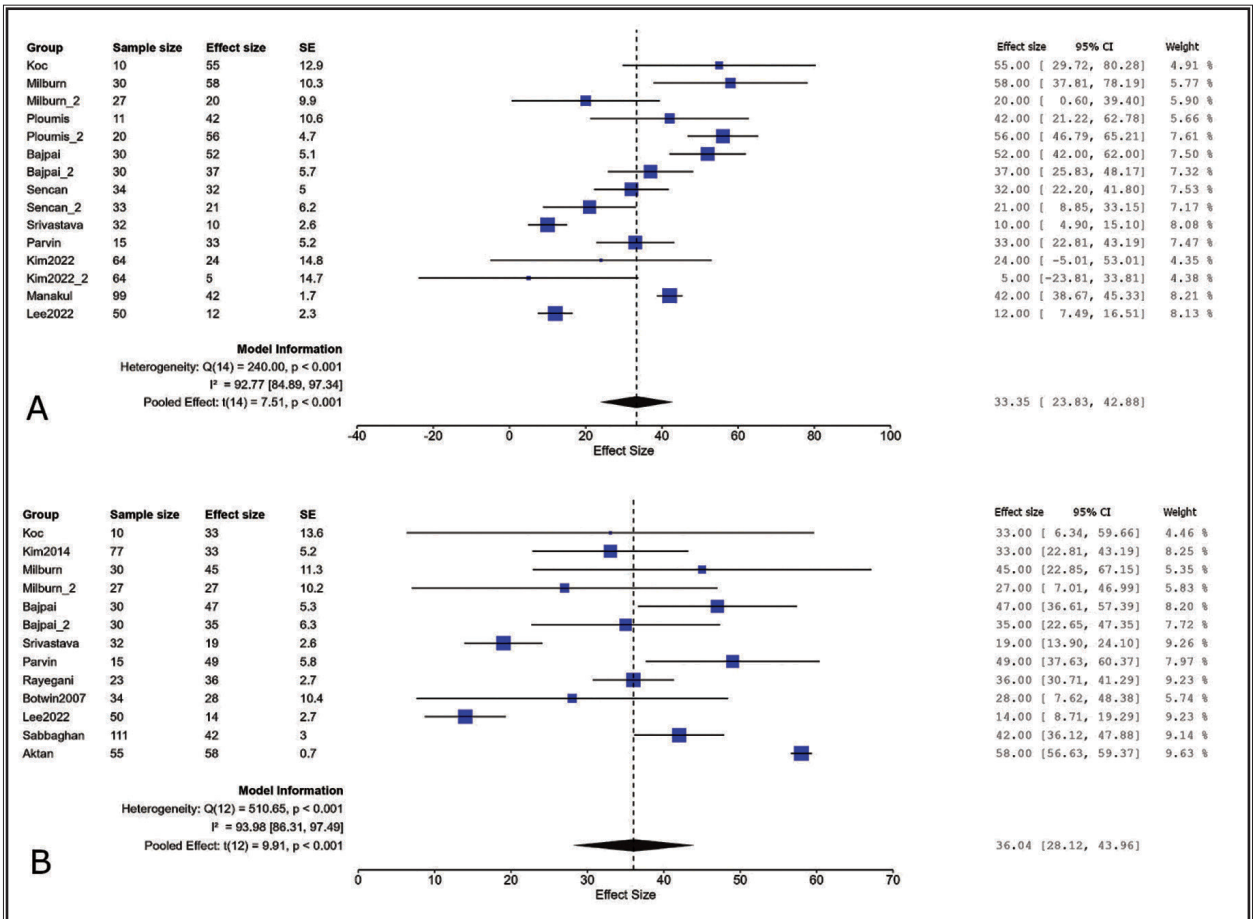


Fig. 4. *Forest plot of the functionality improvement effect sizes, as percentages, in the various groups, one or 2 per study. A: Effect at follow-ups between one and 4 weeks. B: Effect at follow-ups between one and 2 months. The heterogeneity of results was significant at each time point.*
SE: standard error; CI: confidence interval.

In the remaining 5 articles, one study (14) mentioned that 4 out of the 31 patients had vagal reactions before the start of the procedures, which therefore had to be rescheduled. Another study (29), using methylprednisolone, reported hypotension due to vasovagal reactions in 2 patients who were undergoing bilateral TFESIs, as well as one patient who complained of pain at the injection site after an ILESI, among 67 patients in total. Moreover, this study reported lower extremity motor blocks in 3 patients after bilateral TFESIs (selective nerve blockage); all symptoms resolved after an unspecified short-term follow-up, and the patients were discharged safely (29). In a study that included 63 patients with stenosis and 78 with discogenic sciatica (42),

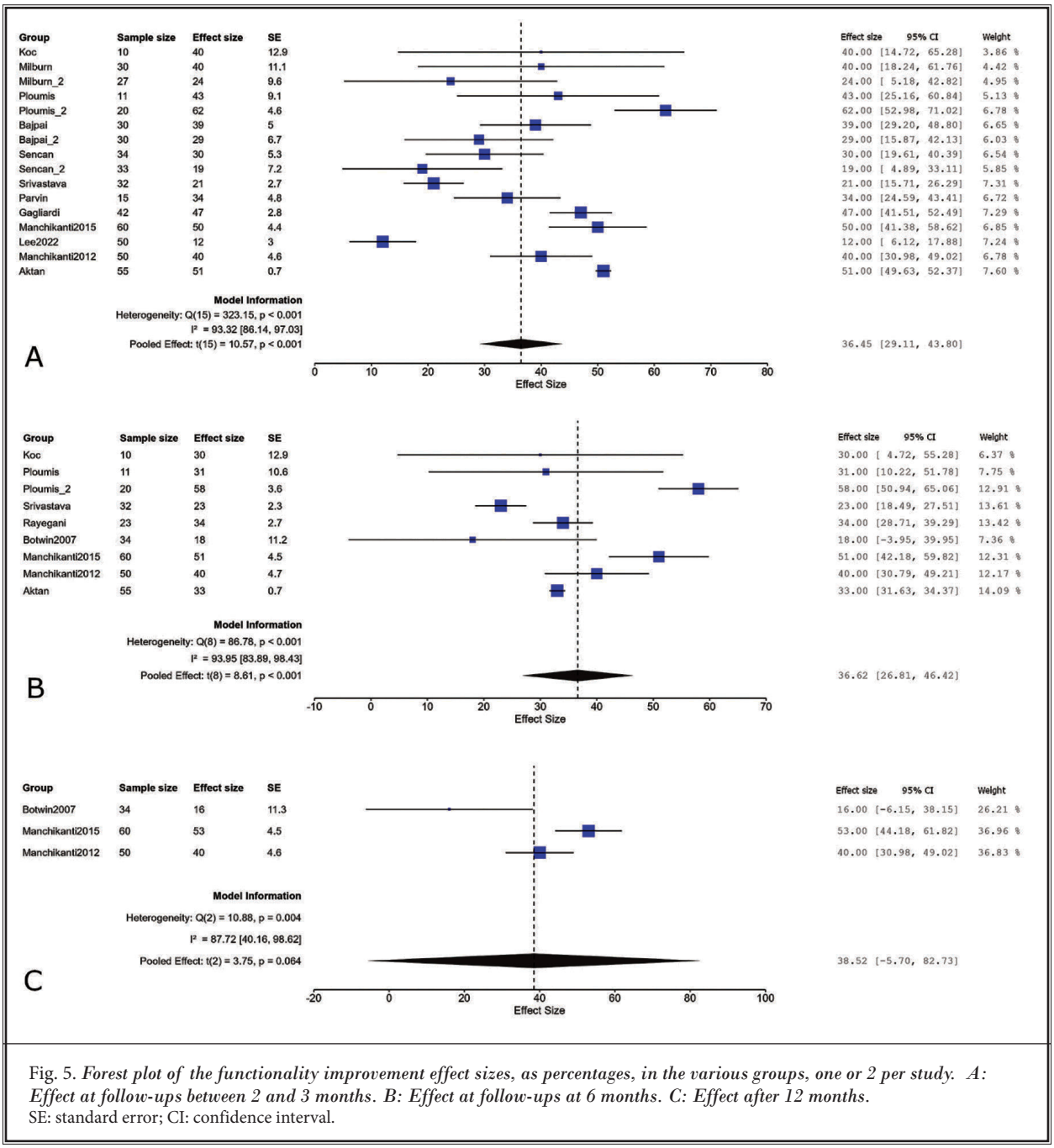


Fig. 5. *Forest plot of the functionality improvement effect sizes, as percentages, in the various groups, one or 2 per study. A: Effect at follow-ups between 2 and 3 months. B: Effect at follow-ups at 6 months. C: Effect after 12 months.*
SE: standard error; CI: confidence interval.

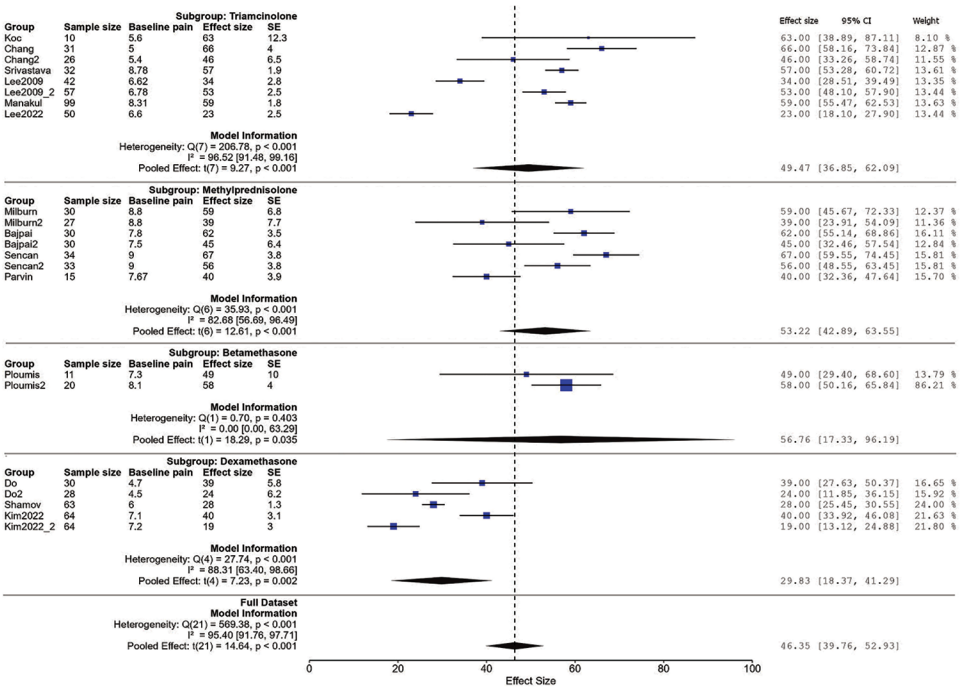


Fig. 6. *Forest plot of the pain relief effect sizes at follow-ups between one and 4 weeks, divided into subgroups based on the steroid injected. The difference between subgroups was significant (P < 0.001).*
SE: standard error; CI: confidence interval.

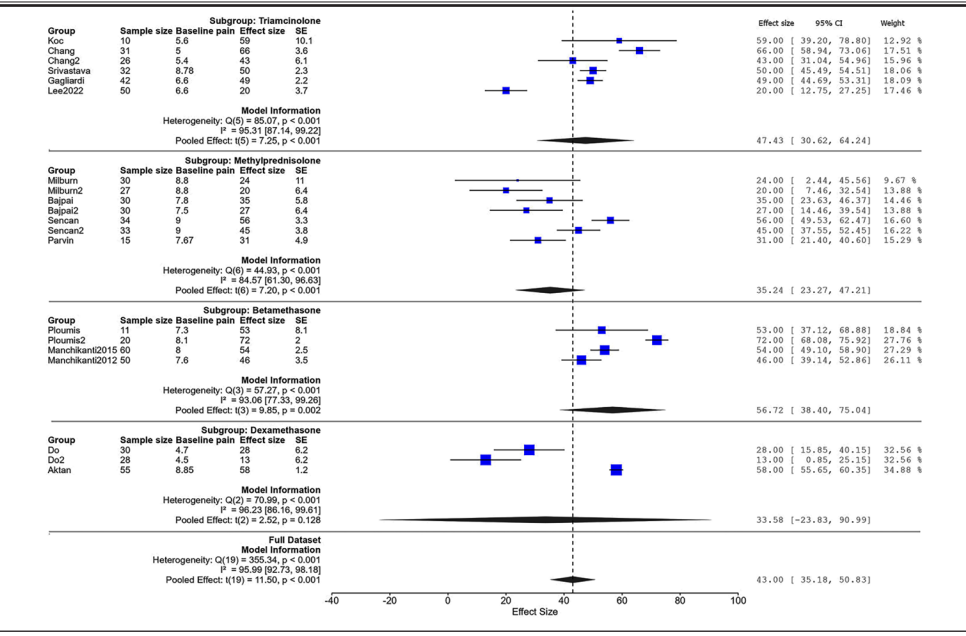


Fig. 7. *Forest plot of the pain relief effect sizes at follow-ups between 2 and 3 months, divided into subgroups based on the steroid injected. The difference between subgroups was significant (P = 0.03).*
SE: standard error; CI: confidence interval.

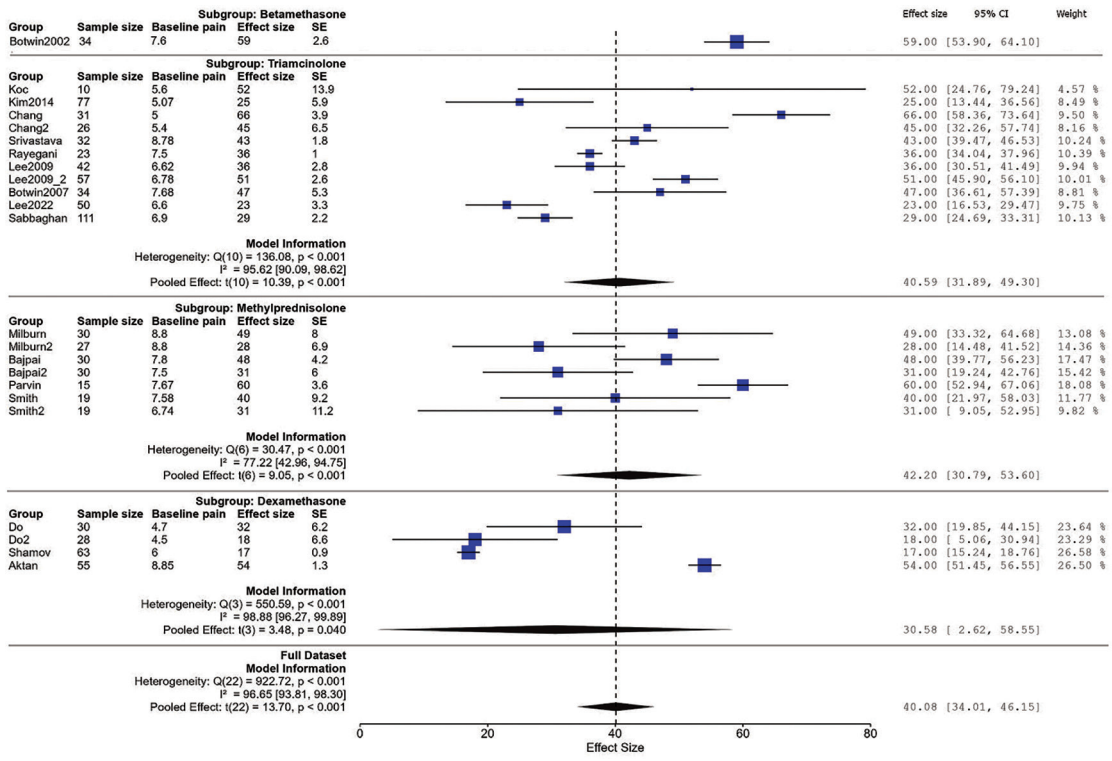


Fig. 8. *Forest plot of the pain relief effect sizes at follow-ups between one and 2 months, divided into subgroups based on the steroid injected. Betamethasone had only one result, which could not be included in the subgroup analysis. The result has been added to the figure for the purpose of illustration. The difference between subgroups was not significant (P > 0.4).*
SE: standard error; CI: confidence interval.

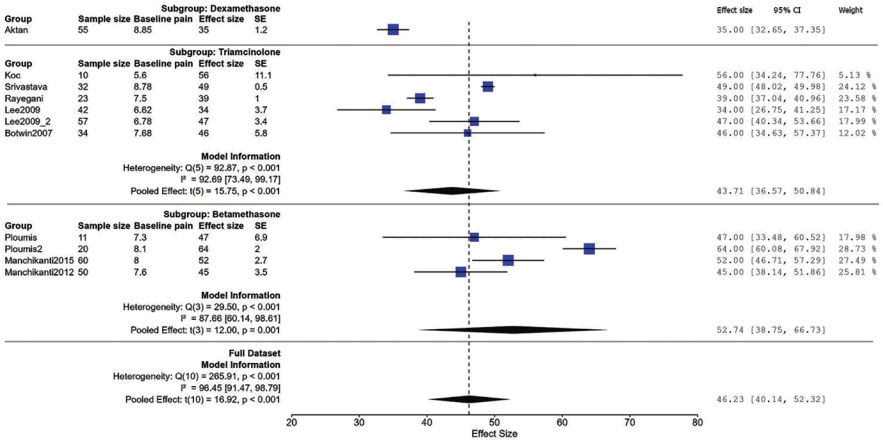


Fig. 9. *Forest plot of the pain relief effect sizes at follow-ups between 4 and 6 months, divided into subgroups based on the steroid injected. Dexamethasone had only one result (added to the figure for the purpose of illustration) and methylprednisolone had none, and they were not included in the subgroup analysis; however, the difference between subgroups approached significance (P = 0.08).*
SE: standard error; CI: confidence interval.

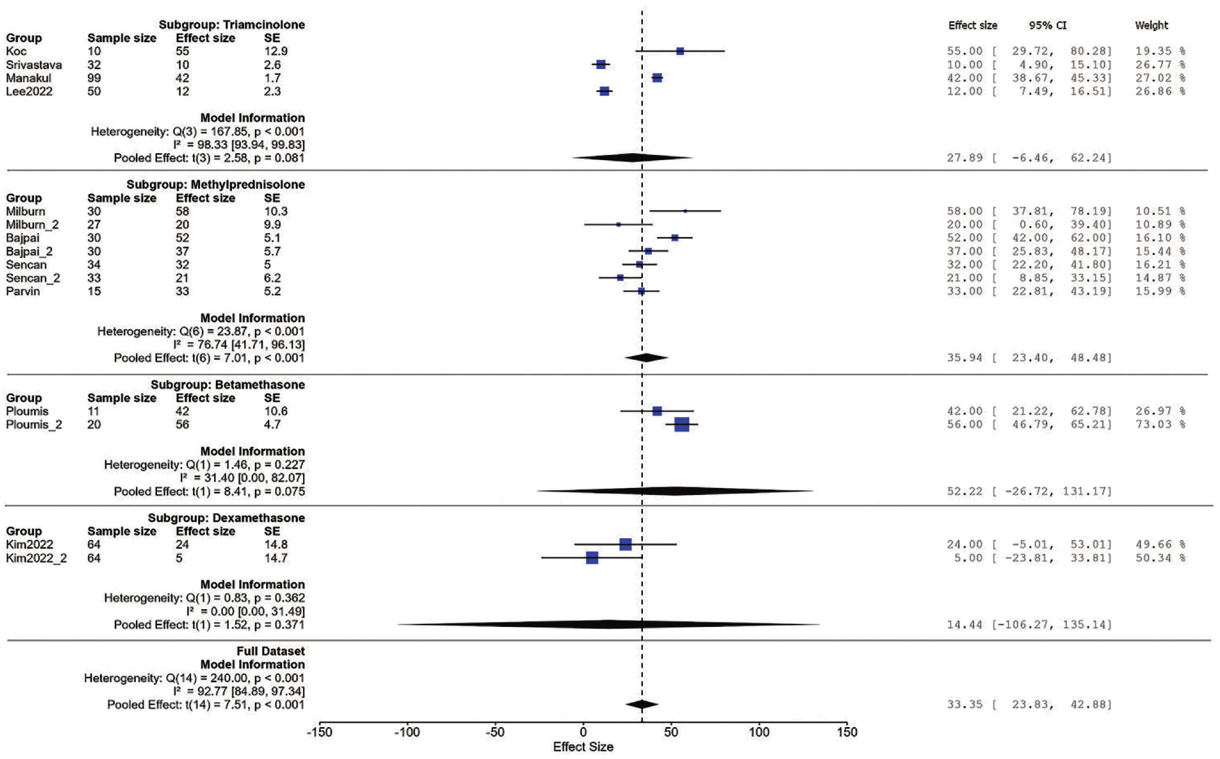


Fig. 10. *Forest plot of the functionality effect sizes at follow-ups between one and 4 weeks, divided into subgroups based on the steroid injected. The Knapp-Hartung adjustment produced wide confidence intervals in the subgroups with 2 results; nonetheless, the difference between subgroups was significant (P = 0.006).*
SE: standard error; CI: confidence interval.

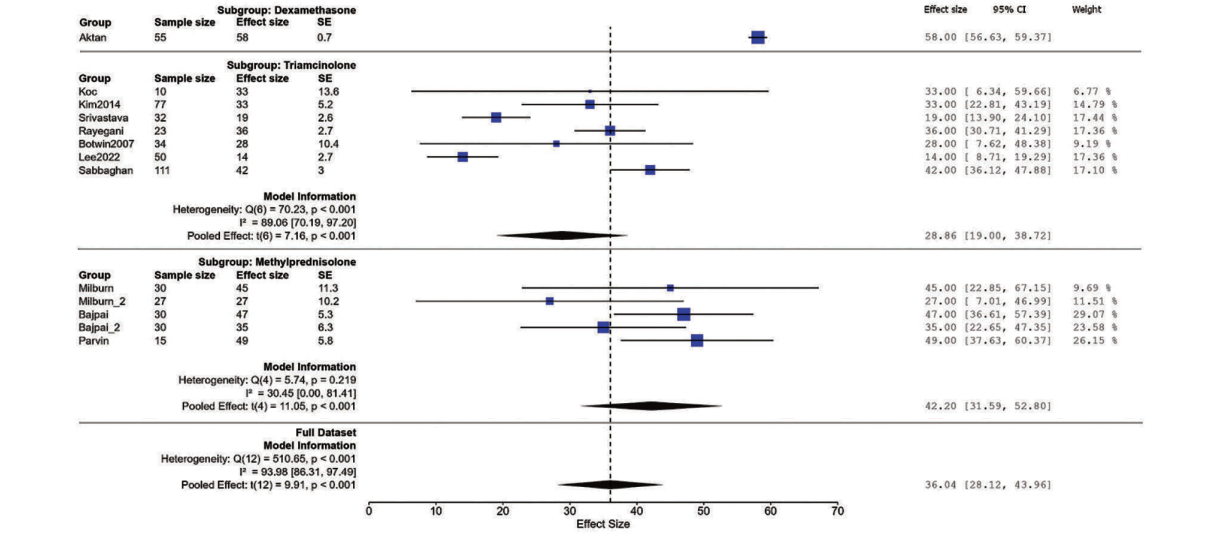


Fig. 11. *Forest plot of the functionality effect sizes at follow-ups between one and 2 months, divided into subgroups based on the steroid injected. Dexamethasone had only one result (added to the figure for the purpose of illustration), not included in the subgroup analysis, and betamethasone had none. The difference between subgroups was significant (P = 0.016).*
SE: standard error; CI: confidence interval.

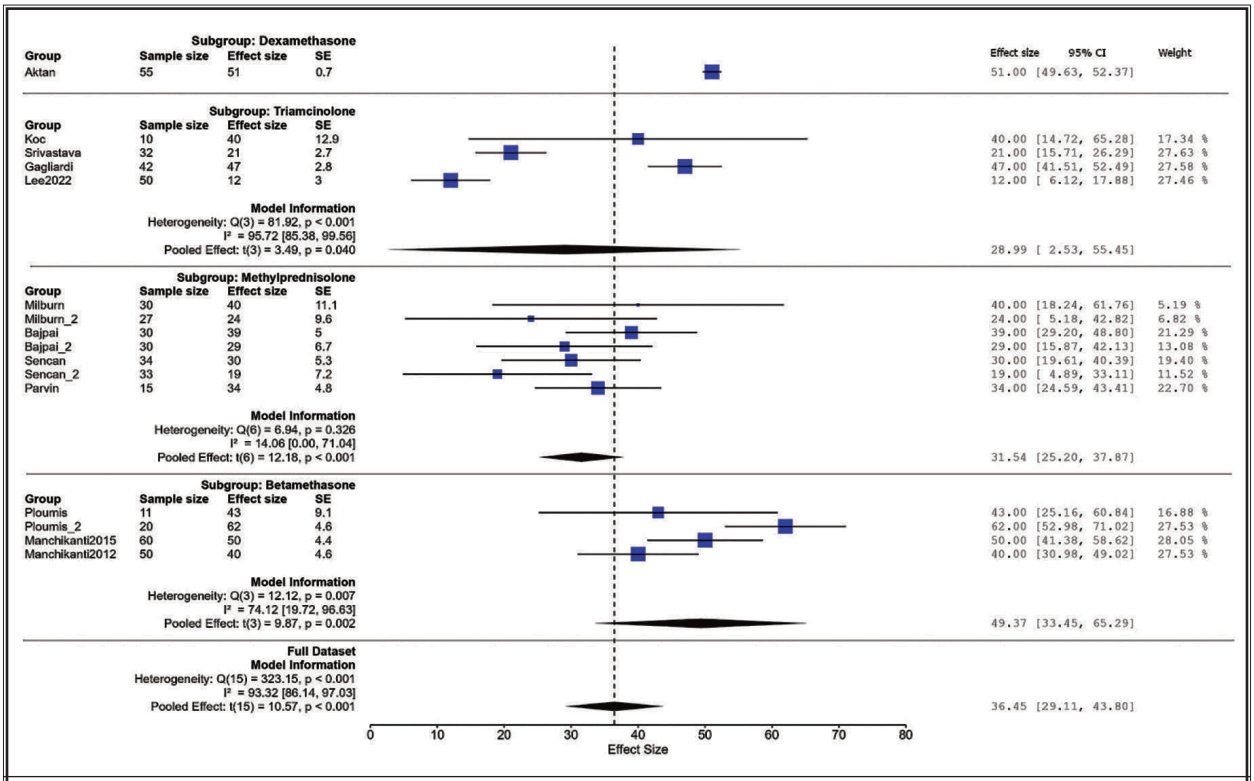


Fig. 12. *Forest plot of the functionality effect sizes at follow-ups between 2 and 3 months, divided into subgroups based on the steroid injected. Dexamethasone had only one result (added to the figure for the purpose of illustration), not included in the subgroup analysis. The difference between subgroups was significant (P = 0.005).*
SE: standard error; CI: confidence interval.

5 additional patients (3.4%, 3 of whom had stenosis) were excluded because the procedure was canceled: 3 had intrathecal penetration of contrast (2 after IL and one after TF injections), and in the other 2 cases (with an unspecified approach) the aspiration showed blood, indicating the penetration of a vessel; nonetheless, no morbidity was associated. A study using triamcinolone via CESI (35) and US guidance reported that one patient out of 47 (2.1%) experienced aggravation of symptoms after the injection and underwent surgery. Finally, in a large retrospective study comparing betamethasone ILESIs to IL injections with local anesthetic only (46), 644 procedures were performed in 120 patients, with 14 (2.2%) subarachnoid entries, one episode of nerve root irritation, and one of pain and swelling at the site of injection.

Discussion

This review examined the effectiveness and safety of different ESI approaches and protocols for central and foraminal LSS. Our analysis showed that these injections were effective at providing pain relief and functionality improvements in the short term (3 months) and possibly for as long as 6 to 12 months, though the long-term effect was highly variable and the evidence weaker, particularly for functional improvements. The type of steroid, mostly neglected in previous studies, and the severity of stenosis appear to wield significant effects on the strength and duration of pain relief. In contrast, different injection routes overall provide similar effectiveness, although for IL injections, that effectiveness varies with the spinal level to which the injections are administered, and the ideal target seems to be the point of maximal stenosis or one level caudad.

Previous studies examining the differences between these approaches in the specific context of LSS are limited: Manchikanti et al (48) compared 2 clinical trials by their own group (45,46), both included in this review, and reported that the IL approach was signifi-

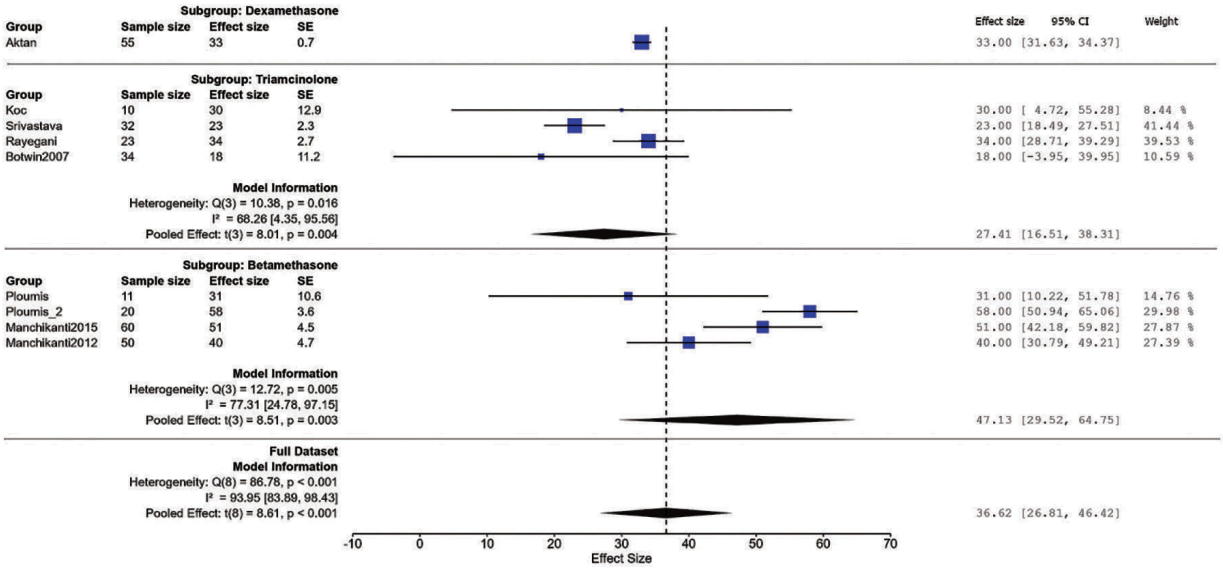


Fig. 13. *Forest plot of the functionality effect sizes at follow-ups between 4 and 6 months, divided into subgroups based on the steroid injected. Dexamethasone had only one result (added to the figure for the purpose of illustration), not included in the subgroup analysis, and methylprednisolone had none. The difference between subgroups was significant (P = 0.002).*
SE: standard error; CI: confidence interval.

cantly more effective than its C counterpart. Sivaganesan et al, in a study on general degenerative spinal pathology and back and leg pain (49), noted that TF or IL injections, as opposed to CESIs, were significant positive predictors of achieving a minimum clinically important difference. However, the different anatomical configuration suggests that TF injections may be more suitable for localized stenoses and monolateral symptomatology (50), involving one vertebral level, whereas the IL and C approaches may be more effective for multilevel pathologies. In this review, the only study comparing IL and TF injections specifically in patients with multilevel stenoses (29) showed that the IL approach was superior, whereas the 2 other studies comparing the same techniques in patients with unspecified stenosis severity (30,31) reported TF superiority and no significant difference, respectively. Additionally, the flow direction of the cerebrospinal fluid hinders the availability of steroids injected caudally to vertebral levels cephalad to L3 (51); therefore, CESIs are suitable mostly for stenoses between L3 and S1. The injection can, however, be performed with the patient in the prone Trendelenburg position to improve the diffusion to superior levels. Nonetheless, the small study (14) in this review comparing C and TF injections in patients with single-level, mild stenoses involving L4-5/L5-S1 nerve roots, showed TF superiority. Moreover, steroid facet joint injections have been proposed as an effective safer alternative for treating LSS (52).

In contrast, significant differences emerged based on the steroid used: betamethasone appeared to provide the strongest and longest effect, both for pain relief and functionality improvements (consistent even after 12 months), followed by triamcinolone (slightly less effective at first but still consistent after 4-6 months), methylprednisolone (similar strength initially, though declining more rapidly after 2-3 months), and finally dexamethasone, with the lowest and shortest effectiveness. These findings have low to moderate certainty, due to the low number of studies involving betamethasone and dexamethasone as well as the variable doses and protocols used.

These findings partially contradict previous reports in the literature; however, to the best of our knowledge, this aspect has rarely been examined in the specific context of LSS. Furthermore, no study compared all 4 steroids. Huda et al (53) reported that methylprednisolone was more effective than triamcinolone for patients with LSS, providing more sustained pain relief and increased walking distance after 6 months in

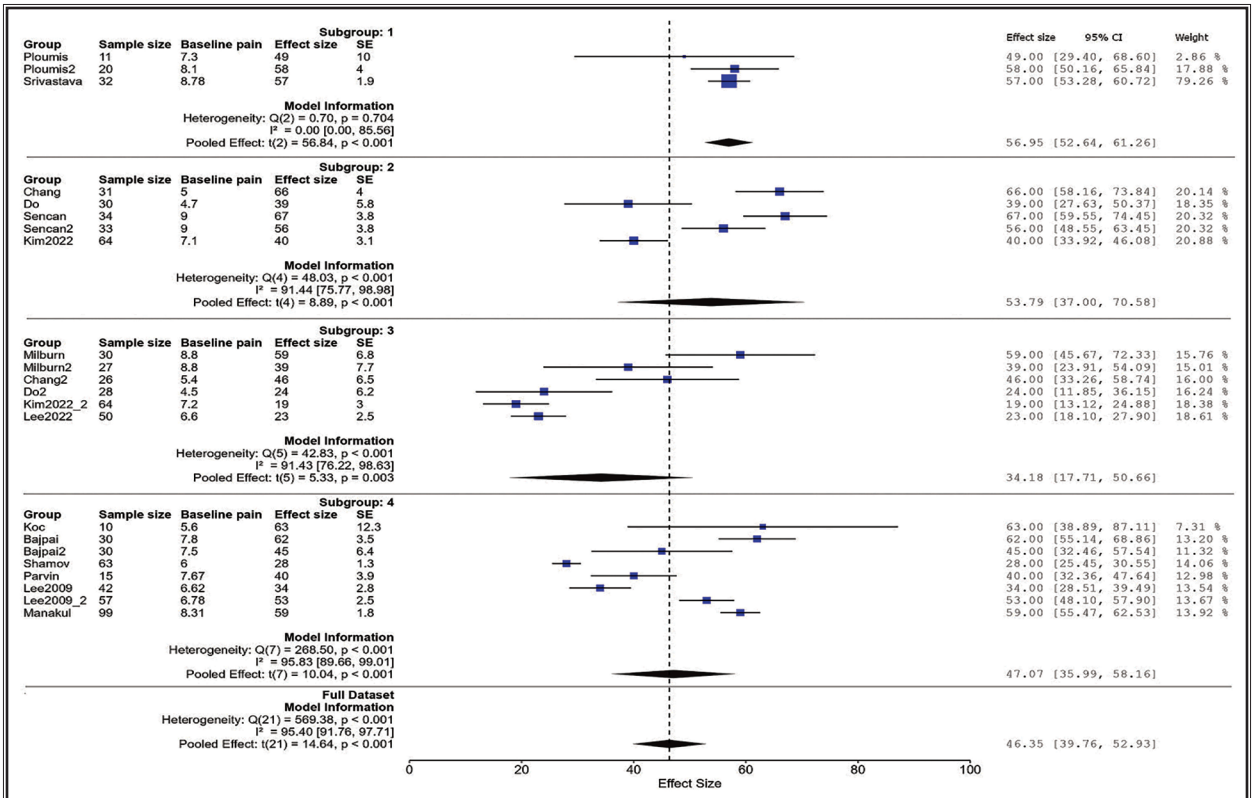


Fig. 14. *Forest plot of pain relief effect sizes at follow-ups between one and 4 weeks, divided into subgroups based on the severity of the stenosis. Group 1: mild/moderate stenosis. Group 2: moderate/severe stenosis. Group 3: severe and extremely severe stenosis. Group 4: unspecified or various severities. The difference between subgroups was significant (P = 0.001).*
SE: standard error; CI: confidence interval.

a randomized trial, in contrast to our results. Kim and Brown (19) compared methylprednisolone and dexamethasone in patients with radiculopathy and reported similar efficacy, with a nonsignificant advantage for methylprednisolone after one to 2 months. In contrast, a retrospective study by Maus et al (54) compared LSS patients who received ESIs of dexamethasone solutions to LSS patients who received particulate steroid suspensions of betamethasone and triamcinolone. The researchers reported that the percentage of patients who achieved effective pain relief 2 months after their injections was significantly higher in the former group than in the latter. A large prospective trial by McCormick et al (55) involving patients with radiculopathy (though only 6% of those had LSS) noted that after one to 4 weeks, TFESIs of triamcinolone were associated with > 50% pain relief in a significantly larger percentage of patients than were betamethasone injections. Generally, depo-steroids reportedly have stronger and more prolonged effects, whereas nonparticulate ones like dexamethasone have more limited effectiveness but greater safety, with lower risks of vascular occlusion (50,56). Finally, Moreira et al (57) retrospectively compared the efficacy of betamethasone, methylprednisolone, and dexamethasone TFESIs in patients with radiculopathy (nerve impingement from disc herniation); the researchers found that a significantly lower percentage of patients underwent repeated injections within a year after receiving dexamethasone than did those who received other particulate steroids. (However, this outcome is unclear, since it may suggest that the ESIs were effective throughout the year, as the authors assumed, or that they were not effective at all, and repeating them would have been pointless). Thus, further research is warranted to compare the 4 steroids in controlled conditions.

Overall, the type of steroid appears to be one of the most significant factors affecting the effectiveness

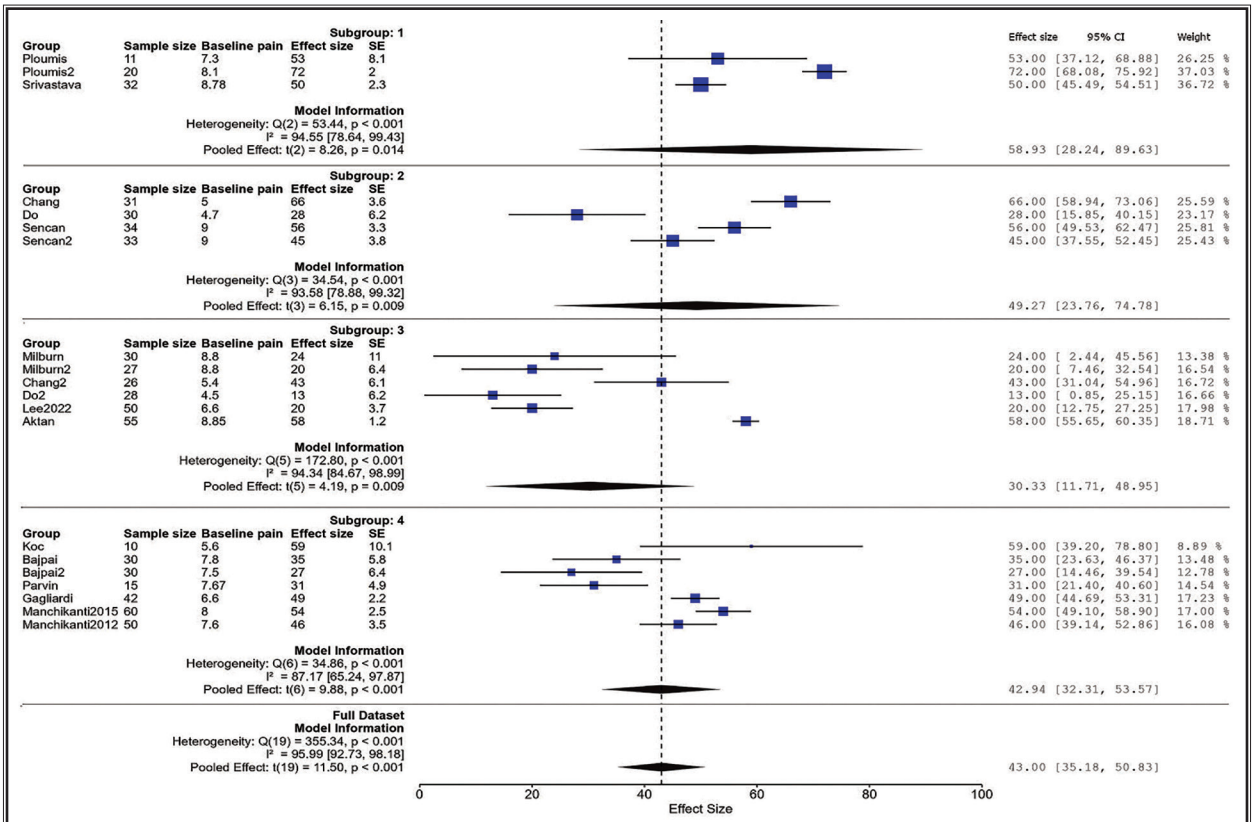


Fig. 15. *Forest plot of pain relief effect sizes at follow-ups between 2 and 3 months, divided into subgroups based on the severity of the stenosis. Group 1: mild/moderate stenosis. Group 2: moderate/severe stenosis. Group 3: severe and extremely severe stenosis. Group 4: unspecified or various severities. The difference between subgroups was significant (P = 0.038).*
SE: standard error; CI: confidence interval.

of the ESI; however, the dose seems to have no significant correlation with the effect. These results suggest that low steroid doses may provide noninferior pain relief and functionality improvements to higher doses while reducing the risks associated with these drugs. Investigations focused on different doses were not found in the literature, although it should be noted that Friedly et al (15) claimed that lidocaine alone provided similar pain relief to that of lidocaine and steroids after 6 weeks (whereas after 3 weeks, the steroids were significantly more effective). At 6 weeks, the steroids were still more effective in Friedly et al's study, but since the *P*-value reported was slightly above the significance level (0.07), the difference was deemed irrelevant by the authors. The steroids used in that study were inconsistent in type and dose, and the article was criticized for questionable methods by Manchikanti (58) and other authors, though Manchikanti later published a systematic review with similar conclusions (16). Further research may clarify this aspect.

Our results also show that the severity of stenosis is a significant factor affecting ESI effectiveness; severe cases are associated with significantly lesser effects on pain and functionality, and lesser improvements in functionality were also noted in moderate cases. This finding is consistent with a previous study by Kapural et al (59), who reported that patients with severe stenosis affecting multiple levels of the spine were less likely to experience pain relief between 8 of 12 weeks after receiving ESIs. Meanwhile, Sivaganesan et al (49) reported that patients with general degenerative lumbar pathology and worse ODI scores at baseline were more likely to achieve a minimum clinically important difference after ESIs.

As for functionality, the smaller quantity of data and the high heterogeneity made the evidence less certain

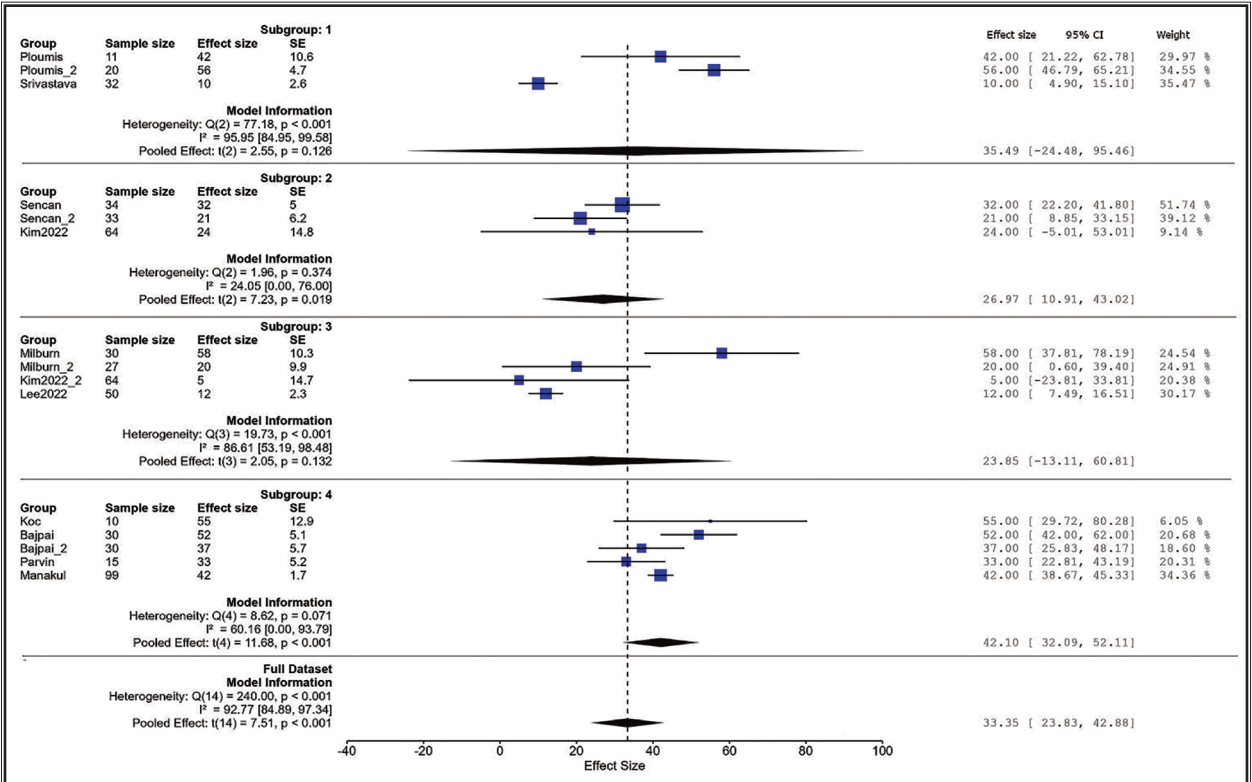


Fig. 16. *Forest plot of functionality effect sizes at follow-ups between one and 4 weeks, divided into subgroups based on the severity of the stenosis. Group 1: mild/moderate stenosis. Group 2: moderate/severe stenosis. Group 3: severe and extremely severe stenosis. Group 4: unspecified or various severities. The difference between subgroups was significant ($P = 0.025$).*
SE: standard error; CI: confidence interval.

and the results more difficult to interpret. Nonetheless, the steroid type seems the most relevant predictor of the outcome, followed by stenosis severity. Interestingly, a recent review suggests that when administered to patients with spinal stenosis, ESIs have a greater effect in reducing disability than in providing pain relief, during both the short and the long term (60).

Overall, this review suggests that the most effective approach for ESIs in cases of LSS is to use betamethasone, possibly even in small doses, though the current evidence is insufficient for a definite recommendation; administration through the TF approach seems more effective in case of single-level stenosis, and a monolateral injection is sufficient. ILESIs and CESIs are likely more suitable for multi-level stenoses, the latter particularly for pathologies involving spinal levels inferior to L2-L3. Patients with mild and moderate LSS are likelier to obtain stronger pain relief than those who have the severe form of the disorder; in addition, Cosgrove et al (61) reported that younger and female patients generally obtain greater benefits with ESIs, though we did not find similar significant effects.

Furthermore, we noted that ESIs for spinal stenosis are safe procedures overall, when performed under imaging guidance (all the studies included in this review performed ESIs with fluoroscopic guidance, except the 3 that used US guidance). However, several studies (9 of 24, 37.5%) did not report the safety outcomes. Occasionally, minor and brief side effects occurred, especially pain or vasovagal reactions, regardless of the injection site; the literature reports a rate of minor complications of 2.4% (50). Possible more serious adverse events are due to incorrect needle placements before the injection, with intrathecal or blood vessel penetration; however, they can be recognized promptly with imaging or aspiration, respectively, and the injection in such cases is avoided. Additionally, rarer major complications include infections, neurotoxicity, neural injury, and systemic pharmacological effects of the steroids with repeated injections (50,56).

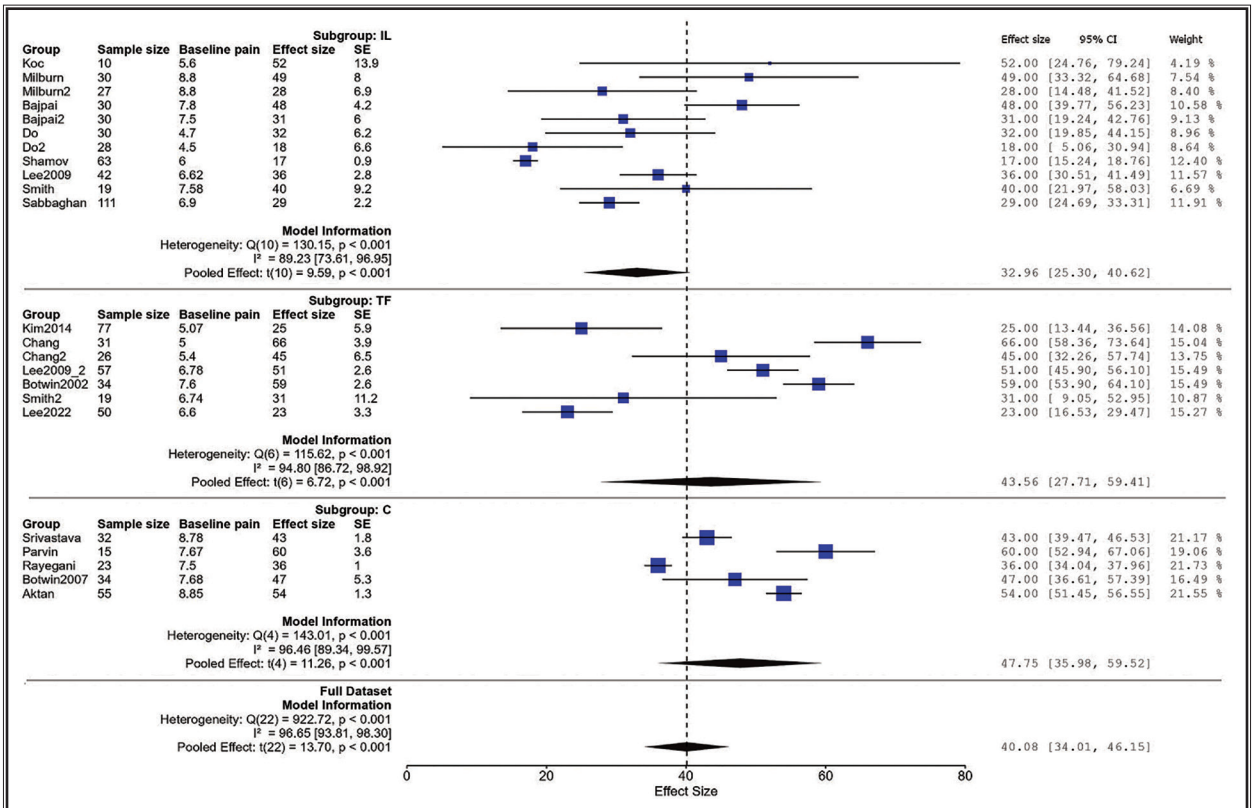


Fig. 17. *Forest plot of the pain relief effect sizes at follow-ups between one and 2 months, divided into subgroups based on the injection route.*
IL: Interlaminar. TF: Transforaminal. C: Caudal. The difference between subgroups was significant ($P = 0.02$).
SE: standard error; CI: confidence interval.

This review has some limitations, such as the small sample sizes of some studies and significant heterogeneity among results, due to different study designs and grouping conditions. Some larger studies were excluded because they did not have a consistent injection protocol or the results were reported differently from our methods. The subgroup analysis was limited by the low number of studies with certain characteristics and variable follow-up times. Further research is needed to confirm the effectiveness of different types of steroids.

Conclusions

This review suggests that ESIs provide effective pain relief and functionality improvements in patients with LSS. The strongest and more prolonged effects tend to occur with betamethasone and other depo-steroids and in patients with mild or moderate stenosis, whereas patients with severe stenosis see a lower level of benefits; pain relief can still be significant after 6 to 12 months. The injection route can be chosen based on the individual patient's status, as the 3 approaches examined (IL, TF, and C) provide similar relief.

Author Contributions

Study concept and design: IW; literature search and article selection: TD, FS; literature review and data extraction: RFM, SKGR; meta-analysis and visualization: FS; writing-first draft: FS, TD; writing-review: IW, FS; final approval: all authors.

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