

Systematic Review

## Particulate vs Non-Particulate Steroids for Transforaminal Epidural Steroid Injections: Systematic Review and Meta-analysis of the Current Literature

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**Background:** The efficacy of particulate and non-particulate steroids in patients receiving epidural steroid injections remains unclear.

**Objective:** The purpose of this meta-analysis was to compare the efficacy of particulate and non-particulate steroids in patients receiving epidural injections for radicular pain over 3 months.

**Study Design:** Systematic review and meta-analysis.

**Methods:** We reviewed PubMed, PubMed Central, Scopus, Central Register of Clinical Trials of the Cochrane Collaboration, Google Scholar, and Directory of open access journals for trials that compared efficacy of particulate steroid with non-particulate. A meta-analysis was performed on treatment related to mean change in visual analogue score (VAS) between the particulate and non-particulate steroids. Two authors independently reviewed the data for inclusion.

**Results:** Seven studies comprising 3,542 patients in the particulate group and 856 patients in the non-particulate group were included. Pooled mean maximum change of VAS was higher by 0.53 (95% CI: 0.14 to 0.92;  $P = 0.007$ ;  $I^2 = 50.2\%$ ) in the particulate group compared to the non-particulate group. The non-particulate group had a larger proportion of patients with more than 50% pain relief than the particulate group [OR 0.81 (95% CI: 0.68 to 0.97,  $P = 0.024$ ).

**Limitations:** Limited number of trials that fit the inclusion criteria and were available for analysis.

**Conclusions:** As the use of particulate steroids seems to be associated with slightly better VAS scores only, clinicians need to weigh their clinical relevance in the light of complications and recent FDA recommendations on the use of particulate steroids.

**Key words:** Meta-analysis, particulate epidural steroids, non-particulate epidural steroids, efficacy, decrease in pain scores

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**B**ack pain with a radicular component is a significant health problem affecting millions (1,2). Treatment options include conservative management, epidural steroids, and surgery in a step-wise approach. Conservative management includes

exercise, weight loss, and physiotherapy. Epidural steroids are used in patients who fail to respond to conservative management. Inflammatory cytokines released from a herniated disc cause chemical irritation of the nerve roots and hence result in radicular pain.

Steroids decrease inflammation around the affected nerve, suppress ectopic discharge, and enhance blood flow to the ischemic nerve root thus leading to a decrease in pain (3-5).

The preparation of steroids used in the epidural space can be divided into 2 groups – particulate such as methylprednisolone, betamethasone, and triamcinolone; and non-particulate like dexamethasone phosphate. Particulate steroids have longer a duration of action due to a local depot effect resulting in continuous release of the active drug from the injection site over a long time period (6).

On the other hand non-particulate steroids are water soluble steroid with small particle size and limited aggregation (7). This results in rapid clearance from the spinal canal and a short duration of action (8). So one anticipates a long-lasting relief of symptoms in patients receiving epidural injection with particulate steroids compared to those who receive non-particulate steroids.

Though epidural steroids have been used in clinical practice for decades now, several case reports have documented potential complications like paraplegia secondary to spinal cord infarction associated with the use of particulate steroids (9-17). Occlusion of the segmental artery accompanying the nerve root by the particulate steroid or embolization of the particulate steroid through the vertebral artery are the possible etiologies involved (18,19).

Only 2 studies have addressed the issue of the microscopic size of the particles within various steroid preparations (8,19). Tiso et al (19) found that particles in dexamethasone and betamethasone were rod like and lucent, whereas particles of methylprednisolone and triamcinolone were opaque and amorphous. Further, particles of methylprednisolone and triamcinolone coalesced into larger particles greater than 100  $\mu\text{m}$ . These particles could occlude capillaries (5 – 8  $\mu\text{m}$ ), metarterioles (20 – 50  $\mu\text{m}$ ), and at times arteries (> 50  $\mu\text{m}$ ), resulting in infarction of large block of neural tissue supplied by that artery. Benzon et al (8) noted particles greater than 1000  $\mu\text{m}$  in size and it to faster precipitation of steroids. Shaking the solution before administration resulted in formation of small particles which coalesced and precipitated into a larger size on entering the vessel thus making it possible for any steroid size to enter and block a vessel of any size.

On the other hand, dexamethasone has a particulate size of less than 5  $\mu\text{m}$ , the lowest density, and the least tendency for aggregation. In the literature, no se-

rious neurological complication has been reported with use of dexamethasone. However, it has limited effectiveness in patients with radicular pain (20). This limited efficacy of dexamethasone when compared to particulate steroids remains a matter of concern.

Clinical studies evaluating the efficacy of different types of steroid injections have shown variable results without a definite conclusion. Few studies report statistically significant efficacy of particulate steroids over non-particulate (21,22), while others fail to show any significant benefit (23,24). Further there are variations in time intervals at which patients are followed and pain relief reported in these studies. The aim of this systematic review and meta-analysis was to compare the efficacy of particulate and non-particulate steroids in patients receiving epidural injections for radicular pain. The primary outcome of the meta-analysis was to compare the treatment related mean change in visual analogue score (VAS) between the particulate and non-particulate steroids. The exploratory outcome was to compare the percentage of patients having more than 50% pain relief.

## **METHODS**

This meta-analysis was undertaken in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines (25).

### **Eligibility Criteria**

#### **Type of Studies**

All the randomized controlled trials, cohort studies, or retrospective studies of patients who received epidural steroids injection were considered.

#### **Participants**

Participants were adults with neck or back pain who received either a cervical or lumbar injection using one of the 3 approaches, i.e., transforaminal, interlaminar, or caudal.

#### **Study Intervention**

Patients in one arm received epidural injections with particulate steroids, whereas patients in the second arm received non-particulate steroids.

#### **Outcome Measures**

The primary outcome was to compare the treatment-related mean change in VAS with use of particulate and non-particulate steroids. We included only

those studies which used VAS or NRS for pain assessment and had a minimum follow-up assessment at one month. In case of studies reporting pain in NRS, values were transformed into VAS. The exploratory outcome was to compare the percentage of patients having more than 50% pain relief with a minimum follow-up of one month. We did not limit the inclusion based on dose of steroids or number of injections.

### Exclusion Criteria

Trials where injections were performed without the aid of fluoroscope.

Trials comparing the local anaesthetics with the epidural steroid injections.

### Information Sources and Search Methods

Two authors (JK, DJ) independently searched PubMed, PubMed Central, Scopus, Central Register of Clinical Trials of the Cochrane Collaboration, Google Scholar, and Directory of open access journals for eligible studies using the various combinations of search words: epidural, steroid, particulate steroids, non-particulate steroids, triamcinolone, betamethasone, dexamethasone, back pain. The bibliographies of all the selected articles were reviewed to find possible additional articles that might have been missed in the initial search.

### Search Strategy

Studies comparing a particulate steroid with a non-particulate steroid (prospective or retrospective) administered either through a lumbar or cervical route using one of the 3 approaches, i.e., transforaminal, interlaminar, and caudal route, published either as full articles or meeting abstracts (in peer-reviewed journals) were considered.

Steroids considered for this review included methylprednisolone, dexamethasone, betamethasone, and triamcinolone.

The aforementioned reviewers performed an independent assessment of the full text of articles assessed for eligibility and made individual decisions whether to include the potential study in the analysis. In case of any disagreement, the opinion of a third researcher was taken into account.

### Validity Assessment

Formal quality assessment for bias in studies was carried out by an independent investigator in accordance with the guidelines of the Cochrane Collaboration (Appendix 1) (26). Studies were not excluded based on their clinical relevance.

### Data Extraction

Required data was collected from the full text of the articles and was tabulated in a Microsoft Excel spreadsheet. Initial data extraction from the eligible trials was done by one of the authors, JK. Data was cross-checked independently by the other 2 co-authors, P.M.S. and D.J. Statistical analysis was performed by P.M.S.

Data collected from each study included name of first author, study design, year of publication, country of origin of study, dose of steroid, baseline VAS/NRS and VAS/NRS during the follow up-period, percentage of patients having more than 50% pain relief, mean number of epidural injections, baseline ODI and percentage of change in ODI after epidural injection. For trials documenting VAS/NRS at various time intervals, we analyzed the lowest values post treatment, allowing us to measure the highest therapeutic effect achieved in each group.

### Quality of Evidence

Quality of evidence for the primary outcome was assessed as per the American Society of Interventional Pain Physicians' (ASIPP) grading to assign best evidence synthesis (Appendix 2) (27).

### Statistical Analysis

Comprehensive Meta-analysis Version 2 (Biostat Inc.) was used for the statistical analysis of the pooled data. Fixed-effect modeling followed by random-effects modeling (after assessment of heterogeneity with fixed modeling) were used to perform meta-analysis. Whenever heterogeneity was found to be higher resulting values are reported from random effect modeling. For continuous data, means and standard deviation (SD) values of VAS were extracted for both groups, a mean difference was computed at the study level and weighted mean difference was calculated in order to pool the results across all studies. If the values were reported as median and interquartile range (IQR) or total range of values, the mean value was estimated using the median and the low and high end of the range for samples smaller than 25; for samples greater than 25, the median itself was used. SD was estimated from the median and the low and high end of the range for samples smaller than 15, as range/4 for samples from 15 to 70, and as range/6 for samples more than 70. If only an IQR was available, SD was estimated as IQR/1.35 (28,29).

The extent of heterogeneity in between the trials was quantified using the  $I^2$  statistic.  $I^2 < 40\%$  was considered unimportant; 30% to 60% = moderate het-

erogeneity, 50% to 90% = high heterogeneity. Results were expressed as mean difference with 95% confidence interval (CI).  $P < 0.05$  was considered statistically significant. Potential publication bias was assessed using a funnel plot and evaluated using the Egger's test.

### Search Results

Figure 1 shows the search results and study selection flow chart. The preliminary search yielded 312

studies from the aforementioned database. Duplicates obtained by individual researchers during their independent review of the database were removed electronically using Endnote. On final evaluation, 8 trials (21-24,30-33) and 4 abstracts (34-37) published in scientific proceedings of peer reviewed journals fulfilled the inclusion criterion. One study and 4 abstracts did not measure the desired primary outcome parameters and were excluded from analysis. The primary outcome

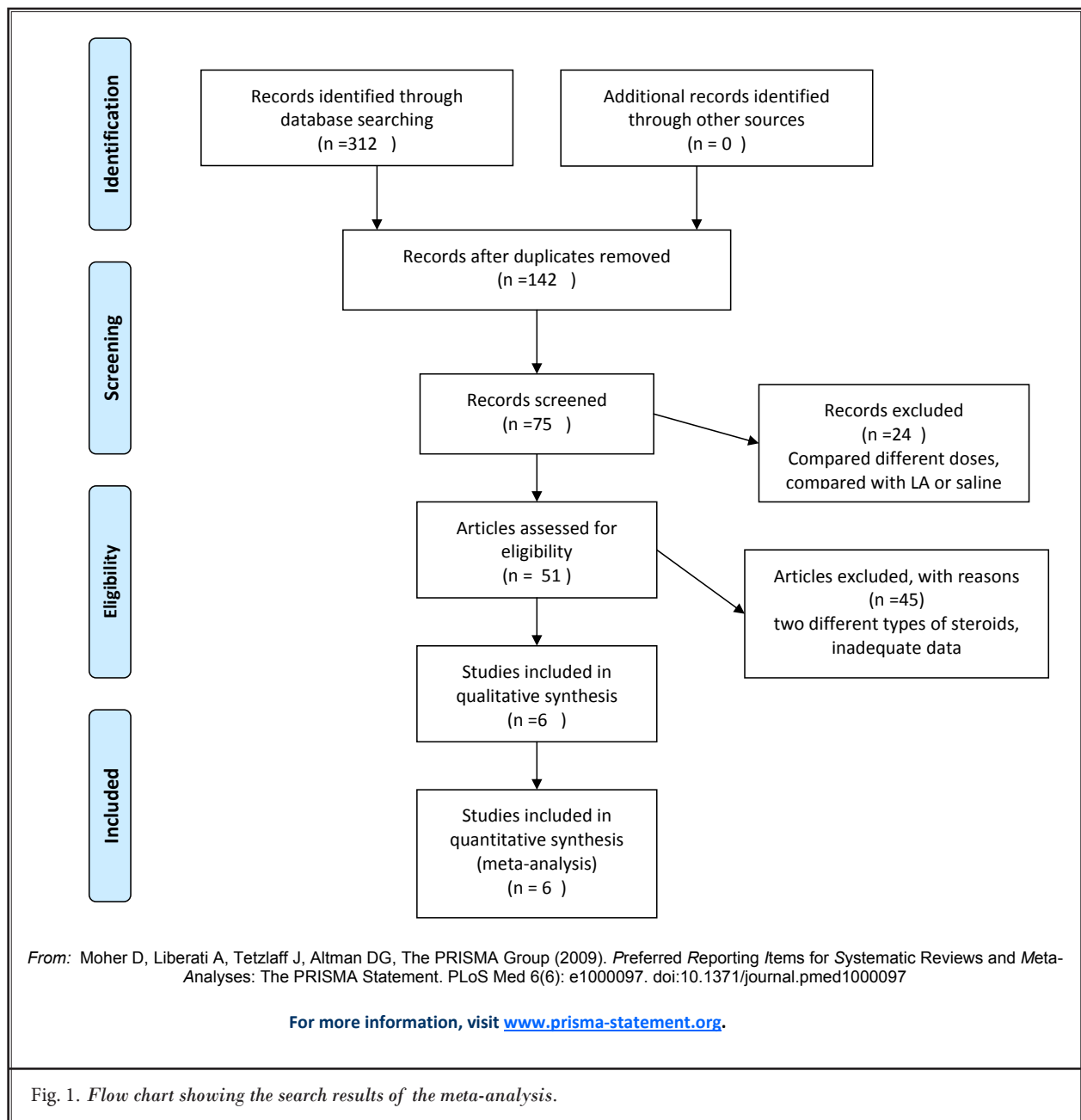


Fig. 1. Flow chart showing the search results of the meta-analysis.

data of the highest post-treatment VAS drop was available for 3,542 and 856 patients in particulate and non-particulate groups, respectively of the 7 studies included (21-24,31-33).

**Trials, Participants, and Interventions (Table 1)**

Out of the 7 studies included in the trial, 4 were prospective randomized trials (21,23,24,32) and 3 were retrospective analyses (22,31,33). Two studies enrolled patients with cervical epidural injections (24,33) while 5 had patients with lumbar epidural injections (21-23,31,32).

Among the particulate steroids, triamcilonone 40 –

80 mg was used in 4 trials whereas methylprednisolone was used in 2. Dexamethasone in a dose range of 10 – 15 mg was the most commonly used non-particulate steroid except one in which aqueous betamethasone (15 mg) was used.

Functional outcome after epidural steroid injection was assessed in 4 trials. Out of these, 3 trials used a validated Oswestry disability index, while Dreyfuss et al (24) used a patient specified outcome measure.

Only a single trial, which compared the complication rate between the particulate and non-particulate group, did not report any complication in either group (31).

Table 1. Summary of the trials, participants, interventions and results.

Author (year)	Design	Approach	Patients enrolled
Kennedy D (2014)	Prospective, multicenter	Transforaminal (lumbar)	(37: 41)
Kim D (2011)	Prospective, single center	Translaminar (lumbar)	(30: 30)
El Yahchouchi CE (2013)	Retrospective	Transforaminal (lumbar)	(1151:481)
Dreyfuss (2006)	Prospective, multicenter	Transforaminal (cervical)	(15:15)
Shakir A (2013)	Retrospective	Transforaminal (cervical)	(220:221)
Noe C (2003)	Retrospective	Transforaminal (lumbar)	(25:15)
Park C (2010)	Prospective	Transforaminal (lumbar)	(53:53)

Intervention	Outcome	Results
Particulate gp-1.5mL: triamcinolone (40mg/mL) Non-particulate gp-1.5ml dexamethasone (10mg/mL)	number of injections, surgical rates, pain scores, Oswestry disability index Time frame – 2weeks/3months/6months	No significant difference in pain scores and functions in between 2 groups. Significant more injections were required in dexamethasone group.
Particulate gp-80mg methylprednisolone Non-particulate gp-15 mg dexamethasone.	% change in pain score, % patients with decreased pain, days of follow up, complications Time frame – 1 month	Lesser decrease in pain scores in dexamethasone group compared to methylprednisolone group. No difference in mean days of follow up. No complications
Particulate gp-80mg triamcinolone(40mg/mL,2mL) Non-particulate gp-10 mg dexamethasone. (10mg/mL)	Pain scores , successful pain relief (<50% reduction in pain score) Time frame – 2weeks/2months	Dexamethasone was superior to triamcinolone in both pain relief and functional outcome
Particulate gp-60mg triamcinolone Non-particulate gp-12.5 mg dexamethasone	Pre and post procedural pain scores, functional outcome. Time frame – 4 weeks	No significant difference in pain scores and functions in between 2 groups.
Particulate gp-40mg triamcinolone Non-particulate gp-15 mg dexamethasone(10mg/mL)	Mean reduction in pain scores (self reported pain score), number of injections Time frame – 4 weeks	No significant difference in mean reduction in pain scores in between 2 groups.
Particulate gp-80mg methylprednisolone Non-particulate gp-15 mg non depot betamethasone	Mean reduction in pain scores and disability index Time frame – 4 weeks	Significant improvement noted in depo methylprednisolone compared to aqueous betamethasone
Particulate gp-40mg triamcinolone Non-particulate gp-7.5 mg dexamethasone	Pain scores , % change in pain score Oswestry disability index Time frame – 4 weeks	Dexamethasone was superior to triamcinolone in short term pain relief

**Primary Outcome**

**Maximum Difference in Mean VAS at Any Time Interval**

Six trials reported data within 2 months and one reported data at 3 months. Pooled mean of VAS was higher by 1.023 (95% CI: 0.29 to 1.76;  $P = 0.007$ ;  $I^2 = 90.59\%$ ) in the particulate group compared to the non-particulate group (Fig. 2). Subgroup analysis evaluating

the pooled values after grouping into lumbar and cervical injections showed pooled estimates of VAS change being higher in the particulate group compared to the non-particulate group by 1.22 (95% CI: 0.25 to 2.18;  $I^2 = 92.522\%$ ) in the lumbar region (Fig. 3). In the cervical region, only 2 studies were available for subgrouping. The particulate group showed a higher fall in VAS than the non-particulate group [OR: 0.44 (95% CI: 0.70 to 1.57;  $I^2 = 56.015\%$ ) (Fig. 4).

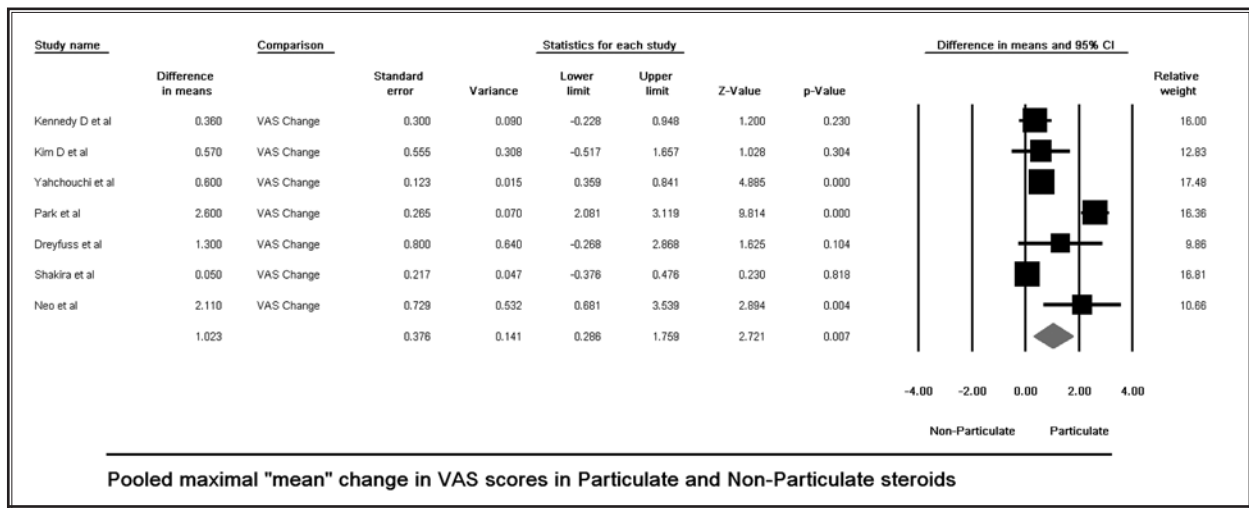


Fig. 2. Forest plot comparing pooled mean maximum change in VAS at any time interval with particulate and non-particulate steroids.

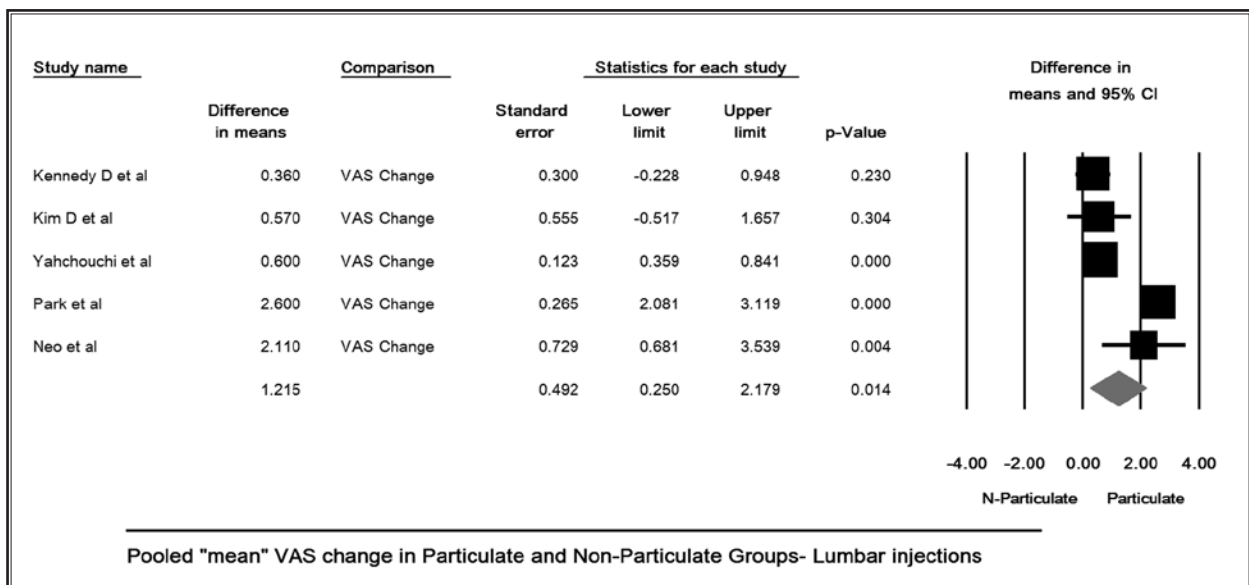


Fig. 3. Forest plot comparing pooled mean maximum change in VAS at any time interval with particulate and non-particulate steroids administered through the lumbar route.

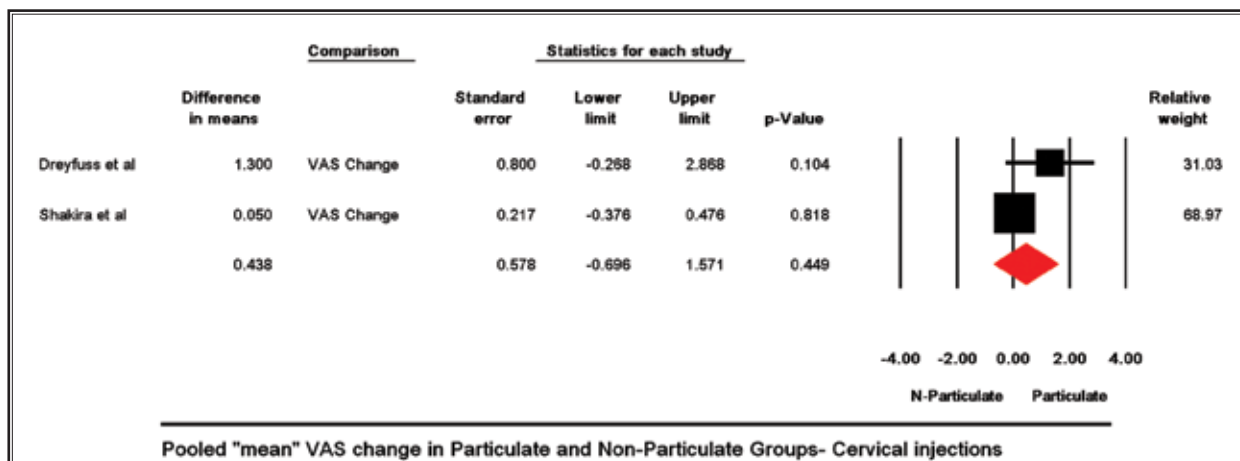


Fig. 4. Forest plot comparing pooled mean maximum change in VAS at any time interval with particulate and non-particulate steroids administered through the cervical route.

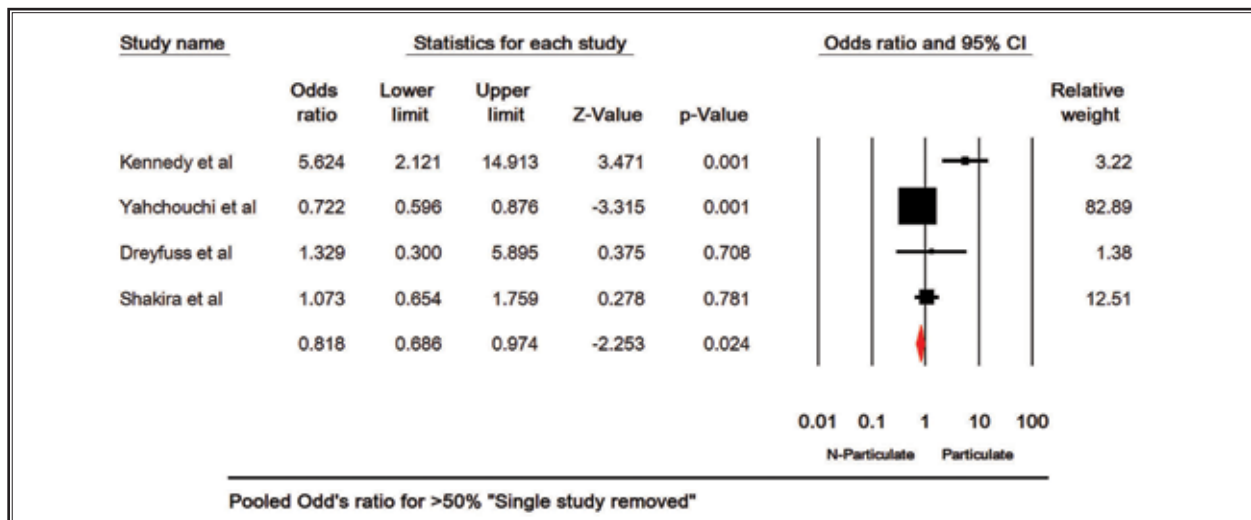


Fig. 5. Forest plot showing pooled odds ratio for more than 50% relief in particulate and non-particulate group.

### Exploratory Outcome

#### More than 50% Pain Relief

Five trials (21,24,31-33) documented patient numbers with more than 50% relief during the course of treatment. In the particulate group, pooled values included a total of 4,298 patients of which 1,856 patients had at least 50% or more pain relief. In the non-particulate group, data for 811 patients was available of which 329 showed relief of 50% or more. The non-particulate group had a larger proportion of patients with more than 50% pain relief than the particulate group

[OR 0.81 (95% CI: 0.68 – 0.97)]. The forest plot showing pooled odds ratio for the same is shown in Fig. 5.

#### Heterogeneity

While analyzing the primary outcome, a sensitivity analysis to lower the heterogeneity with "single study removal method" found that study by Park et al (21) contributed maximally to the heterogeneity. After removal of this study from the analysis, the heterogeneity reduced significantly to a value of only 50.02%. The forest plot of the pooled point estimate after removal of this study is shown in Fig. 6.

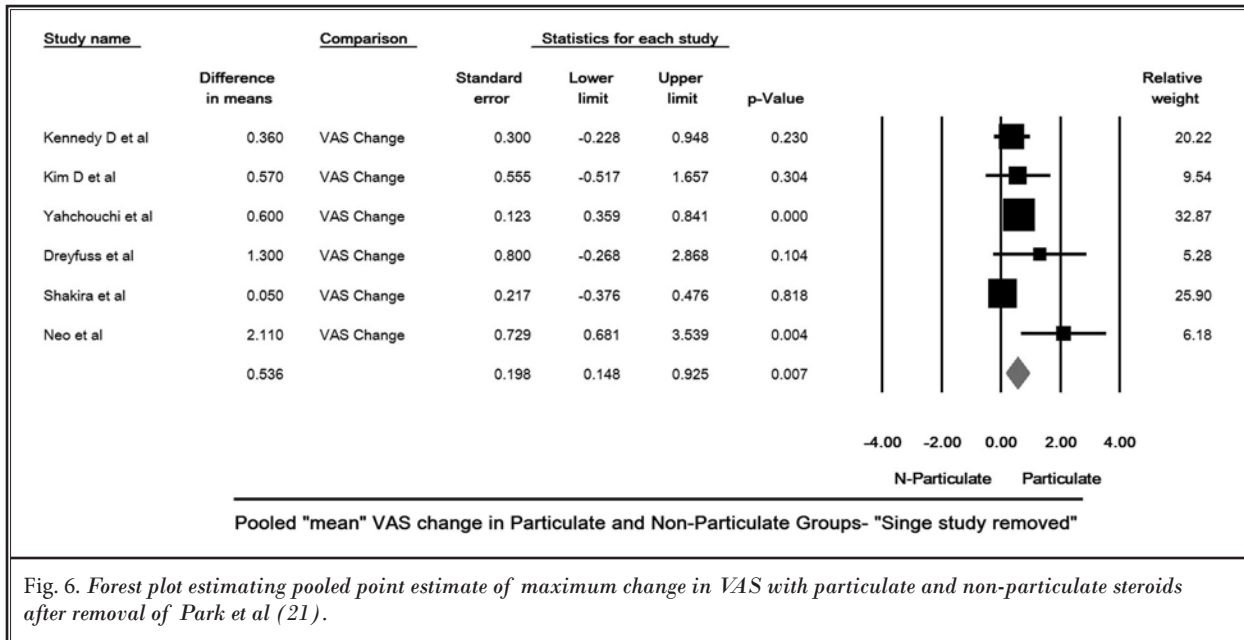


Fig. 6. Forest plot estimating pooled point estimate of maximum change in VAS with particulate and non-particulate steroids after removal of Park et al (21).

Additionally, in order to explore the heterogeneity a meta-regression evaluating contribution of types of non-particulate steroids was also tried without success due to the small number of studies with individual subsets (less than 10) after using type of steroid as the moderator variable.

**Publication Bias**

Funnel plot analysis was conducted. The graphical funnel plot of the included studies for fall in VAS score appeared to be symmetrical (Fig. 7). The publication bias was further quantified using the Egger’s test. The intercept was found at 2.287 (P = 0.247). Hence a significant publication bias is unlikely for the drop of VAS score.

Similarly, the funnel plot for studies reporting frequency of patients with > 50% relief was constructed and evaluated using the Egger’s test. Intercept was found at 3.24 (P = 0.048) (Fig. 8), hence publication bias is likely. It implies that studies showing higher frequency of patients with > 50% pain relief in the particulate group are likely to have been preferentially published in the presently available scientific literature.

**Risk of Bias and Assessment of Quality of Evidence**

Risk of bias was assessed using Cochrane criterion (Fig. 9). The systematic review and quality of evidence was assigned based on best evidence synthesis. The

meta-analysis as per ASIPP grading is best categorized into Level II evidence, as out of 7 trials only 2 studies are moderate to high quality randomized controlled trials and other 5 trials are retrospective studies.

**DISCUSSION**

This systematic review and meta-analysis was conducted to evaluate the efficacy of non-particulate steroids with particulate steroids in patients receiving epidural steroid injections for back pain. Results showed that use of particulate steroids was associated with only a small (8%), though statistically significant, decrease in VAS as compared to baseline VAS of 5 – 6. Our systematic review of 7 trials revealed Level II evidence, as only 2 studies were moderate to high quality randomized controlled trials, 2 were low to moderate quality, and 3 trials were retrospective studies. Further, data were insufficient to conduct the meta-analysis on the safety profile of the particulate and non-particulate groups.

Kim et al found a smaller mean decrease in VAS for the non-particulate group (-19.7%) versus the particulate group (-27.2%) (23). Similarly Dreyfuss et al and Kennedy et al showed greater improvement with the use of particulate steroids (24,32). Although all these studies showed trends favoring the particulate steroids, neither of the studies could demonstrate statistical significance. Park et al (21) was the only study which showed statistically significant improvement in VAS scores with triamcinolone compared to dexamethasone.



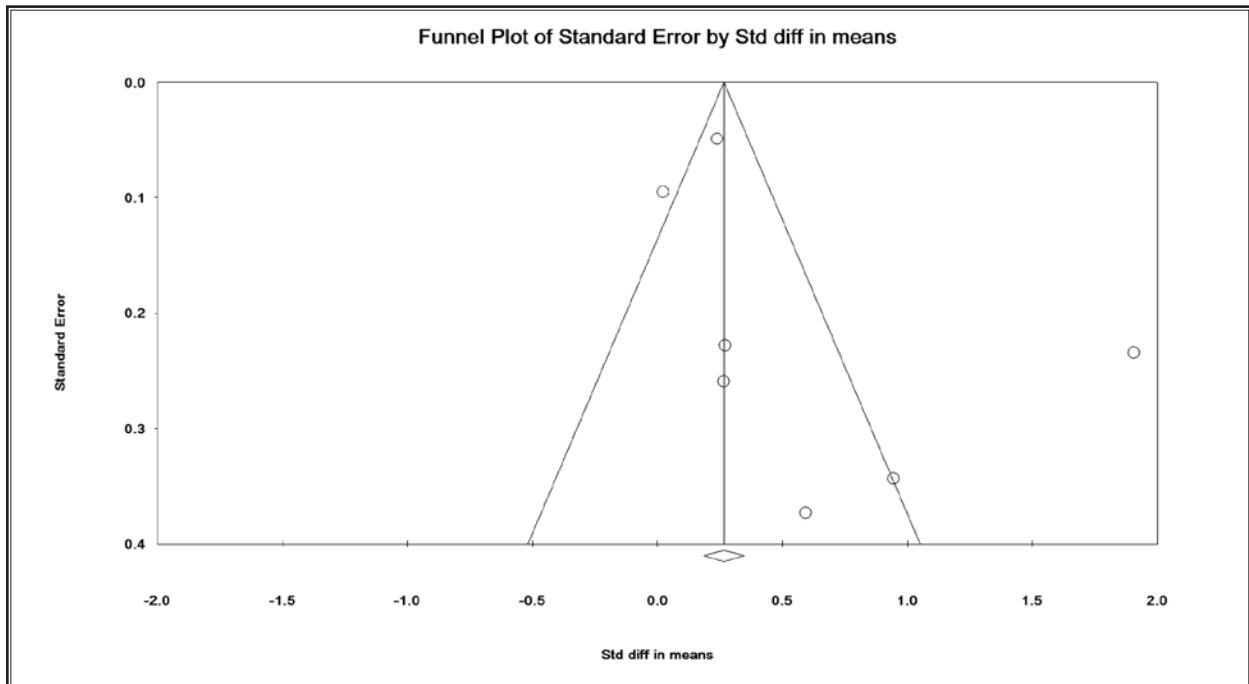


Fig. 7. Graphic funnel plot of the included studies depicting change in VAS score.

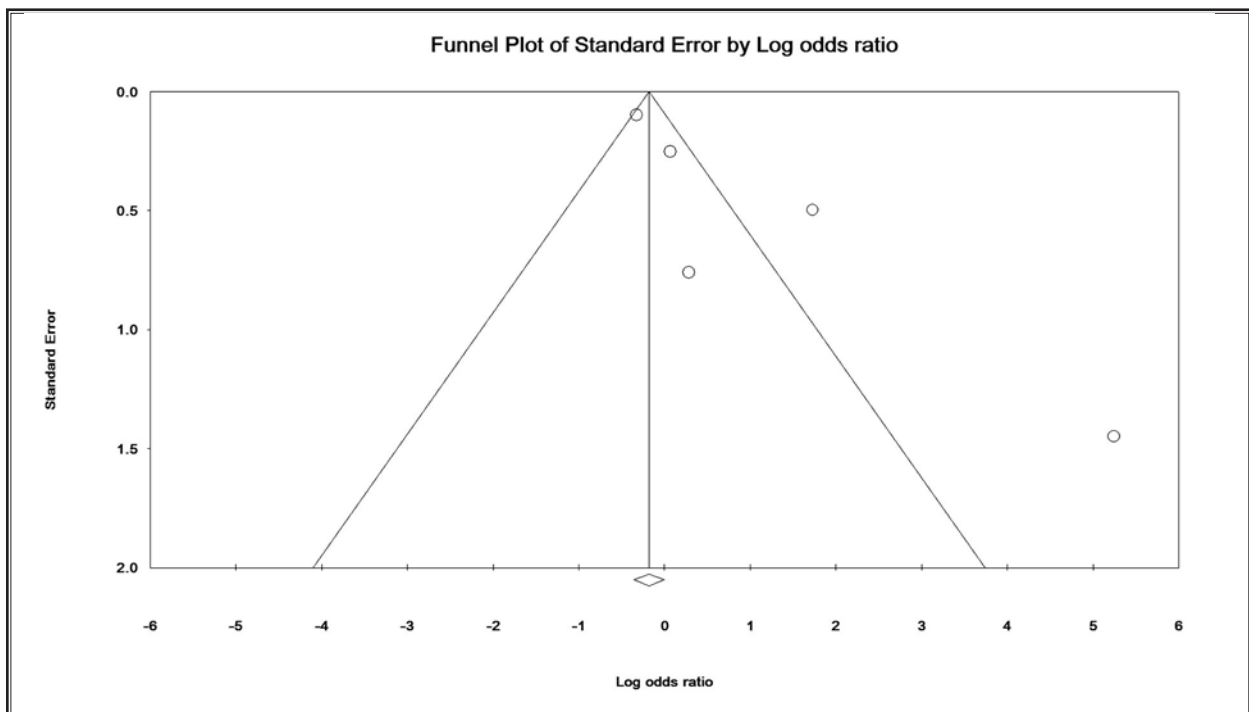


Fig. 8. Graphic funnel plot of the included studies reporting frequency of patients with > 50% relief.

Although this difference in values may seem advantageous at first glance, one must consider its clinical relevance. This increased pain relief of merely VAS score of 1 comes at a price of patient safety. Unfortunately, trials comparing outcomes of particulate versus non-particulate steroids have been limited, with inconsistent safety outcomes (21-24,31-33). Out of 7 studies enrolled, only a single trial of 60 patients receiving dexamethasone or methylprednisolone in lumbar translaminal epidural injection recorded complications (23). On the other hand, the literature is replete with multiple isolated case reports of adverse events. This becomes important in the light of increasing numbers of complications like paralysis, stroke, and even death, which are actually debilitating and often irreversible following

the use of particulate steroids (38-42).

These rare, but potentially devastating, complications of epidural steroid injections have an undefined incidence rate because clinical trials generally have not been well designed and epidemiologic safety data have not been routinely collected (44). In the absence of trials designed to detect rare adverse events due to epidural steroid injections, some useful data have come from a national survey of physician members of the American Pain Society (APS) (43). Of 1,340 surveyed physicians, 21.4% responded, revealing 78 total epidural steroid injection complications in patients receiving cervical transforaminal epidural steroid injections. Serious complications included 16 brain infarcts, 12 spinal cord infarcts, and 2 combined brain/spinal cord infarcts; death occurred in 13 cases. Corticosteroids were used in 70 of the cases with reported complications. The reported corticosteroids included triamcinolone, betamethasone, and methylprednisolone, which were associated with 10%, 11%, and 79% of complications, respectively.

This concern had prompted the Federal Drug Administration (FDA) to review cases in the FDA Adverse Event Reporting System (FAERS) database and in the medical literature. In a recent FDA Drug Safety Communication, the FDA has contraindicated the use of epidural steroid injections through the transforaminal route for cervical pain (44). However, particulate steroids could be used for lumbar transforaminal epidural steroid injections as the transforaminal area in this region is wider than in the cervical region. Further, it has been seen that injuries following non-particulate injections were temporary, whereas paraplegia after particulate steroids were permanent. Therefore, non-particulate steroids (e.g., dexamethasone) should be used for the initial injection in lumbar transforaminal epidural injections.

Another reason postulated for the high incidence of complications is inappropriate needle positioning. Several studies suggest that the incidence of inappropriate needle position may be as high as 30% when lumbar epidural steroid injections are placed blindly using the loss of resistance to air technique. This can result in a variable treatment success rate. So to

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Dreyfuss et al 2006	+	+	-	+		+	-
Kennedy et al 2014	-		+	+	+	+	+
Kim et al 2010	+	+	-	+		+	+
Noe et al 2003	-	-	-	-			-
Park et al 2010	+	+	-	-			-
Shakir et al 2013	-	-	-	-	-	-	
Yahchouchi et al 2013	-	-	-	-	-	-	

Fig. 9. Risk of bias assessment.

increase the validity of our results, we restricted our inclusion criteria to studies that involved administration of epidural steroids using a fluoroscope (45,46).

A study that enrolled 163 patients to receive methylprednisolone, triamcinolone, or dexamethasone in the epidural space for pain relief for sciatica associated with lumbar disc herniation was excluded as the authors used a blind technique to locate the space (47).

We analyzed maximum change in VAS irrespective of the time period as the primary end point as our target was to analyze best possible pain relief reported with use of both particulate and non-particulate steroids. There are limited studies with direct comparisons between particulate and non-particulate steroids and more so show a wide variability in outcome assessment. The majority of the included trials in the analysis evaluated change in pain scores as the primary outcome, therefore change in VAS as the primary outcome increased the generalizability and decreased the heterogeneity. Data were available for 4 studies at one month, one at 2 months, and one at 6 months. In the present meta-analysis various factors could have contributed to the heterogeneity. Variation in pain rating scales in the different trials mandates conversion of different pain-rating scales increasing the heterogeneity. However previous studies have consistently determined that there is a high correlation between pain-rating scales, and scores derived from different scales are often combined in meta-analyses, including those evaluating epi-

dural steroid injections (48,49). Techniques of injections and dosage of the steroid used suffer significant variations from center to center. Debating this point, recent reviews have concluded that minor variations in practice are likely to have no significant effect on outcome (42,44). For example, increasing the particulate-steroid dose of more than 40 mg appears to provide no added benefit. But the conglomeration of these different factors (e.g., injection type and number, dose, volume) may have a cumulative effect.

As a result the heterogeneity in the initial evaluation was 90.59%. The above likely variation is further highlighted by the fact that the removal of a single study by Park et al (from South Korea) (21) lowered the heterogeneity to a moderate level of 50.02%.

Although there are no standard guidelines regarding the minimum number of studies needed to perform a meta-analysis, analyses of limited trials do exist and generally agree with longer-term results.

To conclude, there is limited evidence in literature comparing particulate and non-particulate steroids for epidural injection, more so with regard to the evaluation of complications. The available literature suggests that particulate steroids offer a slightly better VAS as compared to non-particulate steroids and clinicians need to weigh the advantage offered by this small difference with the complications reported in the literature with use of particulate steroids.

*Appendix 1. Sources of bias.*

A	1. Was the method of randomization adequate?	Yes/No/Unsure
B	2. Was the treatment allocation concealed?	Yes/No/Unsure
C	Was knowledge of the allocated interventions adequately prevented during the study?	
	3. Was the patient blinded to the intervention?	Yes/No/Unsure
	4. Was the care provider blinded to the intervention ?	Yes/No/Unsure
	5. Was the outcome assessor blinded to the intervention ?	Yes/No/Unsure
D	Were incomplete outcome data adequately addressed?	
	6. Was the drop-out rate described and acceptable ?	Yes/No/Unsure
	7. Were all randomized participants analysed in the Group to which they were allocated?	Yes/No/Unsure
E	8. Are reports of the study free of suggestion of selective outcome reporting?	Yes/No/Unsure
F	Other sources of potential bias:	
	9. Were the groups similar at baseline regarding the most important prognostic indicators?	Yes/No/Unsure
	10. Were co-interventions avoided or similar?	Yes/No/Unsure
	11. Was the compliance acceptable in all groups?	Yes/No/Unsure
	12. Was the timing of the outcome assessment similar in all groups?	Yes/No/Unsure

*Appendix 2. ASIPP grading of evidence.*

Level I	Evidence obtained from multiple relevant high quality randomized controlled trials or Evidence obtained from multiple high quality diagnostic accuracy studies
Level II	Evidence obtained from at least one relevant high quality randomized controlled trial or multiple relevant moderate or low quality randomized controlled trials or Evidence obtained from at least one high quality diagnostic accuracy study or multiple moderate or low quality diagnostic accuracy studies
Level III	Evidence obtained from at least one relevant moderate or low quality randomized controlled trial study or Evidence obtained from at least one relevant high quality non-randomized trial or observational study with multiple moderate or low quality observational studies  Or Evidence obtained from at least one moderate quality diagnostic accuracy study in addition to low quality studies
Level IV	Evidence obtained from multiple moderate or low quality relevant observational studies or Evidence obtained from multiple relevant low quality diagnostic accuracy studies studies or Evidence obtained from multiple relevant low quality diagnostic accuracy studies
Level V	Opinion or consensus of large group of clinicians and/or scientists.

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