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The role of systemic steroids in the symptomatic treatment of herniated lumbar disks: A Systematic Review and Meta-Analysis

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The role of systemic steroids in the symptomatic treatment of herniated lumbar disks: A Systematic Review and Meta-Analysis

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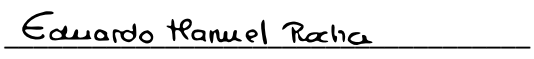
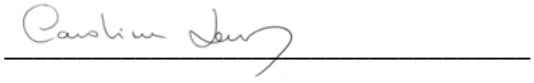


Assinatura do Estudante

Assinatura do Orientador



Assinatura do Coorientador

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Index of abbreviations

NRS = Numeric Rating Scale

ODI = Oswestry Disability Index

RCT = Randomized Clinical Trial

RM-q = Rolland-Morris questionnaire

SD = Standard Deviation

SLR = Straight leg raise

StdMd = Standard Mean difference

VAS = Visual Analogue Scale

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Resumo

Introdução: A dor radicular provocada pela compressão das raízes nervosas lombares é uma queixas frequente na prática clínica. Apesar do aumento da prescrição de corticosteroides existe pouca evidência e alguns resultados conflituosos, acerca da sua eficácia por via parentética.

Objetivos: Realizar uma revisão sistemática com meta-análise, no intuito de atualizar a evidência relativa ao uso de corticosteróides sistémicos no tratamento sintomático da dor radicular em comparação com outros tratamentos ou placebo.

Métodos: Foi realizada uma pesquisa sistemática das bases de dados da Pubmed, Scopus, assim como da Cochrane Central Registers, focando apenas nos artigos referentes à Embase. Foram usados MeSH terms (Pubmed e Cochrane) e palavras-chave (Scopus). Foram eliminados todos os estudos que documentavam uso de glucocorticóides com via de administração não sistémica, assim como estudos que envolviam menores de 18 anos ou pacientes com antecedentes de cirurgia à coluna lombar. Para o *pooled-effect* das diferenças médias ponderadas e *odds ratio*, um *random-effect* foi usado, compensando a elevada heterogeneidade entre os estudos.

Resultados: Foram incluídos 10 estudos randomizados. Os grupos foram considerados comparáveis para todas as caraterísticas após randomização. No período de follow-up, houve diferença significativa para duas correlações envolvendo o Oswestry Disability Index (p=0,017 e p=0,008), assim como para a melhoria a curto prazo (p=0,004) mostrando menor incapacidade no grupo tratado com corticosteróides. Adicionalmente, a incidência de efeitos adversos foi estatisticamente distinta entre os grupos, sendo estes mais frequentes no grupo dos corticosteróides (p<0,001).

Conclusão: À exceção de um score de incapacidade física e da prevalência de melhoria a curto prazo, a favor dos corticosteróides, nenhum estudo apresentou diferença significativa entre os grupos. Tendo em consideração a elevada incidência de efeitos adversos, o uso de corticosteroides sistémicos deverá ser restrito a pacientes com sintomas debilitantes, assim como a outras sintomatologias, desde que agudas e subagudas. A prescrição deve ser individualizada e com discussão dos diferentes efeitos secundários possíveis.

Recomendações: São necessários mais estudos randomizados, com maiores amostras, priorizando a inclusão de métodos de avaliação já reportados por estudos anteriores. Será também relevante a correlação entre a dose de corticosteroides administrada, melhoria dos

diferentes scores e a incidência de efeitos adversos. Para tal, é recomendada a criação de estudos com múltiplos grupos, equiparando diferentes dosagens de corticosteroides a placebos, procurando, perante superioridade a favor do tratamento em causa, a dosagem mais eficaz e com o menor número de reações adversas.

Palavras-Chave: Dor ciática; Radiculopatia; Protusão do disco intervertebral; Degeneração do disco intervertebral; esteróides; corticosteróides.

Abstract

Introduction: Radicular pain originating from lumbar nerve root compression is a frequent complaint seen in clinical practice. Despite the increasing prescription of corticosteroids, there is a lack of scientific evidence, as well as some conflicting results, on the efficacy of their systemic administration.

Objectives: The primary purpose of this systematic review and meta-analysis was to update the existing evidence on the efficacy of systemic steroids on the symptoms and consequences of radicular pain compared with other available treatments or placebos.

Methods: A systematic search of Pubmed, Scopus, as well as the Embase's content of the Cochrane Central Register for randomized controlled trials was conducted. MeSH terms (for Pubmed and Cochrane) and keywords (for Scopus) were used. Studies reporting non-systemic steroid use were excluded, as well as pediatrics and previous history of spinal surgery. Due to high heterogenicity among studies, random-effect standardized mean differences and odds ratios were used.

Results: Ten randomized clinical trials were included. Post-randomization groups were comparable for all tested baseline parameters. Regarding the follow-up, there was a statistically significant difference in the Oswestry Disability Index improvement, with the two comparisons favoring a lesser degree of disability in the steroids group (p=0,017 and p=0,008). A significant difference was also found in the short-responders rate (p=0,004). Adverse events were significantly higher among the treatment group (p<0,001). All other correlations lacked significance.

Conclusion: Except for one disability score and the short-term responders rate, favoring the steroid patients, all the evidence leans towards a neutral effect of corticosteroids in the treatment of radicular pain from lumbar nerve root compression. Combined with a higher incidence of side effects, the use of systemic steroids in clinical practice should only be administered to patients with debilitating or acute to subacute symptomatology, after individual assessment and possible side-effects discussion.

Recommendations: More randomized clinical trials are needed for a more conclusive evidence-based approach to radicular pain. Future studies should use some of the higher sample trials here included as a guide, focusing on measuring the same outcomes with similar time-frames to

those already published. To measure the relation between steroid dosage and outcome improvements, as well as the incidence of adverse effects, studies should create multi-group randomizations, comparing different dosages of corticosteroids with placebos. If superiority is found, this comparison would aim for the safest, while effective steroid dosage.

Keywords: Sciatica; Radiculopathy; Intervertebral disc displacement; Intervertebral disc degeneration; Steroids; Glucocorticoids.

Introduction

Radicular pain originating from lumbar nerve root compression is a frequent clinical syndrome, with an annual incidence between 2 and 14%.[1, 2] The key clinical feature of this disorder, radicular pain, frequently associated with acute or chronic low back pain, is characterized by unilateral leg pain with or without sensory or motor impairment loss symptoms. The radiating symptoms, which often follow the nerve root dermatomal distribution, can include numbness, sharp pin or needle-like pain, as well as shock complaints, targeting the posterior and lateral portions of the leg, ankle, and foot.[3, 4] A straight leg raise test can frequently replicate the patient's discomfort.[5]

The most common cause is rupture of the anulus fibrosus, resulting in intervertebral lumbar disc herniation, compression and irritation of the nerve,[4, 6] having a considerable incapacitating impact on the quality of life, being responsible for work absenteeism and impairing patient's physical and mental health.[7, 8]

Analgesic drugs are often prescribed for conservative treatment, particularly nonsteroidal anti-inflammatory drugs, opioids, antidepressants, and muscle relaxants, as well as systemic steroids.[9, 10] The use of corticosteroids in the clinical management of sciatica has been rising, mainly due to its anti-inflammatory effect, counteracting the cytokines released by the irritated nerve root.[11, 12] Most studies regarding steroids in the symptomatic treatment of radiated radicular pain focus on epidural, peri-neural or intra-articular routes of administration.[13, 14] Nevertheless, there is a lack of scientific evidence, as well as some conflicting results, on the efficacy of systemic corticosteroids (oral, intramuscular and intravenous), frequently used as empiric treatment of sciatica for its easier administration method[15]. Roncoroni et al[15] published, in 2011, a systematic review and meta-analysis on the efficacy of this group of drugs on radicular pain secondary to lumbar root compression, concluding that further studies were needed to achieve a more concrete and objective evaluation. Since then, corticosteroids have continued to be used, with a few more studies adding to the knowledge of their effect on radicular pain.

The primary purpose of this systematic review and meta-analysis was to update the existing evidence on the efficacy of systemic steroids on the symptoms and consequences of herniated lumbar disk compared with other available treatments or placebos.

Methods

Data Search

A systematic search of Pubmed, Scopus, as well as the Embase's content of the Cochrane Central Register for randomized controlled trials was conducted until the 19th of September of 2019. For Pubmed and Cochrane database searches, the following MeSH Terms were used: ('Low Back Pain[MeSH Terms]' OR 'Sciatica[MeSH Terms]' OR 'Radiculopathy[MeSH Terms]' OR 'Intervertebral disc displacement[MeSH Terms]' OR 'Intervertebral disc degeneration[MeSH Terms]') AND ('Steroids[MeSH Terms]' OR 'Glucocorticoids[MeSH Terms]'). The Scopus database was searched with the following terms: ('Sciatica' OR 'Radicular pain' OR 'Radiculopathy' OR 'Discogenic pain' OR 'Lower Extremity Pain' OR 'Herniated Lumbar disk' OR 'Intervertebral Disc Displacement' OR 'Intervertebral Disc Degeneration') AND ('Glucocorticoids' OR 'Corticosteroids' OR 'Steroids' OR 'Methylprednisolone' OR 'Prednisolone' OR 'Dexamethasone' OR 'Betamethasone' OR 'Triamcinolone'), adding (AND NOT DBCOLL (Medl)) to exclude possible duplicates with the Pubmed search, while also restricting the results to articles by applying the integrated filter. All searches were performed from the 7th to the 19th of September 2019, having as a timeframe limit 1 of January 1975 onwards. After an additional hand search for relevant articles and review papers, no additional titles were found. After all the titles were retrieved, a systematic and eliminatory selection was performed, starting with the title, then abstract, ending with a full-text review for final eligibility (Prisma flow diagram 2009[16]). If an article couldn´t be found, an attempt to reach the author was made. A lack of response from the author meant the exclusion of that article.

Inclusion and Exclusion Criteria

Only Randomized Clinical Trials were eligible. Additionally, the inclusion criteria were: (1) Humans with at least 18 years old ; (2) Systemic steroid administration (oral, intravenous bolus or intramuscular); (4) Explicit reports of patients suffering from radicular pain; (5) evaluation of the efficacy of the treatment. Failure to meet these criteria implied exclusion. Also, patients who had comorbidities that could mimic lumbar disc herniation symptomatology, such as nerve root compression by a spinal tumor, were excluded, as well as those who had a history of spinal surgery. Epidural, transforaminal and nerve block injections were eliminated, unless they were compared with the systemic use of a steroid. Other eligible comparisons included placebo or conventional/conservative treatment.

Quality assessment

To preserve the quality of the review, as aforementioned, only RCTs were included. All eligible articles were evaluated using the PEDro Score. This score measures and ranks clinical trials by their methodological quality. Using a non-redundant 10-item checklist, it ranges from 0 (lowest quality) to 10 (highest quality). Papers with 6 or more points are considered of good or excellent quality, suggesting a higher internal validity[17, 18]. Although not being an inclusion criteria, 9 of the 10 selected studies scored 7 or higher.

Data Extraction

All the objective information of each study was extracted, including but not exclusive to patients demographics (sample size, age, and gender), symptoms, follow-up duration, treatment parameters (interventional administration route, dosage and treatment length, additional therapies), withdrawals and completers. Relevant information also included the quality of life at baseline, post-treatment, and follow-up. Data on adverse events, need for surgery post-intervention and the number of responders was also collected and analyzed. The study design, randomization, and blinding procedures were also searched to complete the aforementioned PEDro score.

Outcomes

The efficacy of the treatment was evaluated using the Visual Analogue Scale and the Numeric Rating Scale of pain, the absence of pain on a straight leg raise test, improvement of the sensory findings, change in Oswestry Disability Index or Roland Morris questionnaire disability scales, the need for relief medication, as well as the ability to return to full-time jobs, the incidence of surgery post-intervention or adverse events during therapy.

Statistical Analysis

Treatment and control raw data for each outcome were converted into the same scale, giving preference to 0-10 and 0-100 scores. The duration of pain was converted into days. As such, for functional comparison of some outcomes, the score of the Rolland-Morris questionnaire was converted into a 0-100 score. To compare the RM-q with the SF-36 health survey, the range of the RM-q was converted into a 0-100 scale and inverted (highest being the least disabled)[19]. For the purpose of comparing the different steroid dosages for each RCT, they were standardized using the steroid's natural dosage equivalency[20, 21].

In order to overcome some of the missing data, such as the standard deviation or confidence interval data, a z-score was used, or a t-score based estimation when the sample size was smaller than 30. Chi-square values were used to assess heterogeneity among groups. Due to the high heterogeneity of the sample distribution by treatment or control groups (I^2=84,841 and p<0,001), a random-effects model was chosen, correcting the difference to I^2=0 and p-value=0,441[22]. For all statistics, a confidence interval of 95% was used, with a p- value <0,05 considered as statistically significant. Microsoft Excel was used to estimate the main descriptive statistics. Pooled-effect weighted means and forest plots were computed with the Comprehensive Meta-Analysis software® v3 (Biostat, Inc.).

Results:

Eligible RCTs

As shown in the Prisma flow diagram[16] (Figure 1), the initial search retrieved 2570 potentially relevant studies. Thereafter, a systematic review of each title and/or abstract scaled the search down to 81 potential candidates for full-text eligibility triage. Although potentially relevant, 24 articles (0,93%) could not be found despite an attempt to reach the author. The following systematic review included 10 randomized clinical trials[21, 23-31].

The methodological quality of the studies was measured using the PEDro score (Table I). The average quality assessed was 7,7 (SD=1,42; OR=1,004 (0,504 to 1,999); I^2=0 and p=0,991). All studies had a random allocation, while only 60% (6/10) concealed their randomization. For group similarity at baseline, the sample was reported statistically non-significant in 50% of the trials, although only 60% (3/5) had p-values supporting the presented findings. Two additional studies (2/10) were similar for all but one parameter. When conferring for blindness, participants and assessors were blinded in 9 of the 10 trials for both, while therapist blinding was noted in 80%. Eight of the studies had less than 15% of sample drop-out, and 50% of the RCTs had an intent to treat analysis. Between-group difference was reported in 9/10 trials. 30% of the studies failed to report point estimate and variability.

Steroids were administered orally in three of the included trials[25, 28, 30], and parenterally, either by intramuscular (four trials[21, 23, 24, 27]) or by intravenous injection (three trials[26, 29, 31]). The steroid dosages were standardized for dexamethasone potency equivalence[20] (Table II), and ranged from 8 mg[29] to 156 mg[23], averaging 84,19 mg per trial (SD=53,56; OR=0,757 (0,0446 to 1,285); I^2=39,878 and p=0,302). A detailed description of each RCT treatment protocol is displayed in Table III.

Demographic characteristics

The studies reviewed had a total of 1018 patients (548 in the treatment group, 462 in the control group and 8 lost before randomization). There was a mean of 101,8 (SD=93,5) participants per trial, ranging from 29[28] to 300[31] individuals, with 52,3% of the sample allocated to the steroid group. The total sample in each study and the number of patients in the post-randomization groups were statistically comparable (p=0,316 and p=0,441, respectively). The largest difference was reported on Goldberg et al.[30] (67,3% in the steroid group). Balakrishnamoorthy et al.[29] and Wang et al.[31] had an even distribution, with 50% in each group. The total sample gender was

reported in eight of ten studies, with an average of 41,7% of females (lowest prevalence being 30,8%[21, 23], and highest being 52,4%[27]). When comparing for each group's gender, there was a non-significant difference, with 47,7% of female patients in the steroid group and 43,5% in the placebo group (OR=1,131; I^2=0 and p=0,383). The major difference between each study group was 22,4% in the trial by Hedeboe et al[24] (47,37% of females in the steroid groups, compared to 25% on the control population). Conversely, Porsman et al[23] had the narrowest ingroup difference reported, of 1,33% favoring the control group (32% and 33,33% in the steroid and placebo groups, respectively). Age was reported in 6/10 trials, with a mean of 43,4 years (SD=3; lowest of 38[29] and highest of 47 years[21], with p=1,00). When subcategorizing for each treatment group, the steroid sample averaged 43 years (SD=3,66), 1,9 years less than the control (StsMd=0,042; I^2=12,703 and p=0,688). The largest difference was reported on Holve et al[28], with the control group being older by 6,33 years (mean of 45,64 years). The smallest divergence, of 1 year more in the steroid group, was documented by Wang et al[31] (mean placebo age of 41 years). The baseline characteristics aforementioned are shown in Table IV.

Duration of symptoms was heterogeneous across the studies (Table III), being reported in 8 out of ten. 37,5% of the trials (3/8) included patients whose symptoms had started within one week[26-28], while other trials accepted patients symptomatic for various time periods, from less than three or six months, to as long as 36 months. Three studies[26, 27, 30] were comparable by treatment groups, with a pain onset varying from 2 to 29,7 days, in the steroid group, averaging 15,57 days between the RCTs and from 2 to 31,7 days in the control sample (mean of 16,23 days). Only Goldberg et al[30] reported a difference between the steroid and the control group, being 2 days higher on the latter. The duration of pain among these three studies was considered comparable at baseline (StdMd=-0,059 (-0,262 to 0,144); I^2=0 and p=0,568), shown in Figure 2 (A).

Table IV summarizes each trial baseline and follow-up outcome measurements. Prior to treatment, the spinal level of nerve root compression was comparable in 30% of the RCTs[23, 26, 31]. The L4 nerve root, reported by Finckh et al[26] and Wang et al[31] was considered the origin of the radicular pain on an average of 8,83% of the patients, while L5 and S1, documented alongside with Porsman et al[23], had a frequency of 52,4% (40,38 to 66,67) and 36,5% (17,33 to 53,85), respectively. The effort of each patient's work pre-intervention (light, moderate or heavy) was reported by Hedeboe et al[24] and Porsman et al[23] Heavy work was seen, on an average of 39,1% of the population, moderate effort in 36,6% and light type of work in 24,31%. In Porsman et al[23], most patients were classified as heavy workers (55,1%), while most of

Hedeboe's et al[24] patients were categorized as moderate workers, being the heavy work the least prevalent effort.

Disability and pain at baseline

At baseline, passive SLR pain was comparable in 40% of the studies[25, 26, 29, 30]. Two[25, 30] described the pain prevalence, averaging a positive result in 79,51% of the population. The difference between groups was 23,01% larger in the steroid population (64,77% for the control group), with Haimovic et al[25], reporting a value of 40,48%, compared to 5,54% of Goldberg et al[30]. SLR angle was measured by Finckh et al[26] and Balakrishnamoorthy et al[29], favoring a higher degree of limitation (lower angle of movement without pain) among the steroid group, although without a statistical significance, as shown in Figure 2-B (StdMd=-0,317 (-0,680 to 0,047); I^2=0 and p=0,088). Neurologic deficits were reported in 2 studies[25, 26], with an approximate value of 62,58%, differing by 0,83% (63,90% for the steroid group versus 63,07%). 15,24% of the patients had motor weakness in 20% of the RCTs[21, 30]. Both studies had a higher percentage of motor impairment in the control group, averaging a 2,56% difference. Nonsteroid anti-inflammatory drugs prescription was measured and comparable in Finckh et al[26] and Wang et al[31], with 14,33% reporting intake. In between groups difference was 0,5, with both studies reporting non-significant p-values (0,88 and 0,759, respectively).

Regarding the degree of disfunction, the ODI was measured using data from three trials[26, 29, 30], having a non-significant difference and, therefore, being comparable at baseline (StdMd=-0,03 (-0,211 to 0,205); I^2=0 and p=0,980) (plot C in Figure 2). In addition, two RCTs[30, 31] were correlated, without significant difference (StdMd=-0,078 (-0,247 to 0,091); I^2=0 and p=0,368), using the SF-36 healthy survey and the RM-q (Figure 2, plot D). 40% of the trials reported the overall pain using either the VAS or the NRS scales. Both scores were considered non-statistically different before treatment between the steroid and the control groups - (StdMd=0,2 (-0,041 to 0,441); I^2=7,617 and p=0,104)[26, 27, 29, 31] and (StdMd=0,036 (-0,17 to 0,243); I^2=0 and p=0,731)[26, 31], respectively. Due to their recognized correlation[32], VAS and NRS scores were merged and computed (Figure 3, plot A). Although the mean weighted effect appears to favor the treatment group, it lacks significance (StdMd=0,142 (-0,024 to 0,307); I^2=0 and p=0,093). VAS leg pain, shown in Figure 3-B and compared using data from Finckh et al[26] and Goldberg et al[30], was statistically non-different at baseline (StdMd=0,148 (-0,354 to 0,226); I^2=0 and p=0,665).

Outcomes at follow-up

Table III details follow-up duration for each study. During the follow-up period, the RM-q was scored by two trials, with Friedman et al[27] choosing the one month post-treatment timeframe, and Wang et al[31] measuring both at the 2nd and 8th weeks. The effect direction of these two comparisons, towards the control group, can be seen in Figure 4 (A and B), having both a similar non-significant difference among study groups (StdMd=-0,14 (-0,342 to 0,062); I^2=0 and p=0,174) and (StdMd=-0,23 (-0,56 to 0,1); I^2=0 and p=0,171). Figure 4-C shows an additional correlation for functional comparison, assessed with the ODI[29] (6 weeks), RM-q (1st month for Friedman et al[27] ; 8th week for Wang et al[31]) and SF-36[30] scores, which was considered non-significant (StdMd=-0,064 (-0,396 to ,269); I^2=0 and p=0,708). VAS pain post-intervention was reported by Balakrishnamoorthy et al[29] at the 6th week and by Wang et al[31] at the 2nd and 8th weeks. When comparing the first study with the second week of the latter, a non-significant effect direction towards the steroid group was observed (StdMd=0,166 (-0,259 to 0,592); I^2=0 and p=0,443), while at the 8th week post follow-up, the mean difference favored the control group (StdMd=-0,2 (-0,414 to 0,015): I^2=0 and p=0,068). Regarding the NRS score, two RCTs measured this outcome (1st month for Friedman et al[27]; 2nd and 8th week for Wang et al[31]). Both comparisons (1st month of the former versus week 2 and 8 of the latter) had a neutral effect direction (StdMd=-0,04 (-0,849 to 0,769); I^2=0 and p=0,923) and (StdMd=0,011 (-0,689 to ,712); I^2=0 and p=0,974) respectively. As shown in Figure 5-A, the data retrieved from both the VAS and NRS scales were compared in order to measure the global pain mean difference at a subacute time-frame (1 month[27], 6 weeks[29] and 8 weeks[31]). Although favoring the placebo, as for the highest overall pain score, the difference was non-significant (StdMd=-0,119 (-0,39 to 0,153); I^2=17,484 and p=0,392).

Improvements

For measuring the improvement, the VAS scale, ODI, SF-36 and RM-q were used. Pain reduction, presented in Figure 5-B, was measured using the follow-up at the 6th week from the Balakrishnamoothy et al[29] trial and at the 8th week from Wang et al[31]. Despite favoring the steroid's group, the weighted mean difference obtained was not significant (StdMd=0,096 (-0,254 to 0,445); I^2=0 and p=0,592). Additionally, the frequency of pain improvement was also reported by Goldberg et al[30] and Finckh et al[26], which had an overall VAS reduction of 20 or more (0-100) scale. This outcome seems to favor the steroid group, with the control group differencing 11,53% less (treatment group average reduction of 57,71%). In regard to a more functional comparison, the improvement on the ODI mean differences was documented and correlated

using the 6th week follow-up data from Balakrishnamoorthy et al[29] and the 3rd and 52nd week from Goldberg et al[30]. For both outcomes (Figure 6 A and B), the reduction in the ODI score was statistically significant, favoring a higher improvement in the steroid's group (StdMd=0,292 (0,053 to 0,531); I^2=0 and p=0,017) and (StdMd=0,344 (0,091 to 0,598); I^2=0 and p=0,008). Figure 6-C and 6-D show a disability reduction comparison using the ODI[29], SF-36[30] and RM-q[31] at the (6th, 3rd and 2nd weeks, respectively) and (6th, 52nd and 8th weeks, respectively). Both had no statistical difference, p=0,819 and p=0,822.

Completers

Table V presents individual details of completers, surgical intervention and adverse effect rates. The incidence of completers at the end of the follow-up was comparable, averaging 90,6%, with three RCTs reporting 0% of drop-outs[21, 24, 31] (OR=0,981; I^2=0 and p=0,945). The highest prevalence of reported drop-outs was 37,9%[29]. When comparing both groups, there was a higher percentage of completers favoring the control group by 2,03% (steroid's with 89,18%). Only Balakrishnamoorthy et al[29] had more completers in the steroid group than the control, exceeding by 13,79% (placebo's with 55,17%). During follow-up, post-study surgical intervention was disclosed in 60% of the trials[23-26, 28, 30]. As shown in Figure 7-A, there was a non-meaningful superiority in the steroid's group (p-value=0,418), differing by 7,1% (24,76% in the treatment group). Furthermore, 25,51% of the initial participants had required intervention. Of the 10 initial studies, 60% had information regarding the number of responders post-intervention. Due to the high heterogeneity of the information disclosed, the comparison required their subcategorization in two periods, within three weeks (short-term) and between 3 months to a year (long-term), as presented in Figure 7, plots B and C. As such, short-term responders were seen on average in 51,19%[23-26, 30] of the sample (33,33 to 77,90%), compared to 48,42%[24, 25, 30] with late improvement (25,64 to 89,32%). Among groups, the steroid's, with a 63,6% average early responder rate, had a meaningful 11,56% difference against the 52,04% of the control sample (OR=1,909; I^2=1,158 and p=0,004)[21, 23-26, 30]. The same difference on late responders equaled 4,06% more for the treatment sample, although not significant (46,35% for the placebo group; p=0,224)[24, 25, 30]. The early responders ranged from 33,33 to 97% in the steroid group, and from 27,59 to 88% in the non-treatment group, while on the late responders the same rates varied from 28,57 to 91,08% and from 20 to 85,71%, respectively. Hedeboe et al[24] had the widest difference between groups in both early and late periods, being of 33,42% and 11,58%, respectively, favoring the treatment group. The least difference was reported by Haimovic et al[25], having no difference in the early responders and 4,76% less on the steroid's in the late responders. Rate of sample returning to work and to the everyday activities was reported by

Friedman et al[27] and Holve et al[28], with Balakrishnamoorthy et al[29] data contributing for the return do daily life. As such, 34,17% of the trials steroid population returned to work at the 1st and 2nd months, respectively, with the control average being 2,08% higher. As for the return to everyday activities, it favored the steroid group by 2%.

Adverse Events

Adverse events were reported in 70% (7/10)[23, 24, 26, 27, 29-31] of the reviewed RCTs, with 6 being compared Figure 7-D.[23, 24, 26, 27, 30, 31]. The incidence of these effects differed by 10,82% more in the steroid group (control group averaging 10,29%). This discrepancy, favoring the treatment group, was statistically significant, as seen in 7-A (OR=2,812 (1,768 TO 4,474); I^2=0 and p<0,001). The prevalence ranged from 3,33[31] to 49,16%[30] in the steroid group and from 0 to 24% in the control group. The highest differences between steroids and placebo were found by Goldberg et al[30] and Hedeboe et al[24], with a difference of 25,3% and 26,58% more, respectively, in the steroid group. Contrarily, the narrowest difference was found by Porsman et al[23], with an incidence of 0,17% more adverse events in the control sample. When comparing the entire sample (5/10 studies), side effects were reported in 13,68% of the patients, ranging from 1,67%[31] to 39,7%[30] and being non-significantly different among the RCTs (I^2=9,684 and p=0,401). Glucose anomalies, including serum glucose and glycosuria, were documented in 30% of the RCTs[21, 23, 26]. Two[23, 26] were comparable, being more common, although not significant, after steroid administration, with a difference of 5,23% (p=0,23) more in the treatment group. In fact, only Hofferberth et al[21] reported glucose anomalies in the control group, favoring the latter by a difference of 1%. Additionally, there was not a significant difference amidst groups on indigestion and epigastric complaints, reported in 3/10 studies (11,48% for the steroid's versus 5,16%). The average incidence of glucose anomalies and indigestion or epigastric complaints in all studies was of 2,69%[23, 26] and 8,53%[27, 30], respectively.

Discussion

The results of the present systematic review suggest a lack of difference between the administration of steroids versus a placebo or standard treatment. The computed baseline demographic characteristics aforementioned describe a high heterogeneous sample between treated and non-treated groups, proven by the chi-square test, although non-significant regarding their p-values. The different RCTs were comparable for all quantitatively measured data at pre-treatment, including sample size for the trials total sample and individual group's distribution post-randomization, average age and gender, as well as the duration of pain, SLR angle, ODI and the functional comparison with the RM-q and the SF-36 health survey score. As for the pain disclosed at baseline, neither the VAS, NRS, or VAS merged with the NRS scales were significantly different. The same was true for the overall VAS leg pain. Correcting for the sample heterogeneity with random-effect, all tested measurements at baseline were considered fully comparable and homogenous (low chi-square), reducing the likelihood of sample bias. Regarding the descriptive statistics pre-treatment, positive passive SLR had a subjective tendency towards the steroid groups, with the other data, such as prevalence of neurologic deficits or concomitant need for nonsteroid anti-inflammatory drugs, being similar.

With regards to the follow-up outcomes, the ODI improvement and short-term responder rate were statistically different among study groups, having an effect size favoring the use of steroids in the context of radiating radicular pain. While only two studies had the required data for the ODI improvement comparison, having very different timeframes (6^{th} week of follow-up for one study, 3^{rd} and 52^{nd} week for the other), the responder's significance results from the correlation of six trials (Figure 7-B). As such, while there is a significant reduction in the ODI score in the short-term, the long-term effect may be biased by the different follow-up in both studies. This likelihood is lessened by the major mean weight of the latter RCT. As for other improvements, no additional significant discrepancies were found among groups, being equivalent for the overall VAS and NRS pain, as well as for the overall subacute pain reduction. Despite the disability improvement observed in the ODI, the same was not true for the functional comparisons using the isolated RM-q score or the correlation between the ODI, SF-36 and RM-q scores. When analyzing the non-objective outcomes, the overall return to work and return to daily activities have little to no distinction. In spite of the rate of VAS pain reduction (2 or more points out of 10) reported in two trials, it appears to be significantly higher in the steroid groups, lacking a statistical value to corroborate this hypothesis. Although the apparent similarity of drop-outs amidst treated and non-treated groups, the need for post-study intervention surgery

shows a non-significant trend towards the steroid sample, with more patients in the steroid group undergoing post-study surgery. As for the responder rate, short-term improvement, as aforementioned, was statistically meaningful. For the late improvement rate, there was a lack of significance, suggesting a rebound effect, as described by Roncoroni et al[15]. Regarding the adverse events amidst studies, the evidence supports a correlation between the steroid administration and a higher incidence of side-effects.

To provide a sound, evidence-based systematic review with meta-analysis, only RCTs were eligible. Although no clinical trial registries were searched, accepting the possibility of publication bias, no language filters were applied. The initial searches retrieved a significant amount of potentially relevant titles, with few articles unaccounted for. The vast majority of trials included were of high methodological quality, as shown by the PEDro score. This score, found statistically comparable among the studies, was chosen due to its non-redundant high internal validity checklist[17]. Nonetheless, the studies had considerable differences, such as sample size, with some having low sample sizes, heterogenous time-frames for each follow-up evaluation, as well as inconsistent outcome measurement tools. While some studies did report the same outcomes, often they were reported in non-comparable data, such as rates and means for the same outcome. To overcome these discrepancies, the various scores were pooled whenever feasible. No correlation between administration protocol, route or steroid dosage and outcome effect was attempted.

More RCTs are needed for a more conclusive evidence-based approach to radiated radicular pain. Future studies should use some of the higher sample trials here included as a guide, focusing on measuring the same outcomes with similar time-frames to those already published. To measure the relation between steroid dosage and outcome improvements, as well as the incidence of adverse effects, studies should create multi-group randomizations, comparing different dosages of corticosteroids with placebos. If superiority is found, this comparison would aim for the safest, while effective steroid dosage.

To summarize, except for one disability score and the short-term responder rate, favoring the steroid patients, all the evidence leans towards a neutral effect of steroids in the treatment of radicular pain from lumbar nerve root compression. When combined with a higher incidence of side effects, the use of systemic steroids in clinical practice should be restricted. As such, until further evidence, corticosteroids should only be administered to patients with debilitating or acute to subacute symptomatology, after an individual assessment and possible side-effects discussion with the physician.

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Appendix – Tables

Table I – PEDro score for all eligible Randomized Clinical Trials; *p-value not reported; **For all but one parameter;

Study	Random allocation	Concealed allocation	Groups similar at baseline	Participant blinding	Therapist blinding	Assessor blinding	<15% drop outs	Intention to treat analysis	Between group difference reported	Point estimate and variability report	Total (0-10)
Porsman et al[23]	Yes	No	Yes**	Yes	Yes	Yes	Yes	No	Yes	Yes	8
Hedeboe et al[24]	Yes	Yes	Yes**	Yes	Yes	No	Yes	No	Yes	No	7
Hofferberth et al[21]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	8
Haimovic et al[25]	Yes	No	No	Yes	No	Yes	No	No	No	Yes	4
Holve et al[28]	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
Finckh et al[26]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	8
Friedman et al[27]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	9
Balakrishnamoorthy et al[29]	Yes	Yes	Yes*	Yes	Yes	Yes	No	Yes	Yes	Yes	9
Goldberg et al[30]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Wang et al[31]	Yes	No	Yes*	No	No	Yes	Yes	Yes	Yes	Yes	7

Table II – Corticosteroids potency equivalence (using daily physiologic baselines)[20]

Steroid	Dose (mg)
Cortisol	20
Prednisolone	5
Metilprednisolone	4
Triamcinolone	4
Dexamethasone	0.75
Bethamethasone	0.75

Table III – Demographic parameters: Durations and Treatment protocols

Studies	Disease Duration	Follow-up Duration	Drug	Schedule	Administration Route	Dosage	Standardized for Dexamethasone (mg)	Additional treatments
Porsman et al[23]	<6 weeks	9 days	Dexamethasone Sodium Cloride	Each day: 64mg, 32mg, 16mg, 12mg, 8 mg, 8 mg, 8mg Equivalent	Intramuscular	156 mg	156	Bedrest, thermotherapy and physical therapy
Hedeboe et al[24]	<2 weeks to > 8 weeks	12 weeks	Dexamethasone Placebo	Each day: 64mg, 32mg, 16mg, 12mg, 8 mg, 8 mg, 8mg Equivalent	Intramuscular	148 mg	148	Bed rest and Physiotherapy
Hofferberth et al[21]	36 months (1 to 276 months)	24 weeks	Dexamethasone Placebo	Days 1-5: 120ml; Days 6-8: = 156 ml; Day 9: 164 ml; Day 10: 168 ml Equivalent	Intramuscular	1400 ml	NA	Physiotherapy, 3x20ml of Metamizole sodium monohydrate, thermal treatments and/or bed rest
Haimovic et al[25]	NA	48 months	Dexamethasone Placebo	Each day: 64mg, 32mg, 16mg, 12mg, 8 mg, 8 mg, 8mg Equivalent	Oral	148 mg	148	Bed rest; Meperidine, oxycodone or acetaminophen, if needed
Finckh et al[26]	1 to 6 weeks	4 weeks	Methylprednisolone Sodium Cloride	Bolus Equivalent	Intravenous	500 mg	93,75	Prior: Physical therapy plus acetaminophen, NSAID or Tramadol. Medication forbiden for 3 days post randomization. Glucocorticoids possible 3 days post bolus
Holve et al[28]	<1week	24 weeks	Prednisolone Placebo	Daily - Day 1-3: 60mg; Day 3-6; Day 7-9: 20mg Equivalent	Oral	360 mg	54	NSAIDS and physical therapy; As needed: hydrocodone, propoxyphene, oxycodone or morphine;
Friedman et al[27]	<1 week	4 weeks	Methylprednisolone Placebo	Bolus Equivalent	Intramuscular	160 mg	30	Day 1-7: 2x500mg of naproxen; As needed: 14 pills of 5mg/325mg of oxycodone/acetaminophen;
Balakrishnamoorthy et al[29]	NA	6 weeks	Dexamethasone Sodium Cloride	Bolus Equivalent	Intravenous	8 mg	8	As required: acetaminophen, codeine, ibuprofen or oral oxycodone;
Goldberg et al[30]	<12 weeks	52 weeks	Prednisolone Placebo	Daily - Day 1 to 5: 60mg (3x20 mg); Day 6-10: 40mg (2x20mg/day); Day 11-15: 20mg Equivalent	Oral	600 mg	90	NSAIDS forbidden 3 weeks post randomization.
Wang et al[31]	> 4 weeks	24 months	Dexamethasone Diosmin	Daily - Day 1-3: 10mg Daily: Week 1-2: 3x900mg; Week 2-4: 2x900mg; Week 5-8: 2x450 mg	Intravenous Oral	30 mg	30	If VAS pain > 8: 75mg/day of diclofenac (limit of 7 days and repeatable after one month if required).

Table IV – Charateristics of included studies; SLR=Straight leg raise; VAS=Visual Analogue Visual scale; NRS= Numeric Rating Scale ODI=Oswestry Disability Index; RM-q= Rolland-Morris questionnaire;

Studies	Sample Size	Gender (Female)	Mean age (SD or 95% CI)	Randomization group	Sample per group	Gender per group (Female)	Mean age per group (SD or 95% CI)	Baseline	Follow-up Outcomes
Porsman et al[23]	52	16 (of 49)	44,8 (21 to 67)	Steroid	25	8	47.1	Work load; Affected nerve roots; Duration of pain;	Lenght of stay; Responders (9th day); Myelography; Adverse effects; Surgery Incidence;
				Placebo	24	8	42.1		
Hedeboe et al[24]	39	14	41,8 (24-63)	Steroid	19	9	43.5	Work load; Duration of symptoms	Responders (9th day and 3 months); Myelography (3rd month); Adverse effects; Surgery Incidence (3rd month);
				Placebo	20	5	40.2		
Hofferberth et al[21]	91	28	47 (30-70)	Steroid	38	NA	NA	Symptoms impaired: muscle reflexes, sensitive, paresia and vertebral;	Adverse effects;
				Placebo	53				
Haimovic et al[25]	33	NA	NA	Steroid	21	NA	NA	Resting low back pain; Passive SLR; Focal weakness and sensory loss; Myelography incidence;	Improvement on SLR (7th day); Responders rate (7th day, 1 year and >1year); Surgery Incidence;
				Placebo	12				
Finckh et al[26]	65	NA	NA	Steroid	31	14	49	Affected nerve roots; Duration of pain; Other medication; VAS for leg, back and overall VAS pain; Global pain; Neurologic deficits; SLR angle; Schober test; ODI;	VAS leg pain (1st day; <3rd day; 3rd day; >3rd day;) Decrease in VAS at D1; Neurologic deficits (10th day); Overall VAS (10th day); McGill questionnaire (day 3 and 10); SLR angle (day 3 and 10); Schober test (day 3 and 10); ODI (day 3 and 10); Concomitant Medication (day 3, 10 and 1 month); Adverse effects; Surgery Incidence (1 month);
				Placebo	29	17	45.4		
Holve et al[28]	29	10 (of 27)	42,59 (38,38 to 46,70)	Steroid	15	NA	39,31 (32,92 to 45,70)	NA	Return to normal activities and work (4 weeks); RX and MRI findings; Epidural and surgery rates;
				Placebo	14		45,64 (39,78 to 51,51)		
Friedman et al[27]	82	43	NA	Steroid	39	21	39 (9)	Overall VAS; Duration of symptoms;	Overall VAS (1 week, 4 weeks); Any disability (1 week); Recurrence of back pain (24h and 1 week); Concomitante medication (24h); RM-q (4 weeks); Return to normal activities and return to work (4 weeks); Another health care provider assitance (1st month); Adverse effects;
				Placebo	43	22	37 (8)		

Table IV (Continuation)

Studies	Sample Size	Gender (Female)	Mean age (SD or 95% CI)	Randomization group	Sample per group	Gender per group (Female)	Mean age per group (SD or 95% CI)	Baseline	Follow-up Outcomes
Balakrishnamoorthy et al[29]	58	30	38	Steroid	29	17	38,9 (9,1)	Overall VAS; ODI; SLR angle;	Overall VAS (discharge, 24h and 6 weeks); Lenght of stay; SLR angle improvement; ODI (discharge, 24h and 6 weeks); Time to normal activities (6 weeks); Oxycodone usage (24h and 6 weeks); Adverse Effects;
				Placebo	29	13	36,9 (9,9)		
Goldberg et al[30]	269	120	46 (12,1 SD)	Steroid	181	83	45,6 (11,8)	ODI; Below waist NRS; Duration of pain; Passive SLR; Muscle weakness; SF-36 physical and mental;	ODI (week 3 and 52); NRS below and above waist (week 3 and 52); SF-36 physical and mental (week 3 and 52); Responders rate (week 3 and 52); Adverse effects; Surgery incidence (52nd week);
				Placebo	88	37	46,7 (12,6)		
Wang et al[31]	300	151	NA	Steroid	150	77	42 (7,4)	Duration of pain; Affected nerve roots; Overall VAS; Overall NRS; RM-q; Other medication;	RM-q (week 2 and 8); NRS (week 2 and 8); VAS (week 2 and 8); Satisfaction (24 months); Concomitante medication (24 months); Adverse effects;
				Placebo	150	74	41 (6,5)		

Table V – Completers, surgery intervention and adverse effects rates

Studies	Completers			Surgical Intervention		Adverse effects		
	Both	Steroid	Control	Steroid	Control	Steroid	Control	Description (Steroids vs Placebo)
Porsman et al[23]	94.23	NA	NA	32	25	4	4.17	Glycosuria (4% vs 0%); Paroxysmal tachycardia (0% vs 4,42%)
Hedeboe et al[24]	100	100	100	57.89	60	31.58	5	NA
Hofferberth et al[21]	100	100	100	NA	NA	NA	NA	Epigastric complaints (13% vs 4%); increased weight (44% vs 45%); Increase in serum glucose (>50mg) (34% vs 35%); Ankle edema (2% vs 0%);
Haimovic et al[25]	81.82	76.19	91.67	37.5	0	NA	NA	NA
Finckh et al[26]	92.31	NA	NA	9.68	3.45	9.68	0	Intermitent hyperglicemias (3,23% vs 0%); Facial flush (6,45% vs 0%)
Holve et al[28]	93.1	86.67	100	0	7.14	NA	NA	NA
Friedman et al[27]	95.12	94.87	95.35	NA	NA	32.43	24.39	Drowsiness (16,22% vs 12,2%); Stomach pain (10,81% vs 4,88%); Mood changes (2,7% vs 0%); Bloating (0% vs 2,44%)
Balakrishnamoorthy et al[29]	62.07	68.97	55.17	NA	NA	18	15	Peri-anal itching (1 steroid patient);Nausea; Mild headache; Light-headedness
Goldberg et al[30]	86.99	86.74	87.5	11.46	10.39	49.16	23.86	Insomnia (25,7% vs 10,2%); Nervousness (18,4% vs 8%); Increased appetite (22,3% vs 10,2%); Indigestion (11,2% vs 6,8%); Headache (17,9% vs 14,8%); Joint pain (5,6% vs 11,4%); Sweating (19,6% vs 17%); Other (25,7% vs 18,2%);
Wang et al[31]	100	100	100	NA	NA	3.33	0	Nausea (3,33% vs 0%)

Appendix – Figures

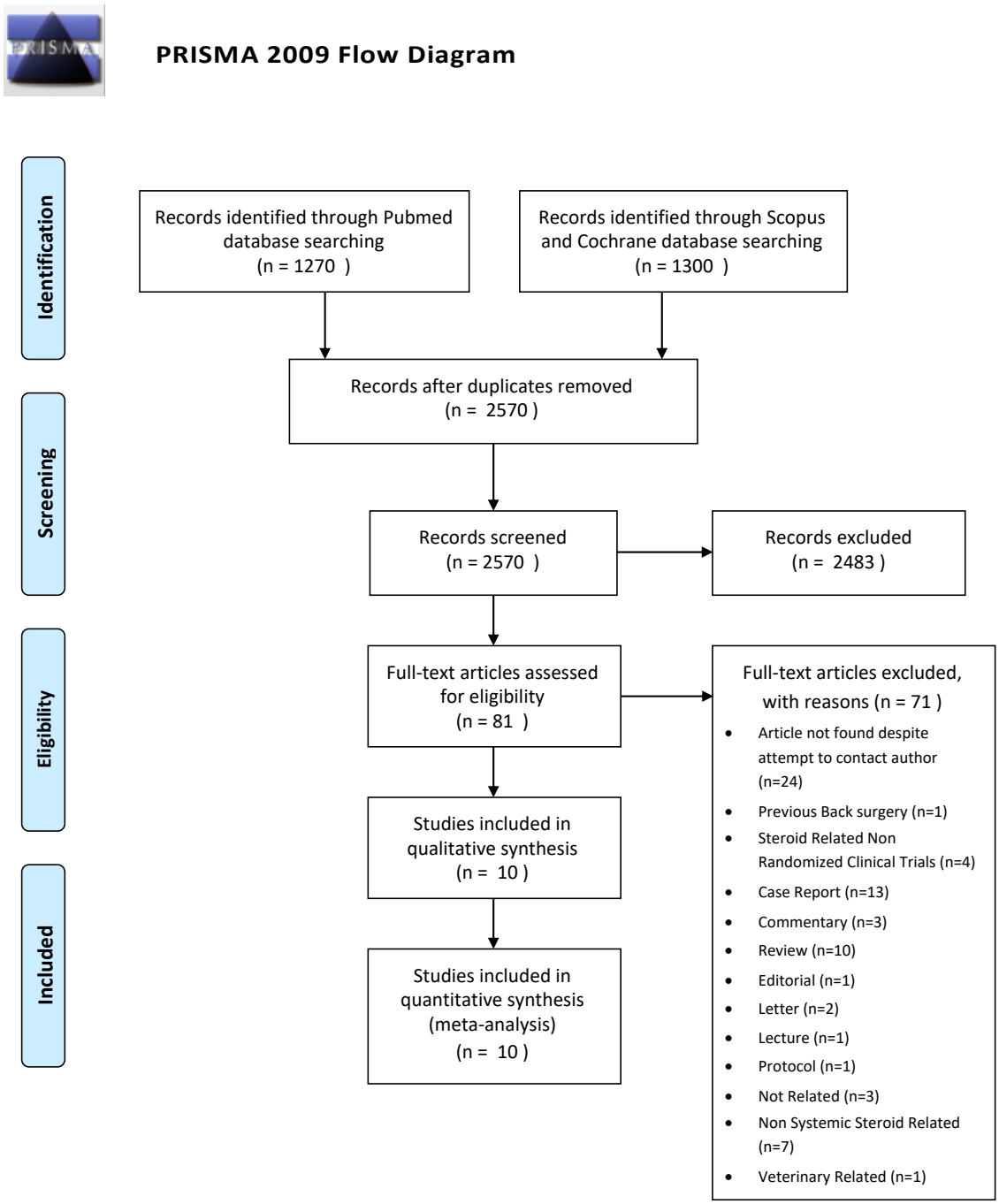

Figure 1 – Prisma 2009 Flow Diagram[16]: Screening process for all potentially relevant articles regarding back and lower leg radiated radicular pain.

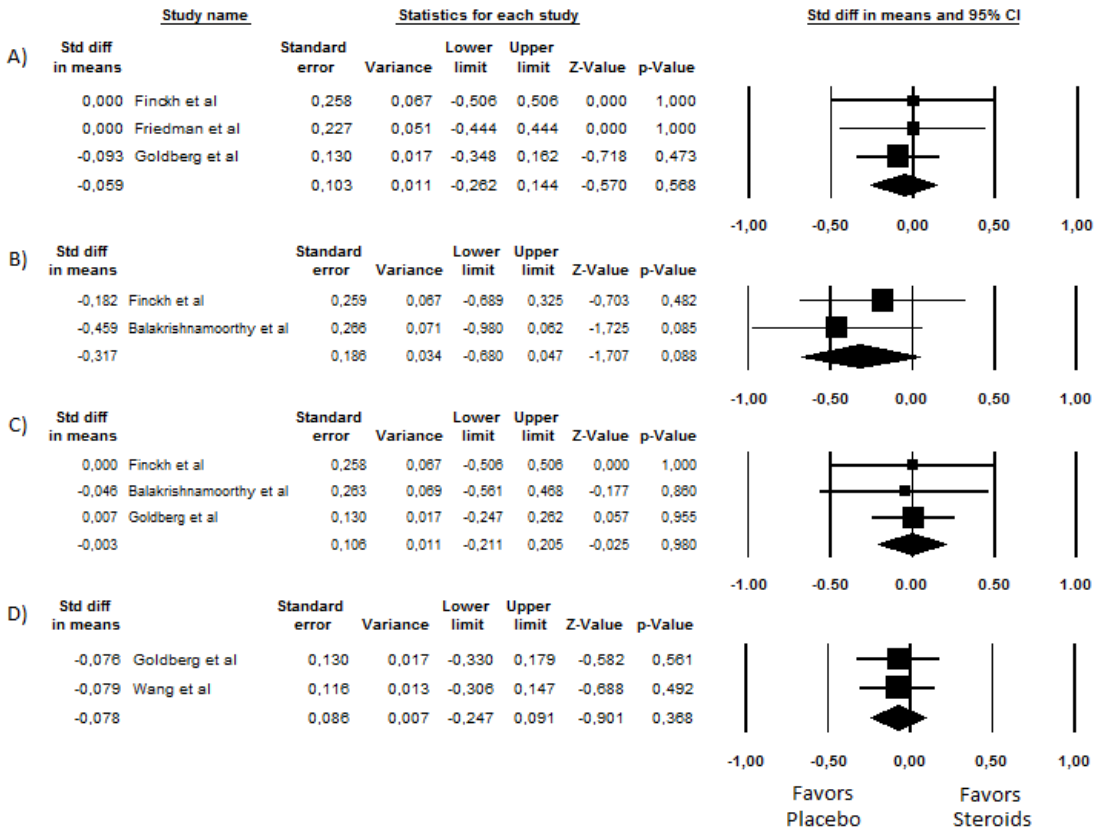

Figure 2 – Baseline mean differences for pain duration, straight leg raise angle and disability scores: (A) Pain duration is comparable at baseline, with a non-significant lower duration in the steroid group – I^2=0 and p-value=0,568; (B) Straight leg raise angle pooled-effect, with a non-significant higher movement without pain in the control group – I^2=0 and p-value=0,088; (C) Oswestry Disability Index was similar at baseline between groups – I^2=0 and p-value=0,980; (D) Functional comparison between Rolland-Morris questionnaire and SF-36 health survey hints a higher disability score among the control group, although not significant – I^2=0 and p-value=0,36.

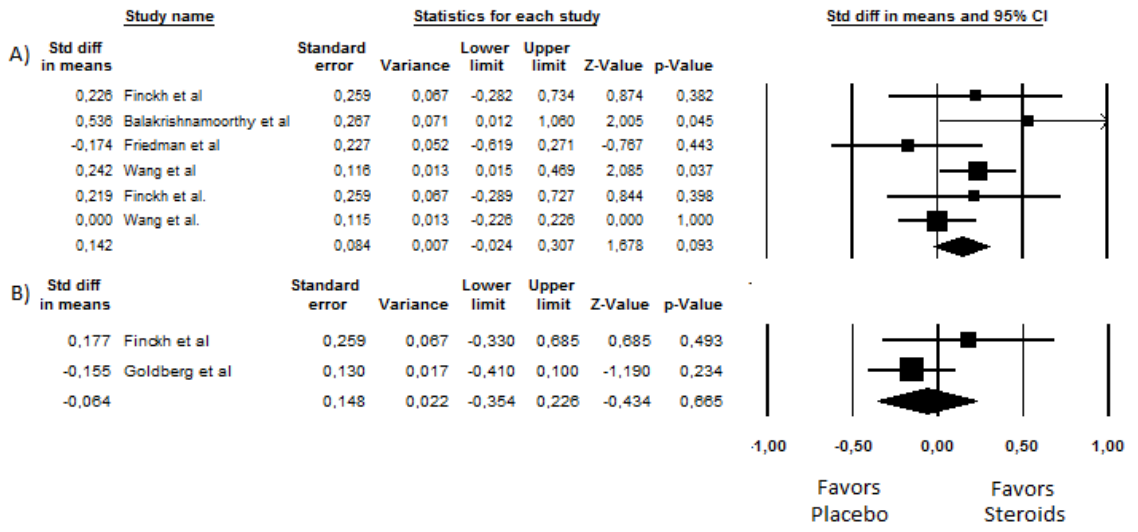

Figure 3 – Baseline mean differences for pain: (A) Overall pain (Visual Analogue Scale and Numeric Rating Scale) pooled-effect suggests a higher pain score in the steroid group, although not significant – I^2=0 and p-value=0,093; (B) Visual Analogue Scale for leg pain pooled-effect direction favors a non-significant higher pain score in the placebo group – I^2=0 and p-value=0,665.

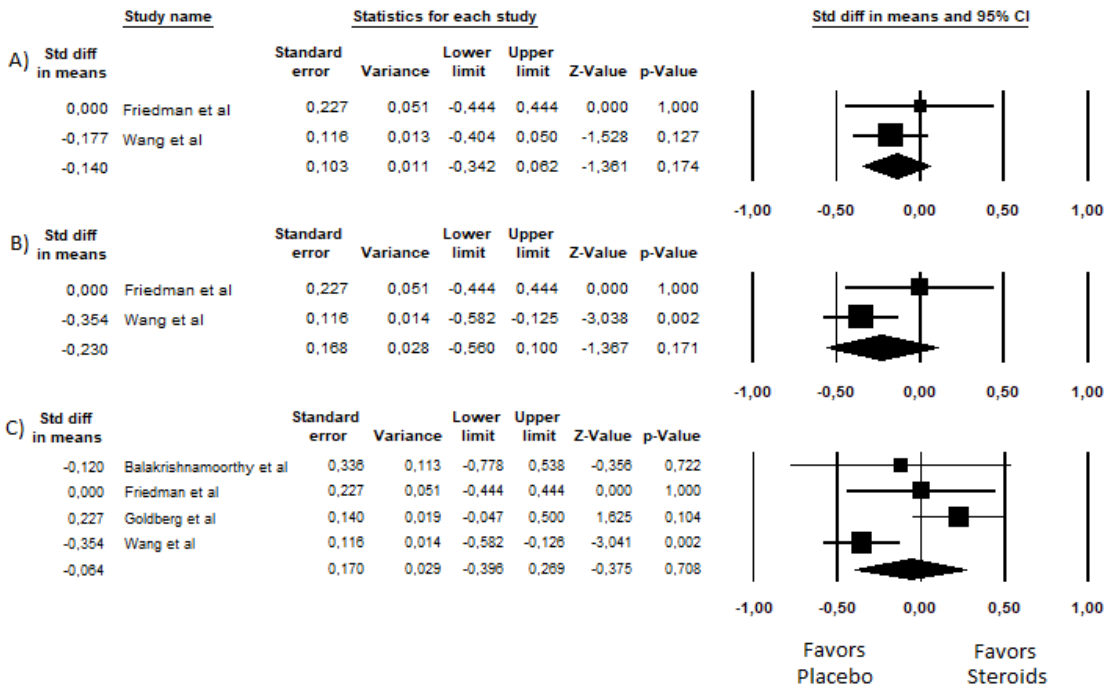

Figure 4 – Follow-up mean differences for disability: (A) Rolland-Morris questionnaire (Friedman et al - 4th week; Wang et al - 2nd week) pooled-effect was comparable, having a non-significant lower disability in the steroid group – I^2=0 and p-value=0,174; (B) Rolland-Morris questionnaire (Friedman et al - 4th week; Wang et al – 8th week) pooled-effect was similar at follow-up, favoring a higher disability the control group, although without significance – I^2=0 and p-value=0,171; (C) Functional comparison between Oswestry Disability Index (Balakrishnamoorthy et al – 6th week), Rolland-Morris questionnaire (Friedman et al – 4th week; Wang et al – 8th week) and SF-36 health survey (Goldberg et al – 52nd week) pooled-effect was comparable, having a non-significant lower disability in the steroid group - I^2=0 and p-value=0,708.

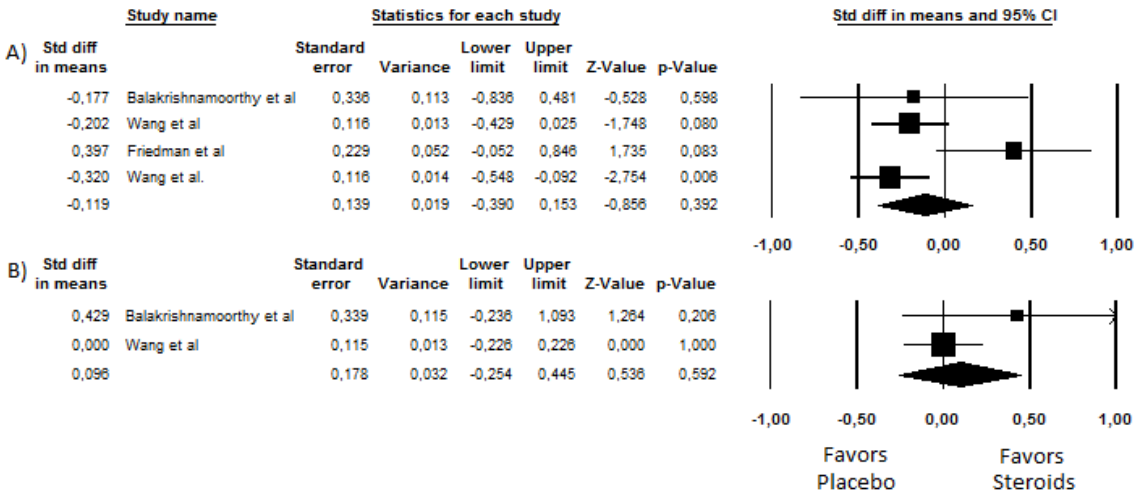

Figure 5 - Follow-up mean differences for pain: (A) Overall pain - Visual Analogue Scale and Numeric Rating Scale (Balakrishanamoorthy et al – 6th week; Friedman et al – 4th week; Wang et al – 8th weeks) pooled-effect was similar among groups, with a non-significant higher overall pain in the control group – I^2=17,484 and p-value=0,392; (B) Visual Analogue Scale reduction for leg pain pooled-effect suggests a non-statistically meaningful higher improvement in the treatment group – I^2=0 and p-value=0,592.

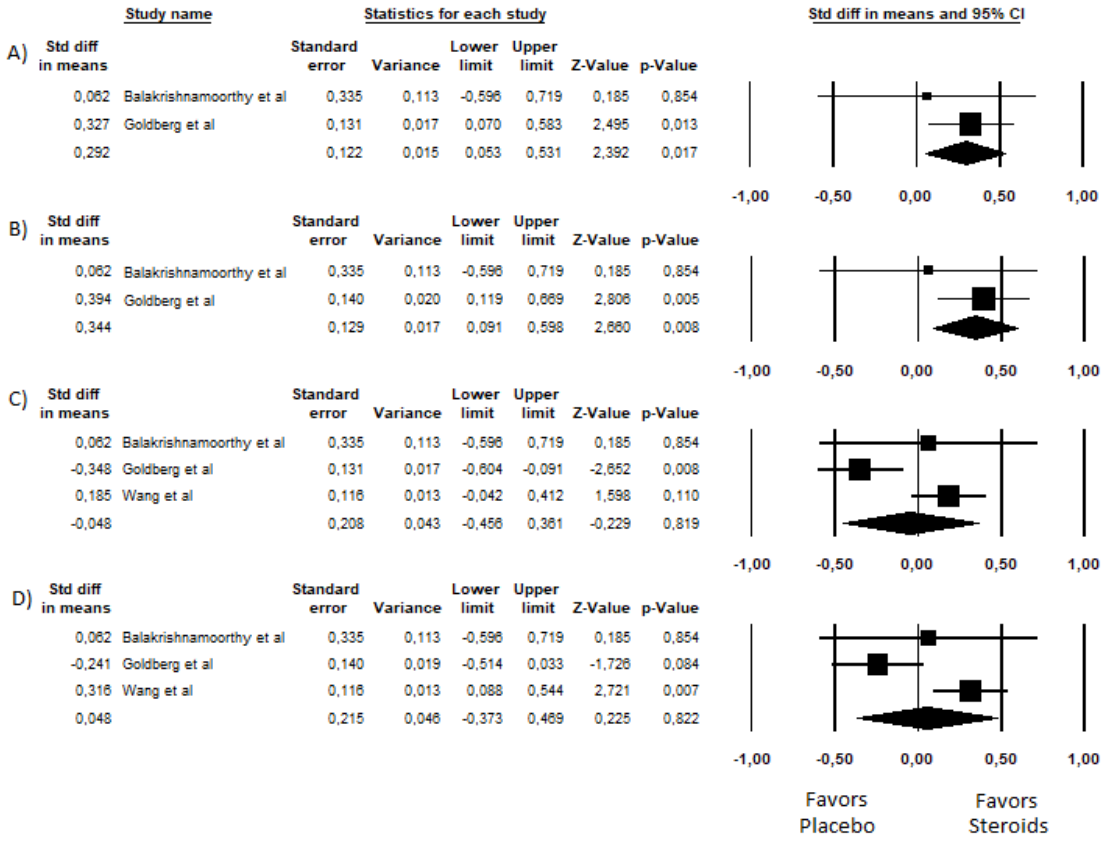

Figure 6 - Follow-up mean differences for disability in comparison with baseline: (A) Oswestry Disability Index improvement pooled-effect is significantly different, favoring a higher disability score reduction among the steroid group (Balakrishnamoorthy et al - 6th week; Goldberg et al – 3rd week) – I^2=0 and p-value=0,017; (B) Oswestry Disability Index improvement is significantly different, favoring a higher disability score reduction among the steroid group (Balakrishnamoorthy et al - 6th week; Goldberg et al – 52nd week) – I^2=0 and p-value=0,008; (C) Functional improvement pooled-effect between Oswestry Disability Index, SF-36 health survey (Goldberg et al – 3rd week) and Rolland-Morris questionnaire (Wang et al – 2nd week) is comparable at follow-up, having a non-significant tendency towards the control group (Balakrishnamoorthy et al – 6th week), - I^2=0 and p-value=0,819; (D) Functional improvement pooled-effect between Oswestry Disability Index (Balakrishnamoorthy et al – 6th week), SF-36 health survey (Goldberg et al – 52nd week) and Rolland-Morris questionnaire is similar, with a non-significantly higher improvement in the steroid group (Wang et al – 8th week) - I^2=0 and p-value=0,822.

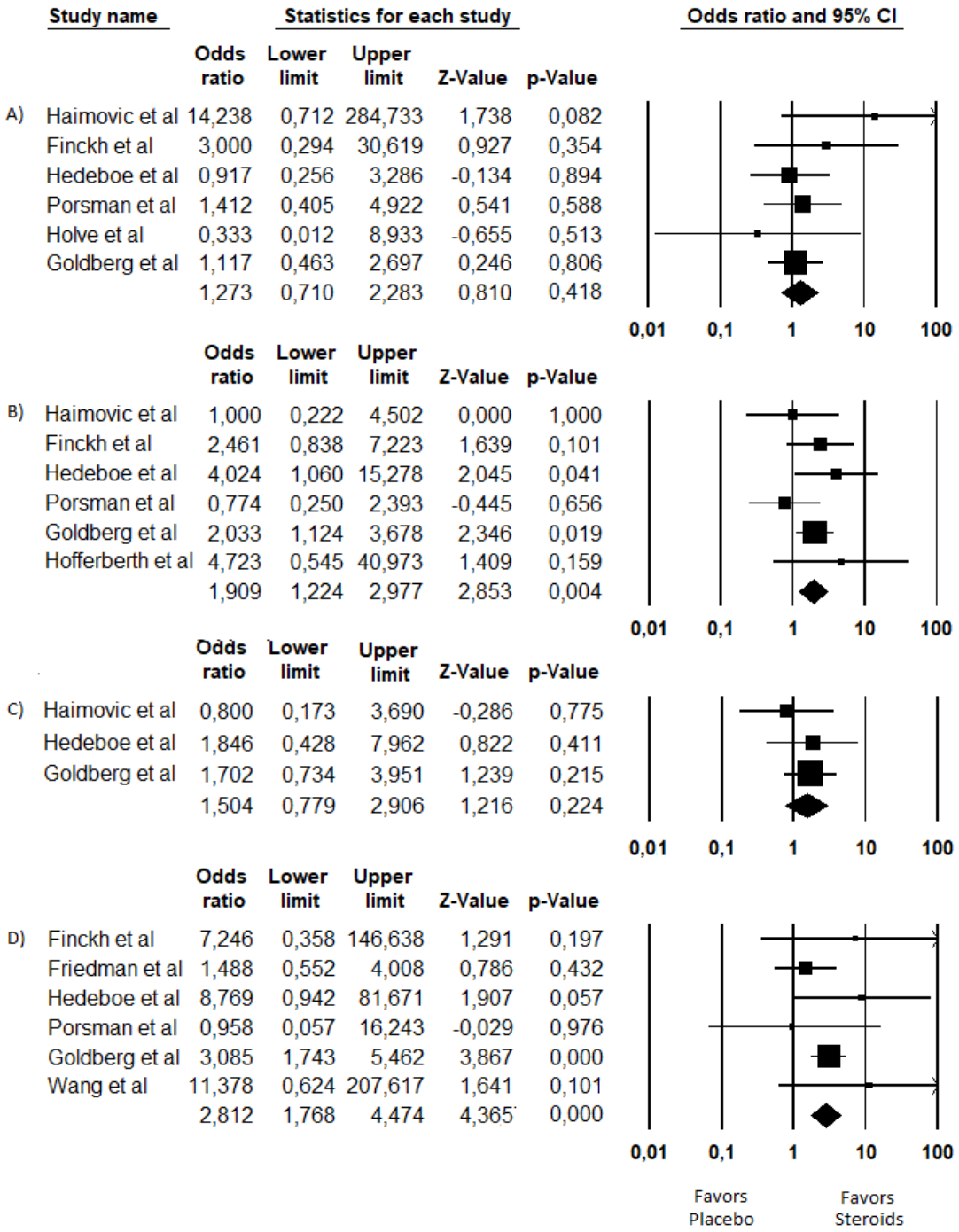

Figure 7 – End of follow-up differences for need for surgical intervention, short-term and late responder rate and adverse effect incidence: (A) Surgical intervention rate pooled-effect was similar between groups, with a non-significant higher incidence in the steroid group – (OR=1,273; (0,71 to 2,283); I^2=0 and p-value=0,418); (B) Short-term responders rate pooled-effect was significantly lower in the control group, suggesting a higher response in the treatment group – (OR=1,909; (1,224 to 2,997); I^2=1,158 and p-value=0,004); (C) Late responders rate pooled-effect was comparable between groups, with a non-significant lower response rate in the non-treatment group – (OR=1,504; (0,779 to 3,951); I^2=0 and p-value=0,224); (D) Adverse effects incidence pooled-effect was statistically different between groups, favoring a higher rate in the corticosteroids group – (OR=2,812; (1,768 to 4,474); I^2=0 and p-value<0,001).