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Running Title- Role of Corticosteroids in Functional Endoscopic Sinus Surgery - A Systematic Review and Meta-Analysis.

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Title –Role of Corticosteroids in Functional Endoscopic Sinus Surgery - A Systematic Review and Meta-Analysis.

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SUMMARY

Background*:* The aim of our study is to systematically review the existing evidence on the role of Corticosteroids in patients undergoing Functional Endoscopic Sinus Surgery (FESS).

Methodology**:** Systematic search of MEDLINE (1950- 2014), EMBASE (1980-2014), metaRegister, Cochrane Library and ISI conference proceedings was carried out.

Result - Eighteen randomised controlled trials with 1309 patients were included. Use of local or systemic corticosteroids with FESS was reported in four categories; operative, anaesthesia related, post-operative outcomes and risk of recurrence. Meta-analysis for operative outcomes demonstrated that, mean operative time (MD -10.70 minutes; 95% CI -15.86, -5.55; P <0.0001) and mean estimated blood loss (MD -28.32 mls; 95% CI -40.93, -15.72; P <0.0001) was significantly lower; and surgical field quality (MD -0.81; 95% CI -1.32, -0.30; P = 0.002) was significantly better in corticosteroid group. Meta-analysis showed that post-operative endoscopic scores (SMD -0.39; 95% CI -0.60, -0.17; P = 0.0004) were significantly better in corticosteroid group compared to no corticosteroid group. There was no increase in risk of sinusitis (RR 0.64; 95% CI 0.32, 1.30; P = 0.22) between use of corticosteroids and no corticosteroids; There was no significant difference in recurrence risk of

Chronic Rhinosinusitis (CRS) in mixed population studies (RR 0.77; 95% CI 0.35, 1.70; P = 0.52) between the two groups but analysis of studies reporting on Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) (RR 0.64;95% CI 0.45,0.91;P=0.01) showed significant difference in favour of the corticosteroid group.

Conclusion

Pre-operative use of corticosteroids in FESS, results in significantly reduced blood loss, shorter operative time and improved surgical field quality. Studies are limited on the intra-operative use of corticosteroids to reduce postoperative pain. Corticosteroids improve postoperative endoscopic scores in CRS and recurrence rates in cases of CRSwNP.

Key words: Functional Endoscopic Sinus Surgery, FESS, Chronic Rhinosinusitis, Corticosteroids.

Introduction

Chronic Rhinosinusitis (CRS) is a common disabling condition resulting in significant healthcare cost and loss in productivity. The prevalence rate of CRS have been quoted from 5.5% in South America, 10.9% in Europe to about 16% in America. [1-3] CRS (including CRS with nasal polyps(CRSwNP)) is defined by European position paper on rhinosinusitis and nasal polyps (EPOS 2012), as "inflammation of the nose and the paranasal sinuses characterised by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip), ± facial pain/pressure, ± reduction or loss of smell; and either endoscopic signs of polyps and/or mucopurulent discharge primarily from middle meatus and/or; oedema/mucosal obstruction primarily in middle meatus, and/or CT changes showing mucosal changes within the osteomeatal complex and/or sinuses".[4] Rhinosinusitis (RS) can be acute when symptoms or signs subside within 12 weeks and chronic (CRS) if these persist for more than 12 weeks.[4] CRS can be with or without nasal polyps (CRSwNP, CRSsNP) and affects 2-16 %[5,6] and 2-3%[4,7] of the population respectively.

CRS is considered as a multifactorial disease. Environmental factors include pollution, smoking, fungus, bacterial and viral infections. Host factors can be, general factors like immune deficiencies and genetic factors; and local host factors causing persistent focal inflammation within the ostiomeatal complex.[8] Initial therapy for CRS includes nasal saline irrigation, topical and systemic corticosteroids and in cases of CRSsNP potentially long term antibiotics; followed by surgical intervention in unresponsive patients. [4,6] Corticosteroids reduce nasal mucosal inflammation and therefore increase drainage of infected mucosal secretions and aid the healing process.

Patients who fail to respond to medical therapy are considered for Functional Endoscopic Sinus Surgery (FESS), which is one of the most common surgical procedure performed.[5,9] Endoscopic sinus surgery was described by Stammberger[10] in 1985 and Kennedy[11] coined the term FESS to highlight its surgical philosophy of mucosal sparing . About 80% of patients have successful outcome but 20% patients suffer from relapse of sinusitis or complications warranting further surgical intervention.[12]

Corticosteroids have been used preoperatively, intraoperatively and postoperatively in FESS for rhinosinusitis. FESS creates a conduit for topical steroids to reach the deeper part of the sinus cavity and act on the mucosa which was previously inaccessible. Intranasal corticosteroids are therefore often included in postoperative treatment regimens. Both local and systemic corticosteroids have also been used preoperatively to reduce inflammation and intraoperative bleeding, thereby improving surgical field.[13,14] It has also been shown that asthmatic patients who are given corticosteroids preoperatively have low incidence of pulmonary complications in the perioperative time period.[15] Corticosteroids have also been postulated in pain control when used intraoperatively.[16] There are several randomised controlled trials evaluating the role of corticosteroids in FESS, however, these studies have reported conflicting results.

The aim of our study was to systematically review the existing evidence on the role of corticosteroids in patients with CRS undergoing FESS. The aim of our systematic review and meta-analysis was to determine whether preoperative corticosteroids affect operative parameters; intra-operative corticosteroids reduce surgical pain; and

postoperative corticosteroids affect patient's symptom scores, endoscopic appearance and recurrence rates.

Materials and Methods

Data sources and literature search

We conducted systematic searches for randomised controlled trials (RCTs). There were no language, publication year or publication status restrictions. The date of the last search was 20.09.2014. We searched MEDLINE, EMBASE, Web of science, metaRegister, Cochrane Library and ISI conference proceedings. A combination of MeSH and text words were used to generate two subsets of citations, one including studies of endoscopic surgery ('endoscopic sinus surgery', 'endoscopic polypectomy', 'FESS', 'functional endoscopic sinus surgery') and the second including corticosteroids ('corticosteroids', 'steroids', 'corticoids', 'dexamethasone', 'fluticasone', 'budesonide', 'mometasone', "prednisone", "prednisolone", "triamcinolone"). These subsets were combined using 'AND' to generate a subset of citations relevant to our research question. The reference lists of all known primary and review articles were hand searched to identify cited articles not captured by electronic searches. The searches were conducted independently by VP and JP.

Study selection

Two review authors (VP and JP) performed data selection and extraction based on predetermined criteria. Studies were selected in a two-stage process. Firstly, the titles and abstracts from the electronic searches were scrutinized and full manuscripts of all citations that were likely to meet the predefined selection criteria were obtained. Final inclusion or exclusion decisions were made on examination of the full manuscripts. In cases of duplicate publication, the most recent or complete versions were selected. We documented our justification for the exclusion of studies.

Data extraction

Two reviewers (JP and VP) completed data extraction. Study characteristics and participant features were extracted from each study regarding: characteristics of trials - setting, design, method of data analysis; participants - study population, number of participants; type of intervention: dose, route of administration, duration of treatment, follow-up and outcomes. Inconsistencies between reviewer's data were resolved

through discussion with a third reviewer (SB) until a consensus was reached. After identifying the studies where additional data were needed, a request was sent by means of electronic mail to the corresponding author of each study. If no response was received, a second request was sent 2 weeks later by means of electronic mail.

Data Synthesis

Inclusion and exclusion criteria

Studies were selected if the target population underwent FESS, and were exposed to corticosteroids and compared with either placebo or no corticosteroids. Only RCTs were included. Trials which included participants of any age, who had any co-morbidity including asthma and aspirin sensitivity, allergic or non-allergic, followed for any duration and CRS with and without polyps were included. Studies were excluded if the patients had taken corticosteroids in the absence of FESS.

Outcomes assessed

The outcomes were assessed under four categories. Operative outcomes, anaesthetic related outcomes, post-operative outcomes and risk of recurrence. Operative outcomes included estimated blood loss (EBL), surgical field quality and operative time. Postoperative outcomes included symptoms score (subjective improvement), endoscopic score (objective improvement) and risk of sinusitis.

Assessment of risk of bias in included studies

We assessed the methodological quality of the included studies and carried out the assessment of risk of bias taking into consideration: method of randomisation; allocation concealment; blinding; incomplete outcome data; selective outcome reporting; and other sources of bias.[17] We used the Cochrane 'Risk of bias' tool in RevMan 5.1,which involved describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry as low, high or unclear risk of bias.[18] We presented this information in a 'Risk of bias' graph and summary.

Statistical analysis

Meta-analysis was performed in line with recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-analyses (QUORUM)

guidelines.[19,20] From each study, dichotomous outcome data were summarised in 2 x 2 tables by two reviewers (VP, JP). The results were pooled and expressed as risk ratios (RR). Continuous variables were analyzed using mean differences (MD), with 95% confidence intervals (CIs). [21] The results were pooled using either a fixed effect[22] or random effect model as appropriate.[21] For symptoms scores, the measurements used were Sino-nasal Outcome Test Score (SNOT 21)by Rotenberg et al. (0-120)[23] and Jorrisen et al[12]. used their own score (0-50). Results for endoscopic scores were derived from four studies; Cote et al[24]. and Rotenberg et al.[23] used Lund-Kennedy endoscopic score (LKES score;range 0-12 in one nasal cavity) [25]; Chang et al.[26] used Philpott-Javer score (range 0-40)[27] and Jorissen et al.[12] used their own scoring system combining inflammation, oedema and polyps (range 0-6). We used standardised mean difference as a summary statistic in this meta-analysis because the included studies assessed the same outcome but measured it in a variety of ways, to standardise the results of the studies to a uniform scale before they could be combined.

Heterogeneity of the exposure effects was evaluated statistically using the I^2 statistic to quantify heterogeneity across studies.[28] A I^2 value of >50% was taken as evidence of substantial heterogeneity and in such cases a random effect model was used. A chi-squared test for heterogeneity was also performed and the p- values are presented.

When only medians were available, these were used as estimates of means. [29,30] When a study failed to present a standard deviation (SD), this statistic was either calculated from the standard error of the mean, 95% CI, t value or interquartile range. [29] Some studies provide only ranges, in such instances the SD was estimated using the formula total range/4. [30] Statistical analyses were performed using RevMan 5 software.

Results

Study selection

Of the 307 citations identified by the search, 39 were selected after initial screening. Following examination of the full manuscripts of these 39 studies, 21 more were excluded; 2 studies compared different corticosteroids, [31, 32] 4 studies were cohort studies with no comparison group, [33, 34, 35, 36] 4 were non-randomised comparative studies, [37,38,39,40] 1 study compared two different doses of a steroid, [41] 5 studies did

not use FESS as surgical technique, [42,43,44,45,46] 3 studies reported incomparable outcomes [47,48,49]and 2 were review articles [50,51]. (Figure 1-Consort diagram).

Eighteen studies satisfied the selection criteria and were included in this review.[12-14,23,24,26,52-63] In total 1309 patients were included in this review. Four studies had an intrapatient control design in which one side of the nasal cavity was compared with the other side (n=182). [24,59,60,62] .These studies were included in the meta-analysis and the two groups treated as independent, and then sensitivity analysis was performed excluding these studies to determine the robustness of the results. The remaining 1127 patients were randomised to the steroid group of 607 patients and 520 controls. Sample size per study varied across the trials and ranged from 19 to 162 participants. Use of corticosteroids with FESS was reported for four categories; operative outcomes, anaesthesia related, post-operative outcomes and risk of recurrence. Operative outcomes were reported by three studies; [13,14,55] anaesthetic outcomes were reported by one study; [58] post-operative outcomes were reported by ten studies; [12,23,24,26,54,55,57, 59,61,62]. and risk of recurrence was reported by six studies. [52,53,56,59,60,63] One RCT reported both on operative and post-operative outcomes, therefore it was included in both categories. [55] Albu et al., reported on patients with and without polyps; [14] data from this study is included in the meta-analysis as Albu et al.(1) and Albu et al.(2). Albu et al(1) represent data of patients with CRSwNP and Albu et al (2) represent data of patients with CRSsNP. In our attempt to get more information about studies with inadequate data, we received no response from the relevant authors. [13,24,53,55]

Study characteristics

A description of the included studies is summarised in Table 1. Risk of bias from the included studies is represented in Figures 2 and 3. Our judgements about each risk of bias item, presented as percentages across all included studies, are shown in Figure 2, and for each risk of bias item for each included study in Figure 3. Generally, included studies had low risk of bias for method of randomisation and blinding, medium risk of bias for incomplete outcome data and selective reporting and unclear risk of bias for allocation concealment.

Outcomes

1. Operative outcomes in response to preoperative corticosteroids

1.1 Operating time

Data addressing this comparison were available from three studies, Sieskiewicz et al [13] Albu et al [14] and Wright et al. [55]Data from Wright et al[55] could not be included because the SD could not be calculated. Pooling the results of the remaining two studies [13,14] showed that, mean operative time was significantly lower in the steroid group compared to the non steroid group (MD -10.70 minutes; 95% CI -15.86, -5.55; P <0.0001; Figure 4.1). I^2 was 19%, suggesting insufficient evidence of any significant heterogeneity (χ^2=2.47,P = 0.29).

A subgroup analysis was done according to population group which showed that in CRSwNP patients there was significant difference favouring steroid group (MD -13.93 minutes;95% CI -21.02, -6.85; P =0.0001; Figure 4.1.1). I^2 was 0%, suggesting insufficient evidence of any significant heterogeneity (χ^2=0.78,P = 0.38). CRSsNP did not show statistically significant difference between the two groups(MD -7.07 minutes;95% CI -14.58, -0.44; P =0.07; Figure 4.1.1).

As Albu et al [14] used local steroids and Sieskiewicz et al [13]used systemic steroids we undertook a subgroup analysis looking at different modes of delivery. This showed a significant difference in favour of corticosteroids both local (MD -10.58 minutes;95% CI -16.69, -4.48; P =0.0007; Figure 4.1.2) and systemic(MD -11.00 minutes;95% CI -20.63, -1.37; P =0.03; Figure 4.1.2). In local corticosteroid subgroup analysis, I^2 was 59%, suggesting significant heterogeneity (χ^2=2.47,P = 0.12).

1.2 Estimated blood loss (EBL)

Data addressing this comparison were available from three studies, Sieskiewicz et al [13] Albu et al [14] and Wright et al. [55] Data from Wright et al [55] could not be included because the SD could not be calculated. Pooling of results from the remaining two studies [13,14] showed that, mean EBL was significantly lower in the steroid group compared to the non steroid group (MD -28.32 mls; 95% CI -40.93, -15.72; P <0.0001; Figure 4.2). I^2 was 0%, suggesting no significant heterogeneity (χ^2=0.55, P = 0.76).

A subgroup analysis was done according to population group which showed significant difference favouring the steroid group in both CRSwNP patients (MD-32.44 mls;95% CI -50.75, -14.12; P =0.0005; Figure 4.2.1) and CRSsNP

patients (MD -24.63 mls;95% CI -41.99, -7.27; P =0.005; Figure 4.2.1).In CRSwNP subgroup analysis, I^2 was 0%, suggesting no significant heterogeneity (χ^2=0.18, P = 0.67).

As Albu et al[14] used local steroids and Sieskiewicz et al [13] used systemic steroids we undertook a subgroup analysis looking at different modes of delivery. This showed a significant difference in favour of corticosteroids both local (MD -28.41 mls;95% CI -42.60, -14.23; P <0.0001; Figure 4.2.2) and systemic (MD -28.00 minutes;95% CI -55.44, -0.56; P =0.05; Figure 4.2.2). In local corticosteroid subgroup analysis, I^2 was 0%, suggesting insignificant evidence of heterogeneity (χ^2=0.55, P= 0.46).

1.3 Surgical field quality

Data addressing this comparison were available from two studies, Sieskiewicz et al [13] and Albu et al. [14]Pooling of the results of these showed that, surgical field quality was significantly better in the steroid group as compared to no steroid group (MD -0.81; 95% CI -1.32, -0.30; P = 0.002; Figure 4.3). I^2 was 0%, suggesting no significant heterogeneity (χ^2=0.16, P = 0.92).

A subgroup analysis was done according to population group which showed significant difference favouring steroid group in CRSwNP patients (MD -0.88; 95% CI -1.50, -0.26; P =0.005; Figure 4.3.1.) but not in CRSsNP patients (MD -0.66;95% CI -1.58, 0.26; P =0.16; Figure 4.3.1). In CRSwNP subgroup analysis, I^2 was 0%, suggesting no significant heterogeneity (χ^2=0.01, P = 0.92).

As Albu et al[14] used local steroids and Sieskiewicz et al [13] used systemic steroids we undertook a subgroup analysis looking at different mode of delivery. This showed a significant difference in favour of corticosteroids both local (MD -0.73;95% CI -1.44, -0.02; P =0.04; Figure 4.3.2) and systemic(MD -0.90;95% CI -1.64, -0.16; P =0.02; Figure 4.3.2). In local corticosteroid subgroup analysis, I^2 was 0%, suggesting insignificant evidence of heterogeneity (χ^2=0.05,P = 0.82).

2. Anaesthetic outcomes in response to intraoperative corticosteroids

This was reported by one study**.** [58] Analysis of data showed that there was no significant difference in post operative pain score at 6 hours postoperatively (p=0.45) and 24 hours postoperatively (p=0.17) in the steroid group as compared to the non steroid group.

3. Postoperative outcomes in response to corticosteroids

Postoperative outcomes in the form of symptom score and endoscopic score were reported by twelve studies. [12,23,24,26,53-57,59,61,62] Data from Rowe-Jones et al. could not be pooled in the meta-analysis as their data were not homogenous with other studies and SD could not be calculated. [54] Individual subjective symptom outcomes mainly, congestion, sense of smell and rhinorrhoea were reported in two studies Stjarne et al. and Enhange et al. but the data could not be pooled for meta-analysis. [56,57]

3.1 Symptom score

Even though postoperative symptom outcomes were reported by seven studies[12,23,53,54,55,56,57] data from only two studies could be pooled for the meta-analysis. Data from Rowe-Jones et al. could not be pooled as their data was not homogenous with other studies. [54] They reported that overall visual analogue score, endoscopic polyp score and total nasal volume was significantly better in the steroid group at 5 years. Data from Dijkstra et al. and Wright et al., could not be included because the SD could not be calculated.[53,55] Dijkstra et al reported no significant difference in total symptom score between the steroid group and control group. [53] Individual Subjective symptom outcomes mainly, congestion, sense of smell and rhinorrhoea, were reported by Stjarne et al., Enhange et al. and Wright et al., but could not be pooled for meta-analysis. [55,56,57] Wright et al. concluded that there was no treatment effect on subjective symptoms noted between corticosteroids compared with placebo. [55] Stjarne et al. reported no significant difference in baseline to end of treatment scores for nasal congestion and subjective sense of smell between the steroid and placebo group. [56] Similarly, Enhange et al. also reported that there were no statistically significant differences in the changes in all these nasal parameters between the steroid and the placebo group after undergoing FESS. [57]

Pooling of data from the remaining two studies[12,23] showed that there was no significant difference in mean post operative symptom score between the steroid

group compared to the non steroid group (SMD -0.01; 95% CI -0.36, 0.33; P = 0.94:). I^2 was 0%, suggesting no significant heterogeneity (χ^2=0.36, P = 0.55).

3.2 Endoscopic score - Data addressing this comparison were available from eight studies. [12, 23, 24, 26, 55, 59, 61, 62] Data from Wright et al., could not be included because the SD could not be calculated. [55] Pooling of data from the remaining seven studies[12,23,24,26,59,61,62] showed that there was significant difference in mean post operative endoscopic scores between the steroid group as compared to no steroid group (MD -0.39; 95% CI -0.60, -0.17; P = 0.0004; Figure 5.1). I^2 was 0%, suggesting no significant heterogeneity (χ^2=4.64, P = 0.59).

A subgroup analysis was performed to assess the results according to the population group. Three studies reported data from mixed population, CRSwNP and CRSsNP, [12, 26, 59] one study reported data from CRSsNP patients [61] whereas three other studies showed data from CRSwNP. [23,24,62.] No significant difference between steroid and no corticosteroids were found in the CRSsNP group (SMD 0.12;95% CI-0.52,.76; Figure 5.1).Analysis of studies reporting on CRSwNP showed significant difference between steroid and no steroid groups (SMD -0.62;95% CI -0.99,-0.24; P=0.001; Figure 5.1). I^2 was 0%, suggesting no significant heterogeneity, (χ^2=0.16, P = 0.92).Analysis of data from the mixed population group also showed significant difference between the steroid and no steroid groups (SMD -0.36; 95% CI -0.64,-0.08; P=0.01; Figure 5.1). I^2 was 0%, suggesting no significant heterogeneity, (χ^2=0.58, P = 0.75)

3.3 Risk of sinusitis

Risk of sinusitis as an adverse event associated with the use of corticosteroids was reported by four studies. [12, 52, 54, 60] Pooling of the results showed no significant difference between use of corticosteroids and no corticosteroids (RR 0.64; 95% CI 0.32, 1.30; P = 0.22; Figure 5.2). I^2 was 0%, suggesting no significant heterogeneity (χ^2=2.01, P = 0.57).

4. Recurrence risk – Risk of recurrence was reported by six studies. [52, 53, 56, 59, 60, 63] Pooling of results of these studies showed no significant difference between use of corticosteroids and no corticosteroids (RR 0.72; 95% CI 0.48, 1.08; P = 0.11; Figure 6). I^2 was 66%, suggesting significant heterogeneity (χ^2=14.85, P = 0.01).

A subgroup analysis was performed to assess the results according to the population group. Three studies reported data from mixed population, CRSwNP and CRSsNP [54, 60,61] whereas three other studies showed data from CRSwNP.[53,57,64] No significant difference between steroid and no corticosteroids were found in the mixed population group (RR 0.77; 95% CI 0.35,1.70;P=0.52;Figure 6). I^2 was 71%, suggesting significant heterogeneity, (χ^2=6.86, P = 0.03). Analysis of studies reporting on CRSwNP showed significant difference between steroid and no steroid groups (RR 0.64;95% CI 0.45,0.91;P=0.01;Figure 6). I^2 was 30%, suggesting no significant heterogeneity, (χ^2=2.86, P = 0.24).

Discussion

Principal findings of the review

This systematic review and meta-analysis of randomised controlled trials for operative outcomes demonstrated that operative time and estimated blood loss were significantly lower, and surgical field quality was significantly better in the steroid group compared to the non steroid group. In relation to anaesthetic outcomes in response to intra-operative corticosteroids there was no significant difference in post operative pain scores between the two groups. For post-operative outcomes in response to the corticosteroids there was no significant difference in symptom scores but endoscopic scores were better for the steroid group between the two groups. The use of corticosteroids was not associated with an increased risk of sinusitis. There was no significant difference in the recurrence risk between those given corticosteroids and controls in mixed population group, but subgroup analysis showed favourable results for steroid use in cases of CRSwNP.

Strengths of the review

CRS is an inflammatory disease and therefore, corticosteroids have long been utilized in its management due to their potent anti-inflammatory properties. Patients who fail to respond to medical therapy are considered for FESS. FESS differs from traditional, radical and less physiological drainage procedures as it restores mucociliary clearance pathways and ventilation by opening the osteomeatal complex and is customized to disease extent. Corticosteroids have been indicated in FESS for various reasons. Our

review included studies reporting use of corticosteroids on the operative outcome, anaesthetic related outcome, postoperative outcome and recurrence risk when used with FESS.

An important factor affecting the success of FESS is a clean surgical field. [64] Poor endoscopic view secondary to bleeding is associated with increased operative time, complications and even cessation of surgery. [64,65] Preoperative corticosteroid treatment has been proposed to minimise bleeding and improve surgical field. [66,67] Corticosteroid reduce intra operative bleeding by not just it's anti-inflammatory effect but also have a positive effect on regulation of vascular tone. Various mechanisms explaining this positive effect of corticosteroids on the vascular tone have been proposed. [68] These include potentiation of action of other α adrenergic agonists like norepinephrine at the receptor level. Our meta-analysis for operative outcomes including operative time, EBL and surgical field quality showed significant benefit from the use of preoperative corticosteroids; both systemic [13] and topical. [14] Even though these studies varied in definitions of CRS (CRSsNP and CRSwNP); timing and commencement of corticosteroids; type, volume and route of administration of corticosteroids, the benefit was seen consistently in all three studies. Though we could not include the data from Wright et al. in our meta-analysis, these authors also concluded that patients who were not given pre-operative corticosteroids showed a higher percentage of severely inflamed mucosa and were associated with technically more difficult surgery. [55]

Patients after FESS may experience pain which might prevent them from returning to normal daily activities. [69] Corticosteroids due to their potent anti-inflammatory effect have been proposed in the management of acute surgical and postoperative pain control. [16] In this respect one study was found to assess the outcome of intra-operative corticosteroid in reducing pain after FESS. [58] This study did not show any benefit of using intraoperative steroid as a tool to reduce post operative pain.

Comparison with other studies

Due to the anti-inflammatory effects and excellent safety profile, topical nasal corticosteroids have become a common treatment modality for CRS. [70] A previous systematic review on use of topical corticosteroids following FESS reporting a

significant improvement in symptoms, endoscopic appearance and delay in polyp recurrence, recommended the use of nasal corticosteroids after FESS. [70] However, these authors did not perform a meta-analysis and summarized their recommendations based on individual studies. Subgroup analysis from a Cochrane review[71] on use of corticosteroids in CRS based on two studies (Jorrisen et al., Lavigne et al) showed benefit of steroid on symptom scores who had sinus surgery. [12,36] However, the study by Lavigne et al. had to be excluded from our study as it recruited patients with failed FESS, and therefore does not fulfil the inclusion criteria.

Recent EPOS 2012 systematic review on the role of corticosteroids in postoperative treatment for adults with CRS recommended, topical corticosteroids for patients with CRSsNP; and both topical and oral corticosteroids in patients with CRSwNP. [4] This document, in a subgroup analysis showed that only patients with prior surgery for CRSsNP had symptom improvement but there was no improvement for those patients without surgery (Page 144 of the document). Similarly, in CRSwNP, patients with sinus surgery responded to topical steroid greater than patients without sinus surgery in polyp size reduction but improvement in symptoms and nasal airflow was not statistically different between the two subgroups (Page 170 of the document). The meta-analysis in the EPOS 2012 document incorporates studies which include patients who have had a history of sinus surgery including polypectomy. Whereas in our meta-analysis all patients underwent FESS. Our meta-analysis showed no significant benefit with the use of corticosteroids in post-operative symptom outcomes.
It has been postulated that, use of corticosteroids in the immediate post operative period may increase the risk of sinusitis. [32] Our meta analysis from four studies which used local corticosteroids, showed that there was no evidence of increased risk of sinusitis with steroid use in postoperative period. We acknowledge that rare adverse events are possibly not detected in RCTs. However, they were extremely low and there was no difference in adverse events between the study groups and control groups in any trial.

Limitations of the review

Limitations of our systematic review include potential biases in the review process regarding the eligibility criteria and data analyses. The inclusion of trials studying mixed populations of polyps and non-polyps patients possibly brings heterogeneity.

We decided to include trials with mixed populations in patients with CRS with or without polyps, since this is inline with the definition of CRS by the European Position Paper 2012. [4]We also included four trial which used a paired intrapatient design, but treating the two groups as independent. Sensitivity analysis omitting these trials showed that the pooled results remained consistent. Trials required data imputation where standard deviations were missing and we conducted data imputation, as guided by the Cochrane Handbook for Systematic Reviews of Intervention. [28] The majority of these studies were limited to small sample size and adopted different symptom and endoscopic scores. Clinical diversity, including variability in the agents used; dose, route, duration and the delivery methods, led to heterogeneity in the studies included in this review. We tried to overcome this risk of heterogeneity by doing a subgroup analysis where data was available but this was not possible to do in all comparisons. Our review even though it had significant heterogeneity in some outcomes, has attempted to bring the existing evidence together and represents the best evidence on this subject available.

Clinical implications of the review

Our systematic review and meta-analysis supports the use of pre-operative corticosteroids prior to FESS as it significantly reduces operative time and blood loss and significantly improves surgical field quality. Studies in relation to anaesthetic outcomes in response to intra-operative corticosteroids during FESS are limited with no significant benefit in post operative pain score and rescue analgesic requirement. More studies are required to assess the benefit of corticosteroids in this respect. Postoperative use of corticosteroids following FESS is not associated with any significant improvement in symptom scores but it is associated with better endoscopic scores in CRSwNP. Use of corticosteroids was not associated with increased risk of sinusitis, which is reassuring. There was no significant difference in the recurrence risk shown in mixed population studies of CRS, CRSwNP showed favourable results towards the steroid use. However, these results need to be interpreted with caution because these studies were limited to small sample sizes and adopted different symptom and endoscopic scores and reported a small number of bleeding, infection and recurrence events.

Summary

Preoperative use of local and systemic corticosteroids in FESS, results in significantly reduced blood loss, shorter operative time and improved surgical field quality. Studies are limited on intraoperative use of corticosteroids to reduce post operative pain. There is no significant benefit seen with the use of postoperative corticosteroids following FESS in improving symptom scores. Corticosteroids improve postoperative endoscopic scores. Risk of recurrence is reduced by postoperative corticosteroids in CRSwNP although this role is unclear in CRSsNP patients. Well-conducted large RCTs are required using, standardised inclusion criteria; specified dose, duration and route of corticosteroids; validated subjective and objective outcome measures; including reporting on long term recurrence rates and complications.

Key Points-

- Preoperative use of local and systemic corticosteroids in FESS, results in significantly reduced blood loss, shorter operative time and improved surgical field quality.
- Studies are limited on intraoperative use of corticosteroids to reduce post operative pain.
- The limited data available do not point to significant benefit with the use of postoperative corticosteroids following FESS in improving symptom scores.
- Corticosteroids improve postoperative endoscopic scores. Risk of recurrence is reduced by postoperative corticosteroids in CRSwNP although this role is unclear in CRSsNP patients.
- Well-conducted large RCTs are required using, standardised inclusion criteria; specified dose, duration and route of corticosteroids; validated subjective and objective outcome measures; including reporting on long term recurrence rates and complications.

AUTHORSHIP CONTRIBUTION

Vishal Pundir- Conception, planning, literature search, data extraction, analysing and writing up.

Jyotsna Pundir-Literature search, data extraction, analysing data.

Gillian Lancaster-Data analysis

Simon Baer & Paul Kirkland-Data analysis and initial draft.

Marjolein Cornet, E.S.Lourijsen, Christos Georgalas- Writing up and editing the draft.

W.J.Fokkens- Conception of project, writing up and editing the draft.

CONFLICT OF INTEREST

Wytske Fokkens is involved in a study with a drug eluting stent (Sinuband), has performed a number of studies with (local) corticosteroids in patients with CRS sponsored by GSK and MSD.

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Legends

Table 1. Characteristics of the studies included in the review- Role of Corticosteroids in Functional Endoscopic Sinus Surgery - A Systematic Review and Meta-Analysis

Figure1. Consort diagram - Study selection process for the systematic review of Role of Corticosteroids in Functional Endoscopic Sinus Surgery - A Systematic Review and Meta-Analysis

Figure 2. 'Risk of bias' graph: For the systematic review – Role of Corticosteroids in Functional Endoscopic Sinus Surgery - A Systematic Review and Meta-Analysis - Each risk of bias item presented as percentages across all included studies.

Figure 3. 'Risk of bias' summary: For the systematic review – Role of Corticosteroids in Functional Endoscopic Sinus Surgery - A Systematic Review and Meta-Analysis - Each risk of bias item for each included study.

Figure 4 – Forest plot of comparison - Operative outcomes

Figure 4.1.1 -Forest plot of comparison: Steroids versus No steroids.
Outcome: 1.1 Operative time. Subgroup Analysis- Population Groups

Figure 4.1.2 -Forest plot of comparison: Steroids versus No steroids.
Outcome: 1.1 Operative time. Subgroup Analysis- Mode of Drug Delivery

Figure 4.2.1 Forest plot of comparison: Steroids versus No steroids
Outcome: 1.2 Estimated blood loss. Subgroup Analysis- Population Group

Figure 4.2.2 . Forest plot of comparison: Steroids versus No steroids
Outcome: 1.2 Estimated blood loss .Subgroup Analysis-Mode of Drug Delivery

Figure 4.3.1- Forest plot of comparison: Steroids versus No steroids
Outcome: 1.3 -Surgical field quality. Subgroup Analysis- Population Groups

Figure 4.3.2- Forest plot of comparison: Steroids versus No steroids
Outcome: 1.3 -Surgical field quality. Subgroup Analysis-Mode of Drug Delivery

Figure 5 – Forest plot of comparison – Post-operative outcomes

Figure 5.1-Forest plot of comparison: Steroids versus No steroids
Outcome: 3.2 Post operative endoscopic score

Figure 5.2-Forest plot of comparison: Steroids versus No steroids
Outcome: 3.4 Risk of infection (Sinusitis)

Figure 6 Forest plot of comparison-Recurrence Risk

Table 1. Characteristics of the studies included in the review - Role of Corticosteroids in Functional Endoscopic Sinus Surgery- A Systematic Review and Meta-Analysis

Author/ Number in intervention and control group	Inclusion Criteria	Exclusion Criteria	Intervention Protocol	Control Protocol	Follow-up	Outcomes
Jorrisen et al[12] 2009 Intervention -46 Controls-45	Age ≥18 years Bilateral nasal polyposis and/or CRS, as diagnosed by history, nasal endoscopy and CT-scan. Failure to conventional medical treatment or contra-indications to medical treatment and required FESS for their disease.	Patients who had undergone sinus surgery in the last 5 years and those with surgical contra-indications, primary ciliary dyskinesia, asthma requiring inhalant CS treatment, aspirin hypersensitivity, immunodeficiency or cystic fibrosis. Patients who received systemic and topical CS within 4 weeks, IM CS within 3 months, antihistamines or leukotriene receptor antagonists within 10 days, nasal decongestants within 24 hours, and nasal sodium cromolyn, atropine or ipratropium bromide, or antifungals within 1 week of screening. Patients with contra-indications for intranasal or oral use of CS or hypersensitivity to the study drugs. Pregnant or breast feeding women.	Oral Betamethasone 2 mg for 7 days, followed by topical MFNS 200µg b.i.d for 6 months after FESS.	Matched placebo tablets and intranasal spray for 7 days and 6 months, respectively.	6 months	Total Endoscopic Scores Combination Endoscopic Scores Total Symptom Scores Rescue Medications Adverse Events
Sieskiewick et al[13] 2006 Intervention -18 Controls-18	Age-20-65 Yrs CRSwNP	Uncompensated arterial hypertension, hemostatic disorders, diabetes, Deviated nasal septum, inferior turbinate hypertrophy	30 mgs prednisalone daily 5 days before the operation.	Without steroids	100%	Total mean blood loss Operative field Surgical operative time
Albu et al [14] 2010 Intervention-35 Controls-35	CRSsNP and CRSwNP(Grade 1 polyps)	Coagulation disorders, hypertension , cardiac disorders, unilateral sinus disorders, unstable asthma , regular use of decongestant within one month of surgery, simultaneous septal or inferior	MF 200 µg (2 sprays in each nostril 2 times a day) for 4 weeks preoperative.	Placebo spray same dose for 4 weeks.	100%	Operative data- Duration of surgery Surgical field Estimated blood loss

		turbinate surgery, odontogenic sinusitis, extra mucosal mycotic sinusitis, NSAID intolerance, diabetes, history of intra and extranasal sinus procedure, CRS with grade 2 and 3 polyps.				
Rotenberg et al[23] 2011 Intervention -20 Controls-21	Age > 18 years, Diagnosis of CRSwP as per the American Academy of Otolaryngology guidelines, A Samter's triad phenotype, Failure of a minimum of 6 months of standard medical management prior to ESS, and severe disease as documented by a minimum LKES of 8.	Smokers, revision sinus surgery, CS for conditions other than CRSwP, and patients with diseases that were relative or absolute contraindications for CS use.	Saline irrigation mixed with 2 ml of 0.5-mg/ml budesonide per bottle of Sinus-Rinse, using half of the solution twice daily (for a total of 1000 lg budesonide daily).	saline irrigation	6 months	SNOT 21 Score LM CT Scan Score LKES ACTH Ranges IOP.
Cote et al[24] 2010 Intervention -19 Controls-19	Patients with CRS with polyposis refractory to medical treatment	Ineligible for informed consent, unwilling or unable to comply with post operative visits necessary for data collection, intolerance to triamcinalone.	Randomised cavity - 2 ml of 40mg/ml triamcinolone impregnated dressing.	2 ml of normal saline solution-impregnated dressing.	6 months.	LKES Score POSE Score
Chang et al[26] 2011 Intervention -16 Controls-16	Age 17 to 80 years Bilateral chronic rhinosinusitis with or without polyposis, failed maximal medical treatment, and required bilateral FESS for the treatment of CRS.	Unilateral sinus disease, Bleeding disorder; Genetic disorder such as cystic fibrosis, Immunosuppressed, or Undergoing surgery for excision of a tumour	budesonide-soaked Merocel pack	Non medicated Merocel Pack	4 weeks	Endoscopic Grading of postoperative Mucosal Healing. Biopsy Grading Scores
Bross-Sariano et al[52] 2004 Intervention - 108 Controls-54	Sinonasal polyposis	Not documented	Steroid group-saline lavage then Group I-FP 400 µg /day(54 patients) Group II-beclomethasone dipropionate 600	Saline lavage	12 months	Relapse rate of Polyps or Infection rate

			µg/day(54 patients)			
Dijkastra et al[53] 2004 Intervention - 106 Controls-56	Age > 18 years Nasal polyps or CRS requiring treatment. Abnormality on CT Scan confirming diagnosis.	Use of systemic CS or other medication influencing nasal mucosa during study. Significant anatomical abnormalities persisting after FESS +- Septoplasty History of acetylsalicylic acid intolerance, Pregnancy, Cystic fibrosis, serious concurrent disease Rhinosurgery in past 6 weeks.	FPANS 800 µg BD (53 cases) FPANS 400 µg BD (53 cases).	Placebo BD	1 year	Symptom reduction after FESS Relapse rate Effect of CS in post operative period.
Rowe Jones et al[54] 2005 Intervention -55 Controls-54	Patient with symptoms of CRS received 3 weeks of Fluticasone propionate, 100 µg (2 spray). If failed, they were considered for FESS. Patients with 4 episodes per year of acute, recurrent RS of at least 10 days duration and a persistent CT scan score of at least 3, excluding an isolated polypoidal opacity within a sinus.CT scan changes had to be present at least 4 weeks after an acute infection.	Pregnant women; age > 60 years or <16 years; patients taking regular oral steroids; patients taking > 1500 µg of inhaled CS per day; patients with antro-choanal or isolated polyps; patients requiring combined external approach and ESS patients requiring frontal sinus ostioplasty procedures; patients who had undergone sinus surgery within the last 12 months; patients with mucocoeles; patients with tumours.	FPANS 200 µg b.d.	Placebo spray comprised all constituents of standard FPANS spray, excluding fluticasone propionate.	5 years	Visual analogue score Total sum of all 6 visual analogue scores, Endoscopic polyp, oedema, discharge scores, Nasal mucociliary clearance time Olfactory detection threshold values Nasal volumes. Rescue medication Failures rate
Wright et al[55] 2007 Intervention -11 Controls-15	Age-18 yrs old, CRSwNP, Failed or refused full medical treatment.	Immunocompromised status and mucociliary disorders, allergic fungal sinusitis.	30 mg prednisalone 5 days preoperatively and 9 days post operatively.	Placebo tablets	6mths	Duration of surgery Difficulty of surgery Estimated blood loss Endoscopic score (LKES & POES) Symptom severity Questionaire score
Stjarne et al[56] 2009 Intervention -79 Controls-80	Age-18 years or older Bilateral nasal polyps.	Polypectomy within the previous 6 months; unhealed nasal surgery or trauma; > 5 previous polypectomies; or ongoing concurrent nasal infection,	Mometason furoate, 200 µg once daily.	Matching placebo spray	6 months +-7 days	Rate of relapse Time to relapse Side Effects

		rhinitis medicamentosa, hereditary mucociliary dysfunction, nasal structural abnormalities, or an idiosyncratic reaction to CS. Active or latent pulmonary tuberculosis; other significant medical conditions that could interfere with evaluations (eg, cystic fibrosis); or a history of hypersensitivity to the study medication, Women who are Pregnant, lactating, or not using an adequate prophylactic measure.				
Enhange et al[57] 2009 Intervention -30 Contols-38	Age 18 years Bilateral nasal polyps and Asthma	Unfit for GA; Polypectomy in last 6 months; Illness or medication that may interfere with the study; Idiosyncratic reaction to CS; Prohibited medication within wash-out period; Participated in clinical trial within 30 days Pregnant or lactating women; Women of child bearing potential not using adequate anti-contraceptive method Study personnel or patients related to study personnel; Aspirin Senstivity	Fluticasone proprionate nasal drops 400 µg b.i.d for 10 weeks	Matched placebo	14 weeks	Nasal symptoms scores. Asthma symptoms score. Peak expiratory flow rate Need of b2-agonists. Peak nasal inspiratory flow (PNIF) Butanol threshold test for olfactory function. Nasal endoscopy. Pulmonary function and bronchial histamine sensitivity.
Al-Qudah et al[58] 2010 Intervention -32 Controls-30	All patients undergoing elective FESS with ASA1/2.	Patients under 16 yrs, Previous systemic CS treatment for > 3 months at any time or within 1 month before randomization. Grade 3 nasal polyps.	8 mg of i/v dexamethasone sodium phosphate preoperatively.	2ml of i/v saline solution	24 Hours	Postoperative pain score-PACU – 6 and 24- Hours. Patients needing rescue anaesthesia.
Murr et al [59] 2011 Intervention -38 Controls-38	Adult patients with or without nasal polyps scheduled to undergo primary or revision FESS, and in whom placement of the sinus stents was deemed to be both feasible and	Patients were excluded if they had known history of intolerance to corticosteroids, an oral steroid–dependent condition, a history of immune deficiency, insulin-dependent diabetes, or allergic fungal sinusitis.	Bioabsorbable drug-eluting sinus stents releasing a total dose of 370 μg of MF is blended into the polymer structure	Non-eluting control stent.	45 days	Endoscopic Scores Recurrence rates Adhesion rates. Medial Turbinate Lateralization rates.

	medically appropriate		of polylactide-co-glycolide, which releases the MF by diffusion in a controlled fashion over approximately 30 days.			
Marple et al[60] 2011 Intervention - 105 Controls-105	CRS with or without nasal polyps	Patients were excluded for a known history of immune deficiency, insulin-dependent diabetes, allergy or intolerance to corticosteroids, oral steroid-dependent condition, clinical evidence of acute bacterial sinusitis, or clinical evidence of invasive fungal sinusitis. Ocular exclusionary criteria included history or diagnosis of glaucoma or ocular hypertension,closed angle, presence of cataracts grade +3 or higher, or presence of posterior subcapsular cataract.	Propel sinus implant which contains 370 μ g mometasone furoate, embedded in a polymer matrix that provides local, controlled release of the drug over 30 days.	Non-drug-releasing implant	30 days	Recurrence rates Adhesion rates. Medial Turbinate Lateralization rates. Intraocular pressure increase.
Rudmik et al [61] 2012 Intervention -18 Controls-18	Age ≥18 years old Chronic rhinosinusitis persistent symptoms despite medical management undergoing minimum bilateral ESS .	Nasal polyposis , uncorrectable coagulopathy; emergency surgical procedures; and presence of a systemic inflammatory disease.	Sinu-Foam with dexamethasone mixture .4 mL of dexamethasone (4 mg/mL) in 4 mL of sterile water.	Sinu-Foam syringes with placebo mixture (8 mL of sterile water)	3 months	Endoscopic Score.
Jin et al[62] 2012 Intervention -20 Controls-20	CRSwNP failing medical treatment and undergoing FESS	Revision Endoscopic Sinus Surgery Cases. Immunosuppressed Patients	2 ml of 40mg/ml triamcinolone impregnated dressing.(for a week)	2 ml of normal saline solution-impregnated dressing.(for a week)	3 months	LKES Score
Passali et al[63] 2003 Intervention -33	Patient with Grade 3 CRSwNP refractory to medical treatment	No exclusion criterion mentioned in the paper	Mometasone Nasal Sprays-200micrograms for	No specific Treatment	3-6yrs	Recurrence rates Rhinomanometry results

Controls-40			30 days			

Mometasone Furoate (MF), Post Anaesthetic Care Unit (PACU), Lund-Kennedy endoscopic score (LKES), Perioperative Sinus Endoscopy Scores POSE, Fluticasone Propionate Aqueous Nasal Spray (FPANS) , Sino-Nasal Outcome Test Score (SNOT 21),Lund Mackay CT Scan Score (LM Score), Adernocorticotropic Harmone (ACTH) Intra Optic Pressure (IOP); GA general anaesthesia; CS corticosteroids

Figures

Figure 4 – Forest plot of comparison - Operative outcomes

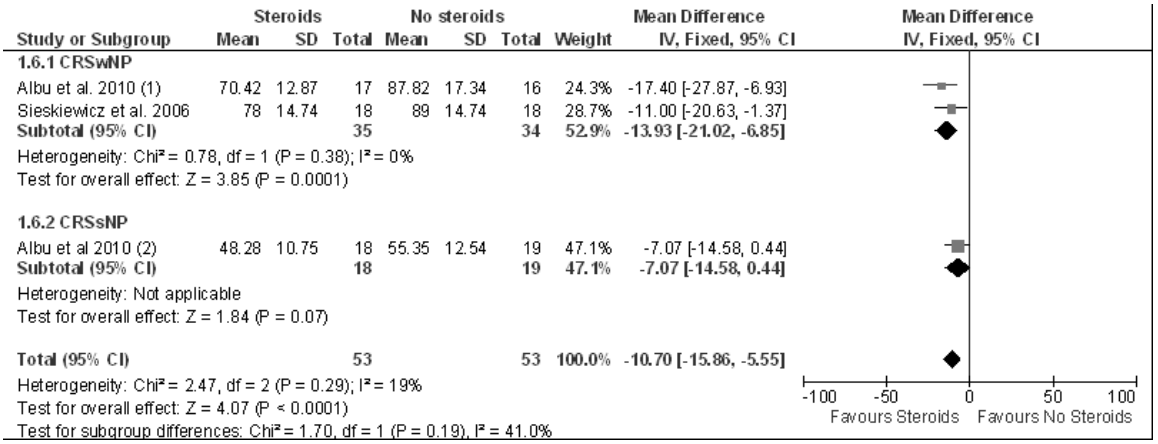


Figure 4.1.1 Forest plot of comparison: Steroids versus No steroids Outcome: 1.1 Operative time. Subgroup Analysis- Population Groups

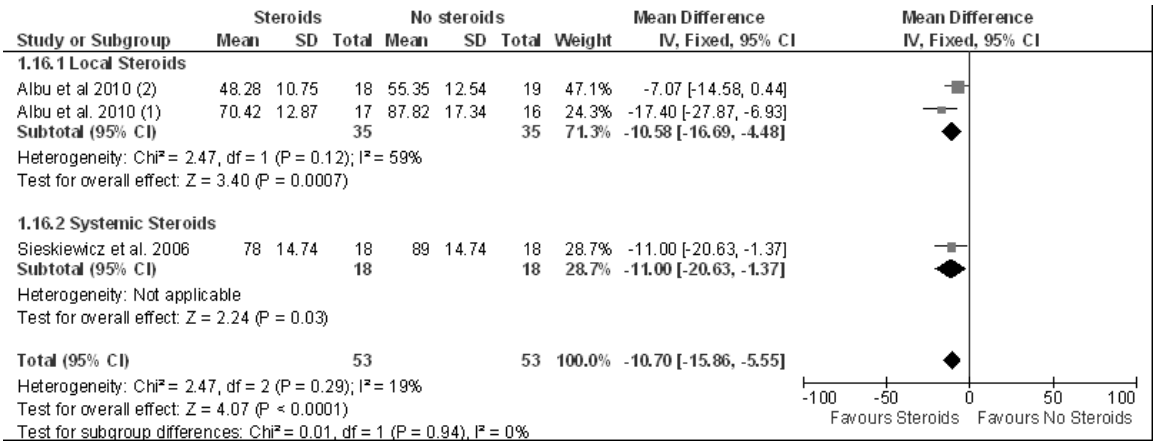


Figure 4.1.2 Forest plot of comparison: Steroids versus No steroids Outcome: 1.1 Operative time. Subgroup Analysis-Mode of Drug Delivery

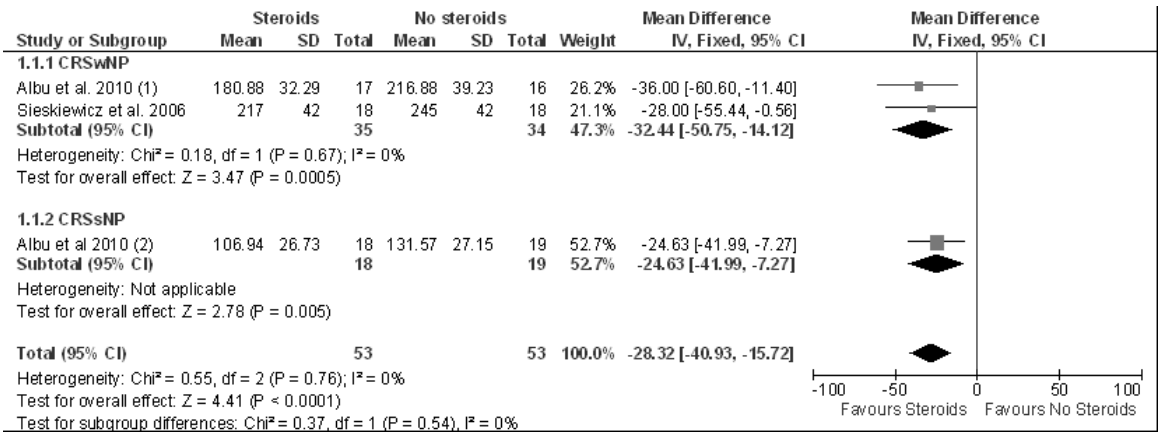


Figure 4.2.1 Forest plot of comparison: Steroids versus No steroids Outcome: 1.2 Estimated blood loss. Subgroup Analysis- Population Group

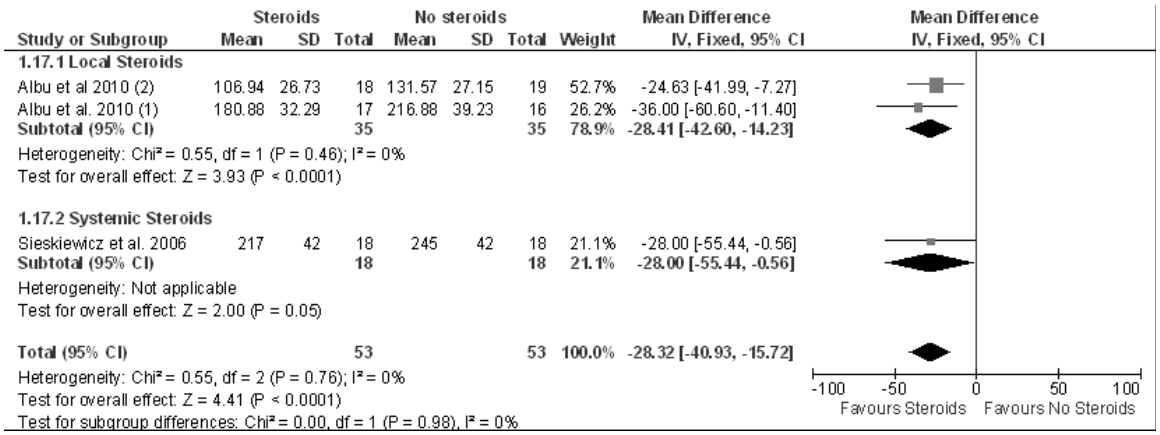


Figure 4.2.2 .Forest plot of comparison: Steroids versus No steroids Outcome: 1.2 Estimated blood loss .Subgroup Analysis-Mode of Drug Delivery

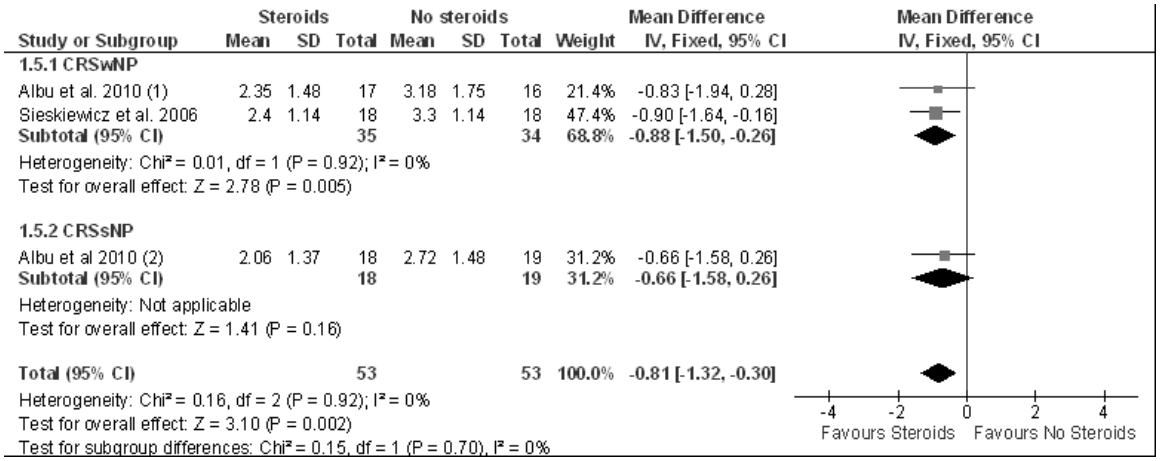


Figure 4.3.1- Forest plot of comparison: Steroids versus No steroids Outcome: 1.3 -Surgical field quality. Subgroup Analysis- Population Groups

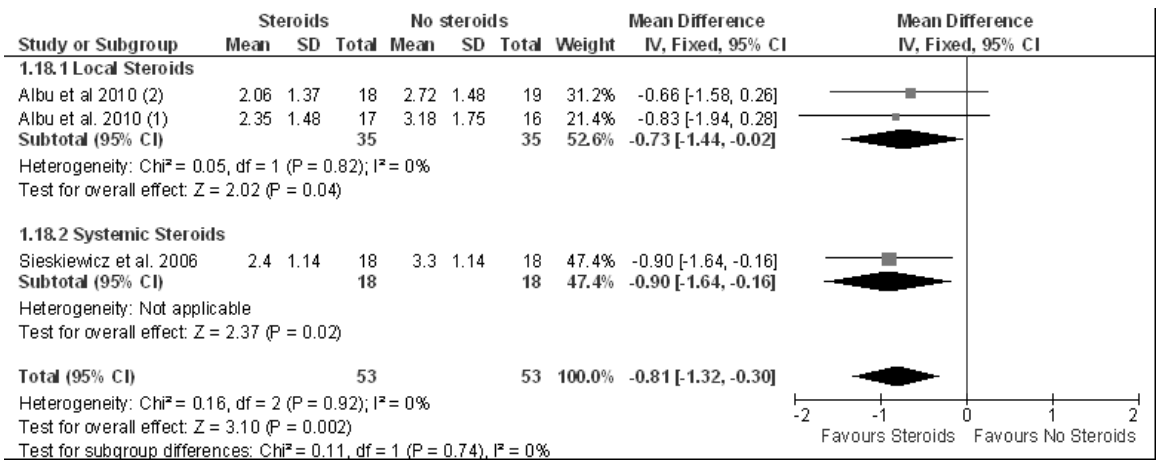


Figure 4.3.2- Forest plot of comparison: Steroids versus No steroids Outcome: 1.3 -Surgical field quality. Subgroup Analysis-Mode of Drug Delivery

Figure 5 – Forest plot of comparison – Post-operative outcomes

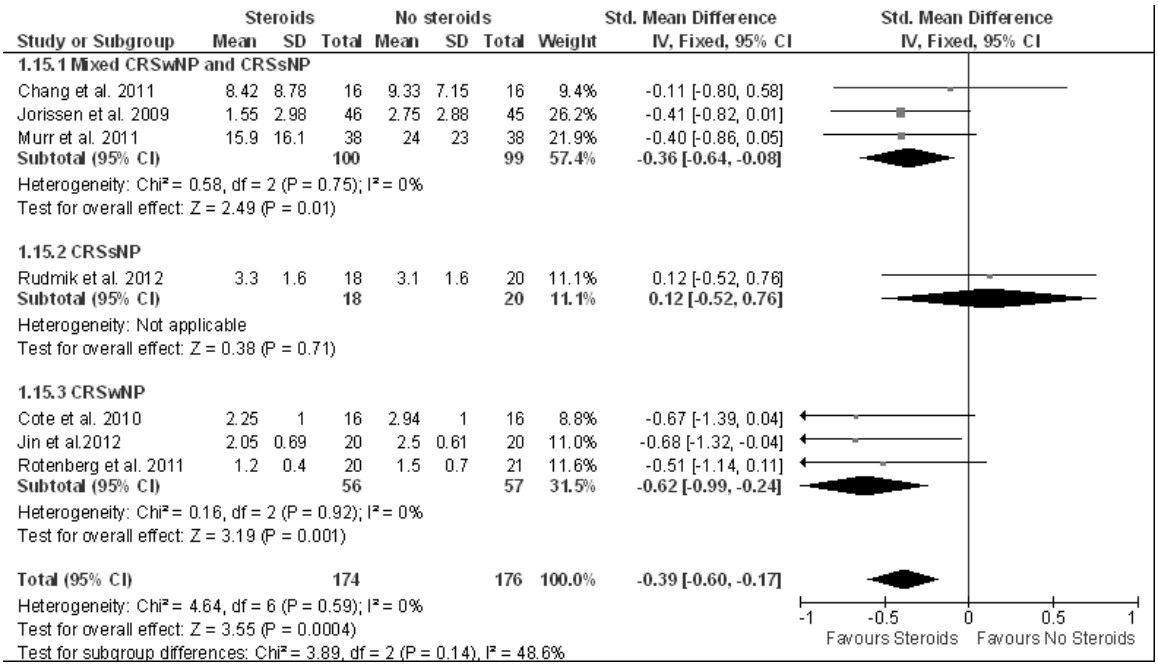


Figure 5.1 Forest plot of comparison: Steroids versus No steroids Outcome: 3.2 Post operative endoscopic score

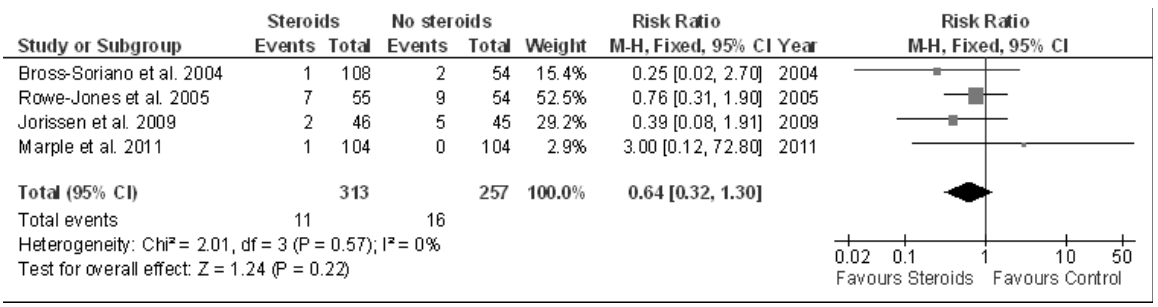
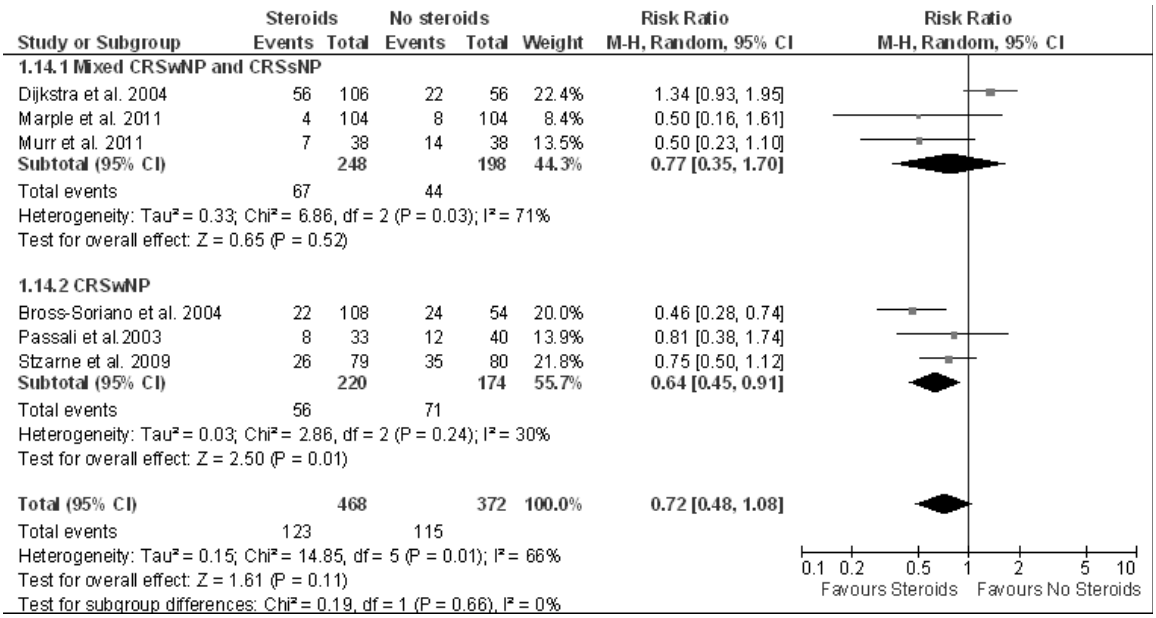


Figure 5.2 Forest plot of comparison: Steroids versus No steroids Outcome: 3.4 Risk of infection (Sinusitis)

Figure 6 – Forest plot of comparison – Recurrence risk



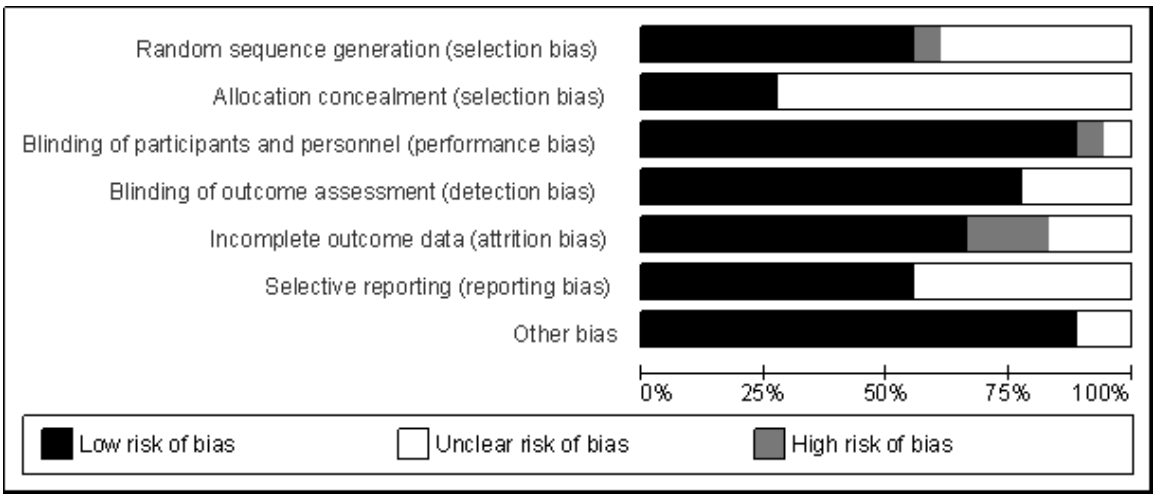


Figure 2-Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies

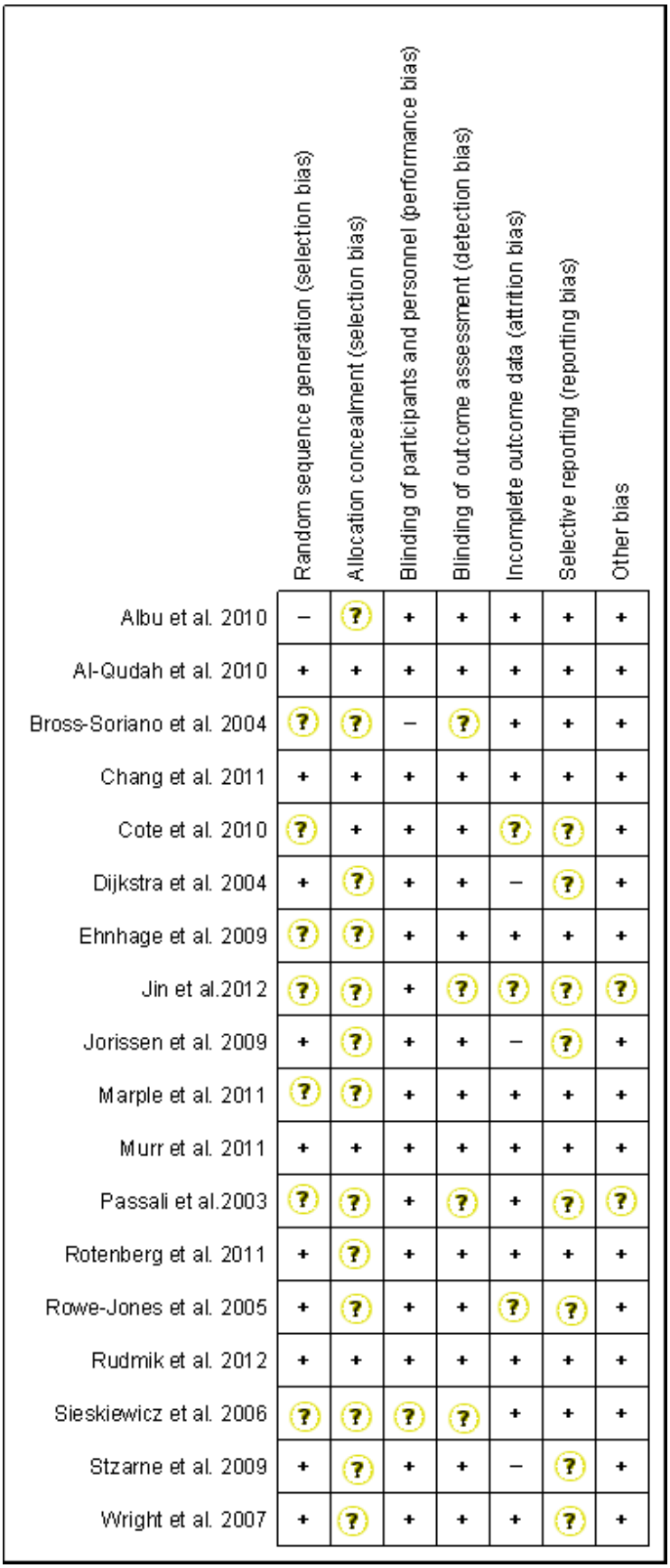


Figure 3-Risk of bias summary: review authors' judgments about each risk of bias item for each included study

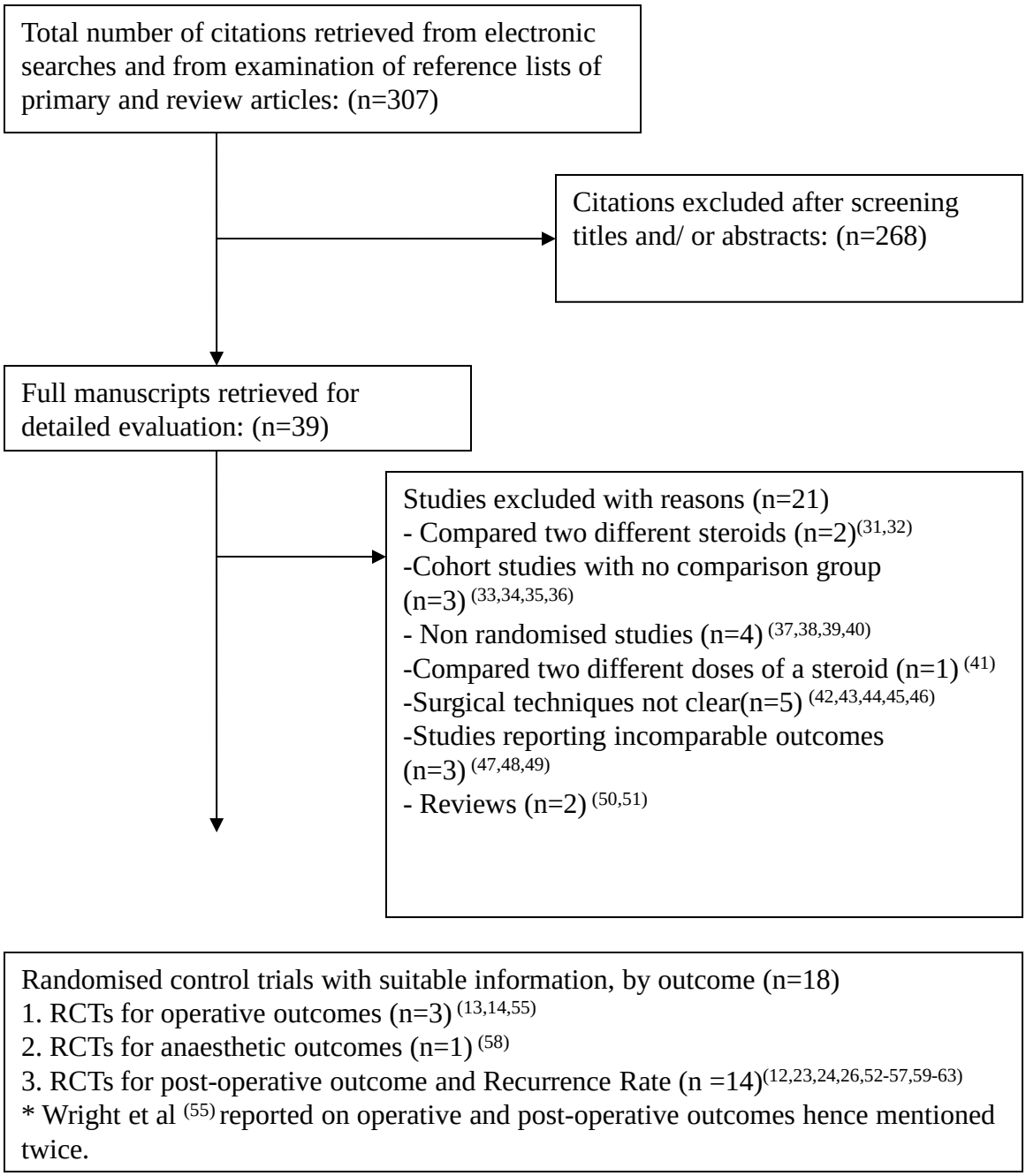


Figure1. **Consort diagram - Study selection process for the systematic review of Role of Corticosteroids in Functional Endoscopic Sinus Surgery- A Systematic Review and Meta-Analysis**