Effect of dexamethasone on reducing pain and gastrointestinal symptoms associated with cesarean section: a systematic review and meta-analysis

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Keywords: Dexamethasone, cesarean, pain, nausea, vomiting

Abstract

Background: *Dexamethasone has analgesic and antiemetic actions that have been documented in the literature. Therefore, we performed a systematic review and meta-analysis to investigate its overall effectiveness in reducing a variety of negative outcomes after cesarean section.*

Objectives: *To investigate the efficacy and safety of dexamethasone for reducing pain associated with cesarean section, nausea, vomiting, pruritus, postoperative need for analgesia, postoperative antiemetic requests and headache.*

Methods: *We searched PubMed, Cochrane CENTRAL, SCOPUS, and Web of Science for relevant clinical trials. We then performed a systematic review and meta-analysis, including only randomized, placebo-controlled clinical trials. Our main population target was women undergoing elective cesarean delivery. The intervention under consideration was dexamethasone administered both by intravenous (IV) or subcutaneous (SC) over a variety of doses. The comparator was a placebo. Our main outcomes included: (1) perceptions as indicated by pain scores, (2) occurrence of nausea and (3) occurrence of vomiting. Secondary outcomes included: (4) occurrence of pruritus, (5) need for postoperative analgesia, (6) need for postoperative antiemetic drugs and (7) occurrence of headache. We assessed the quality of included studies using the risk of bias tool described in Cochrane's handbook for systematic reviews of interventions.*

Results: *We found that dexamethasone seemed to significantly reduce scores for pain at rest ($p<0.001$), as well as occurrence of nausea ($p<0.001$) and vomiting ($p<0.001$). The drug also*

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showed significant reduction of negative symptoms in other secondary outcomes, including need for postoperative analgesia (p<0.001) and postoperative antiemetic drugs (p<0.001). However, the drug showed no significant effect in reducing headache and pruritus or in improving pain at movement scores.

Conclusion: *Dexamethasone appears to decrease perception of pain at rest and protects against nausea and vomiting. However, it does not seem effective against headaches or pruritus.*

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Introduction

Cesarean delivery is an intensive procedure that demands a longer healing process than vaginal delivery. Nevertheless, it is one of the most prevalent surgical procedures in obstetrics and gynecology. As such, it has been performed with increasing frequency in recent years,[1] and has played a prominent role in decreasing perinatal morbidity and mortality. Cesarean section (CS) may be medically mandatory for various reasons, including when labor is not progressing, in cases that have of a history of multiple gestations, when the fetus experiences an emergency or severe health concern, if the mother has a contagious virus or when there are complicating conditions, such as diabetes or hypertension.[2,3] During this procedure, patient discomfort is addressed with general anesthesia, and epidural or spinal blocks. However, patients may also experience a number of postoperative complications, including pain, vomiting, pruritus, headache and nausea.[4]

Dexamethasone is a glucocorticoid, known for its potent anti-inflammatory effect, which can be used as a postoperative pain control agent in many surgeries, including obstetrical and gynecological procedures.[5-7] In addition, it can be used as an antiemetic in various surgeries.[8,9] Although the mechanism of action of glucocorticoids is not fully understood, suggested theories include inhibiting the production of inflammatory mediators such as prostaglandin and bradykinin, preventing reduction of the "pain threshold" that occurs during surgeries, and decreasing tissue swelling through its anti-inflammatory effects and thereby inhibiting nerve compression by inflammatory tissue.[10-12]

Multiple studies confirm the analgesic and antiemetic effects of dexamethasone in various surgeries such as laparoscopic hysterectomy and CS.[13,14] The literature is full of clinical trials investigating the effect of dexamethasone on pain, nausea and vomiting. However, only a few of the systematic review and meta-analysis studies have investigated only the postoperative efficacy of dexamethasone, as Allen et al. did when they investigated its effect after both hysterectomy and cesarean section operations.[15] In addition, we intended to investigate the postoperative effects of dexamethasone when it is administrated at different doses (2.5, 8, 10, or 16 mg) and by different routes (intravenous (IV) or subcutaneous (SC)). However, the existing heterogeneity between studies and the low number of studies that investigate some doses (such as 2.5 or 16 mg) acted as limitations on this study and suggest areas for future research.

As a result, we aim to investigate the impact of any dose of dexamethasone administered either by IV or SC routes on perception of pain and the incidence of nausea and vomiting.

Materials and Methods

In this analysis, we followed PRISMA guidelines.[16] We performed a systematic search for published, randomized clinical trials comparing dexamethasone (given in any dose, by any route of administration except by transverse abdominal plane block or intrathecal route) with placebo for decreasing post-CS pain. Efficacy was determined using pain scores -- as estimated using a Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS) -- as well as occurrences of nausea and vomiting to determine primary outcomes in patients scheduled for elective CS at term. Our secondary outcomes included relative occurrence of headache, pruritus, postoperative rescue analgesia and postoperative rescue antiemetic.

Searching and Eligibility Criteria

To find data for this study, we searched PubMed, Web of Science, the Cochrane Central Register of Controlled Trials, and Scopus. The search strategy used was ((((((((((((((Dexamethasone) OR Dexamethasone (MeSH Terms)) OR Methylfluorprednisolone) OR Hexadecadrol) OR Decameth) OR Decaspray) OR Dexasone) OR Dexpak) OR Maxidex) OR Millicorten) OR Oradexon) OR Decaject) OR Decaject-L.A) OR Decaject L.A) OR Hexadrol)) AND ((((((((((Cesarean) OR Cesarean Section) OR Cesarean Section(MeSH Terms)) OR Caesarean Sections) OR Abdominal Delivery) OR C-Section) OR C-Sections) OR Abdominal Deliveries) without language restriction, up to August, 2020.

Eligibility criteria were as follows: (1) limited to women undergoing CS, (2) intervention: dexamethasone IV or SC, (3) comparator: placebo, (4) outcome data: pain, nausea and vomiting, and (5) study design: randomized clinical trials. We excluded animal trials, conference abstracts and irrelevant articles.

Data extraction

We extracted the following data from each of the prior studies that met the inclusion criteria: (i) anesthetic drug and technique; (ii) dose, timing and route of administration of dexamethasone; (iii) basic characteristics of study participants such as age, weight, body mass index (BMI), weeks of gestation, duration of operation, drugs used for relieving pain or gastrointestinal (GIT) symptoms, as well as the scales used to assess pain scores; (iv) outcome measures including pain score, and incidences of nausea, vomiting, headache, pruritus, postoperative rescue analgesia, postoperative rescue antiemetic and retching.

Risk of bias for included studies

We assessed the risk of bias (ROB) in each of the studies according to the Cochrane's risk of bias tool.[17] We imported articles using EndNote (X8.2), removing duplicates. Remaining studies were then screened according to eligibility criteria. We extracted data and performed an analysis using RevMansoftware.

Data Synthesis and Analysis

For our study, we performed an analysis

of the data our selected studies reported during the first 24 hours postoperatively. Pain outcomes were reported in a variety of ways: some studies reported pain at movement, others reported at rest pain, and some studies did not report if pain occurred during movement or at rest but were assumed to have been taken at rest, as in Allen et al.[15] Extracted dichotomous data were analyzed using relative risks (RRs) with 95% confidence intervals (CIs). A lack of statistical significance across groups was assumed if the value of CI at 95% was 1. Meanwhile, in continuous data, the likelihood of statistical significance was represented using means and standard deviations, while standardized mean difference (SMD) with 95% CI were used for summarization.

A value of 1 at 95% CI was chosen to indicate a lack of statistical significance. Formulas recommended by Hozo et al.[18] were used to determine mean and standard deviation from data expressed as median and range in the studies evaluated in this research. In most cases, a fixed text model was used as a default. However, when outcomes were heterogeneous, a random-effects model was used. Significant heterogeneity was defined as P (value for heterogeneity) < 0.1 and as I2> 50%. In a search for causal factors, heterogeneous outcomes were solved first by attempting the leave-one-out method, then by performing subgroup analysis. Forest plots were used as graphical representations of outcomes for both groups. Funnel plots, as described by Egger et al., were used to assess any publication bias.[19] When outcomes were not consistently reported, and quantitative analysis was inappropriate, they were reviewed qualitatively.

Results

Results of the literature search

Our literature search found 1344 published articles. After removing 346 duplicates, the remained 998 articles were used for title and abstract screening. During this process, we excluded 934 additional studies, so that 64 studies remained for full-text screening. After the full-text screening, 40 articles were excluded as they did not match the inclusion criteria. As a result, only 24 articles were included in our study. (Figure 1) The included studies had a combined total population of 2840 patients, 1560 in dexamethasone groups and 1280 in placebo groups. Some studies used dexamethasone 8 mg by IV route,1[1,13,20-35] while others used 16 mg dexamethasone by both SC and IV routes as separate groups.[36,37] One study reported three dexamethasone groups using various doses (2.5 mg, 5 mg, and 10 mg) by IV route.[38] Another study used 2 mg of dexamethasone,[39] while a third used 0.6 mg/kg of dexamethasone (10 mL).[40] Some studies introduced the intervention pre-operatively, [11,13,23,27,28,30,34] while other studies introduced the intervention intra-operatively. [21,22,24-26,29,31-33,35,37,38,41] The remaining studies introduced the intervention post-operatively. [20,36,39] One study did not report the time of administration.[40] (Supplemental Table 1)

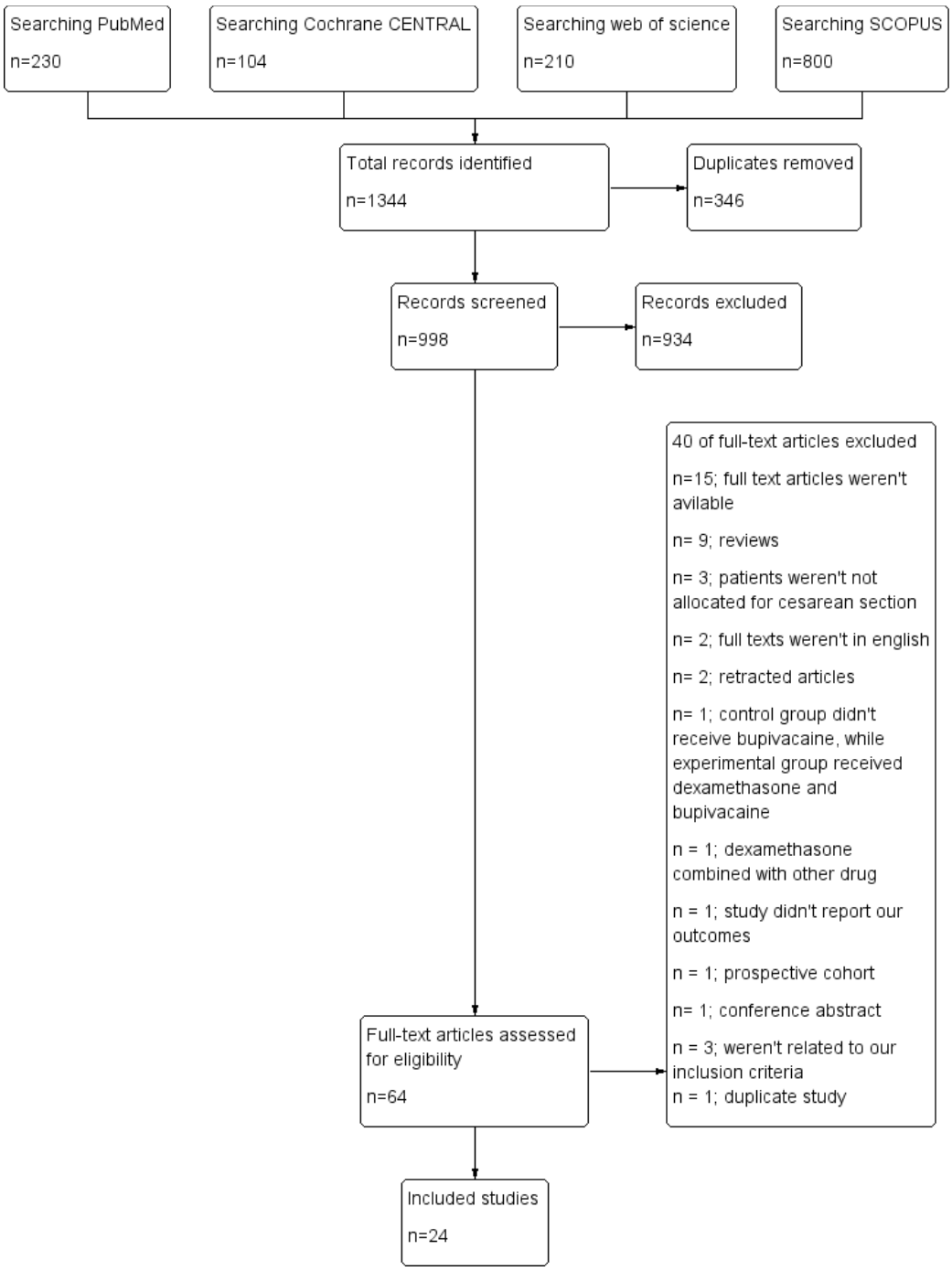

Figure 1. PRISMA flow diagram for searching results and screening process

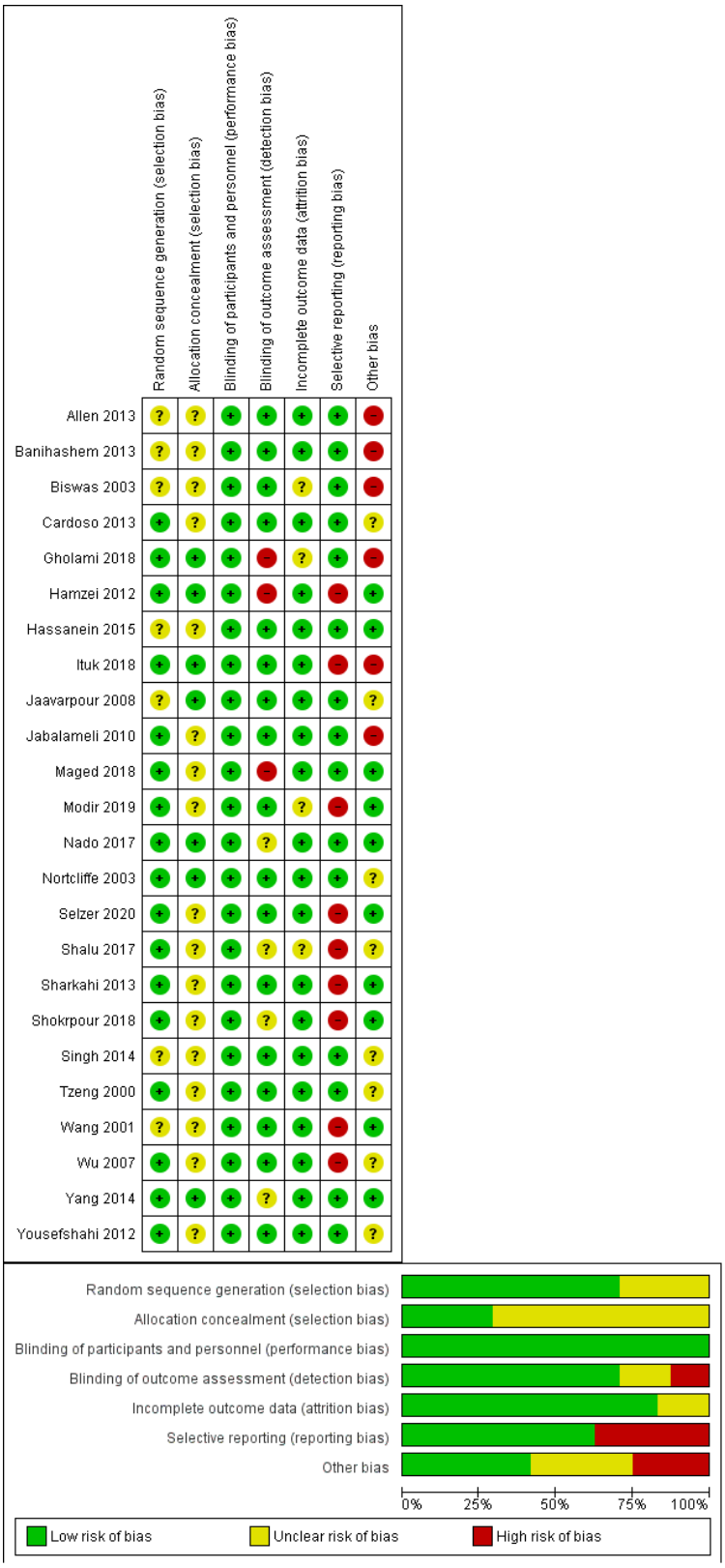

Figure 2. Risk of bias summary of included studies

Results of risk of bias assessment

Assessment of risk of bias in the included studies is outlined in Figure 2. With regard to random sequence generation, all studies were at low risk for bias except for seven studies rated at unclear bias as they did not report sufficient information. [24,27,28,30,32,35,38]

In most of the studies included in this research, the allocation concealment process was clearly stated.[20,29,31-33,40,41] However, seventeen of the randomized, controlled studies (RCTs) used had unclear risk as authors did not indicate if they performed allocation concealment.[11,13,21-28,30,34-39]

All studies showed low-risk performance bias with regard blinding of participants and personnel. While almost all studies demonstrated blinding of outcome assessors, four studies did not report enough information to determine the extent of blinding.[22,23,33,41] Furthermore, three trials had a high risk of bias as they were single-blinded.[29, 36, 40]

Almost all studies showed low risk for bias due to incomplete outcome data, except four trials did not explicitly report on missing data points.[22,28,39,40]

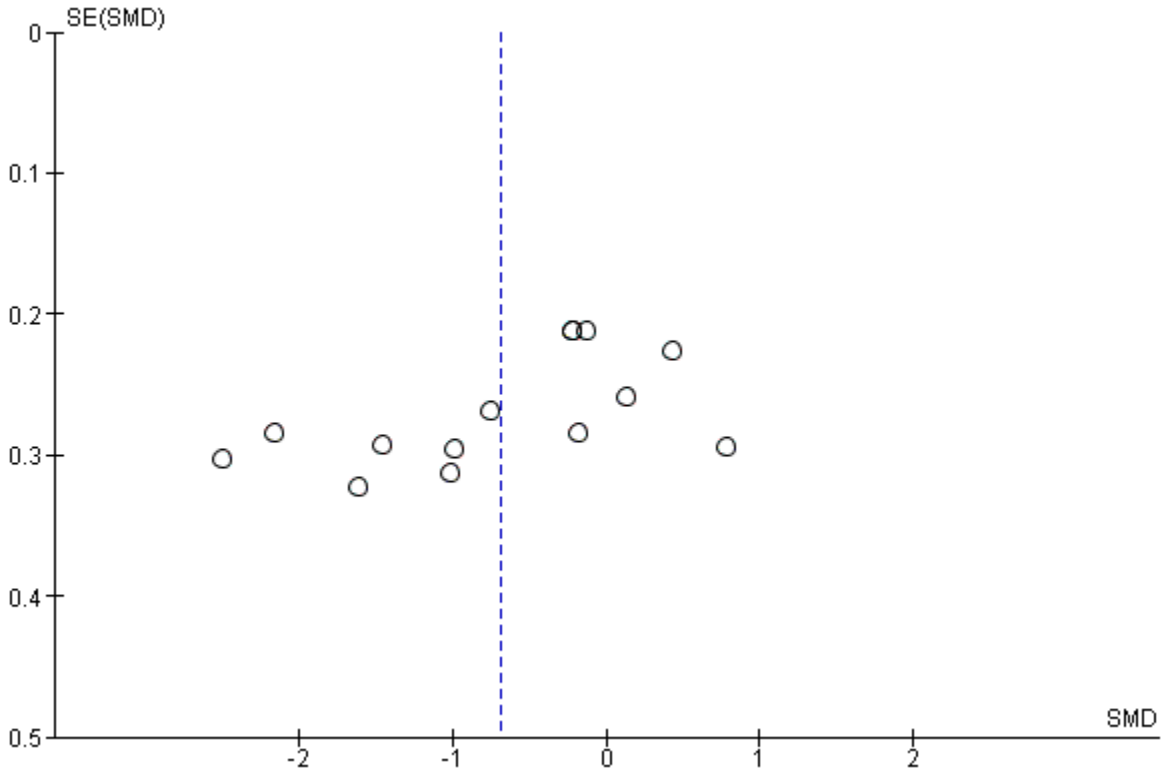

Figure 3. Publication bias in pain at rest outcome

The majority of studies included in this research showed low risk for bias due to selective reporting strategies. Only nine studies were considered high risk: five studies reported data ineligible for meta-analysis[11,22,34,38,39] and four studies did not report important primary outcomes.[21,23,29,31] Ten studies were free from other bias.[21,23,29,30,33,34,36,38,39,41] Eight studies had unclear risk; two did not evaluate P-values for rescue analgesic outcomes,[20, 25] and six studies did not publish protocols.[11,13,22,24,26,32]

The rest of the studies showed high risk for adjusted small sample size,[27,28,31,32,40] and for ending before completing enrollment of their subjects.[35]

More than ten studies reported three outcomes; therefore, publication bias estimation was possible. A Begg's funnel plot showed no publication bias regarding vomiting and pain-at-rest outcomes (Figures 3, 4), as these studies were scattered symmetrically. However, outcomes for nausea were significant for publication bias. (Figure 5)

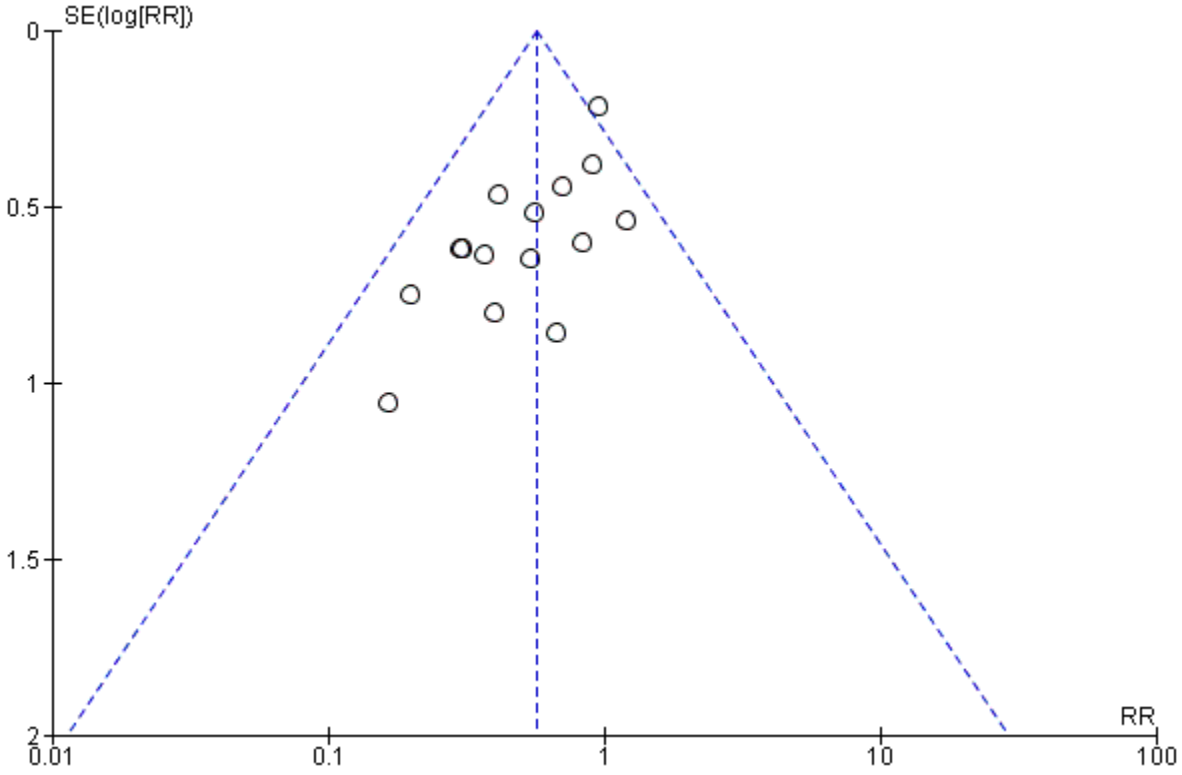

Figure 4. Publication bias in vomiting outcome

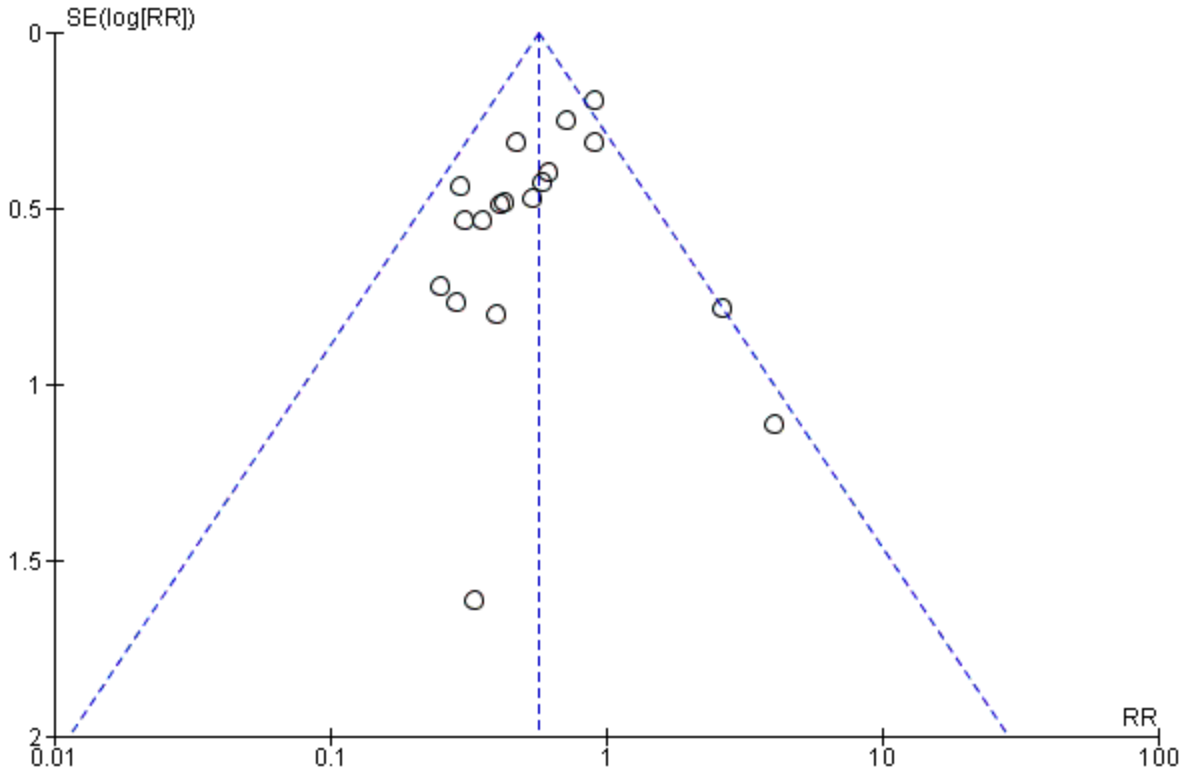

Figure 5. Publication bias in nausea outcome

Synthesis of Results

Findings for the various adverse outcomes of CS were evaluated for homogeneity as opposed to heterogeneity of findings across included studies, dosages and methods of administration (IV v. SC). Each potential adverse outcome varied with respect to these features. In some instances, there was little difference between dexamethasone groups and those given placebo. In other cases, the frequency with which dexamethasone relieved adverse symptoms varied across dosages and method of administration (IV v. SC). Findings that favored dexamethasone groups indicated that the majority of original study findings showed reduction or elimination of negative symptoms or medication needs.

Pain scores

Thirteen studies reported outcomes based on pain scores.[11,13,20-22,27,31,32,34-38] Some studies reported pain scores at movement while others reported scores at rest. Unique to the four studies that reported pain at movement,[11,13,31,35] was a lone study that reported data that was not eligible for analysis. In this case, Cardoso et al., reported a significant decrease in at-movement pain at 24 hours post-procedure in the dexamethasone group of 5 (14%) as compared with the placebo group of 15

(43%, P =0.01).[13] Of the three remaining studies in our meta-analysis,[11,31,35] pain scores were not significantly decreased in dexamethasone groups (SMD = -0.54, 95% CI (-1.39, 0.31), P = 0.22). A random-effects model was used to resolve the heterogeneity (P = 0.001, I^2 = 85%) in these findings. (Figure 6A) Because heterogeneity was solved by the leave-one-out method, data from Wu et al. was not included in findings for pain.[11] As a result, the standard mean deviation (SMD) became -0.10, 95% CI (-0.50, 0.29), P = 0.61. With this change, the results became homogeneous (P = 0.59, I^2 = 0%). (Figure 6B)

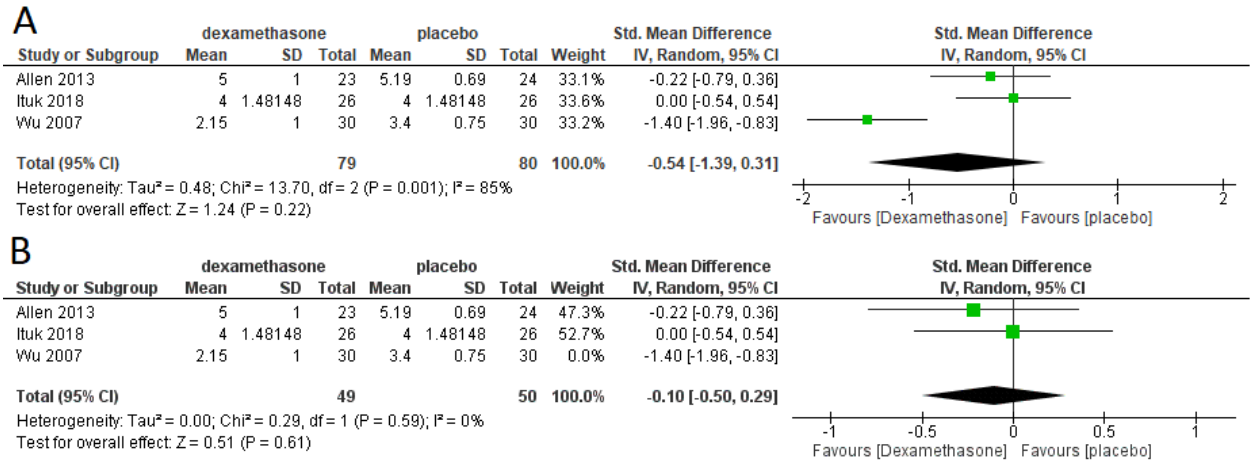

Figure 6. Effect of dexamethasone on relieving movement pain

Figure 6A. Effect of dexamethasone on relieving movement pain before removing Wu et al.
Figure 6B. Effect of dexamethasone on relieving movement pain after removing Wu et al. to solve the heterogeneity

The remaining studies reported findings for pain at rest.[11,13,20-22,27,31,32,34-38] Of these, three studies were not eligible for analysis. Cardoso et al. reported no difference in the incidence of pain at 24 hours between participants receiving 8 mg IV dexamethasone (n = 5, 14%) and placebo (n = 10, 29%),[13] while Shalu et al. reported a significant decrease in pain scores at 24 hours in a group given IV dexamethasone (mean = 5) as compared with a group given IV saline (mean = 6, p <0.001).[22] In addition, Selzer et al. found no significant difference in pain score between two groups at 48 hours.[34] With these exclusions, ten studies remained for analysis.[11,20,21,27,31,32,35-38] Overall, the total mean standard deviation for pain scores across all studies for participants receiving dexamethasone was significant (SMD = -0.78, 95% CI (-1.23, -0.32), P = 0.0009). (Figure 7A) Pooled results were heterogeneous (P = 0.00001, I^2 = 91%). This heterogeneity was assumed to be the result of random effects but could not be resolved by either by leave-one-out or subgroup analysis. Similarly, subgroups based on dose, route of administration, country of residence, anesthetics used, or administration time did not solve

heterogeneity.

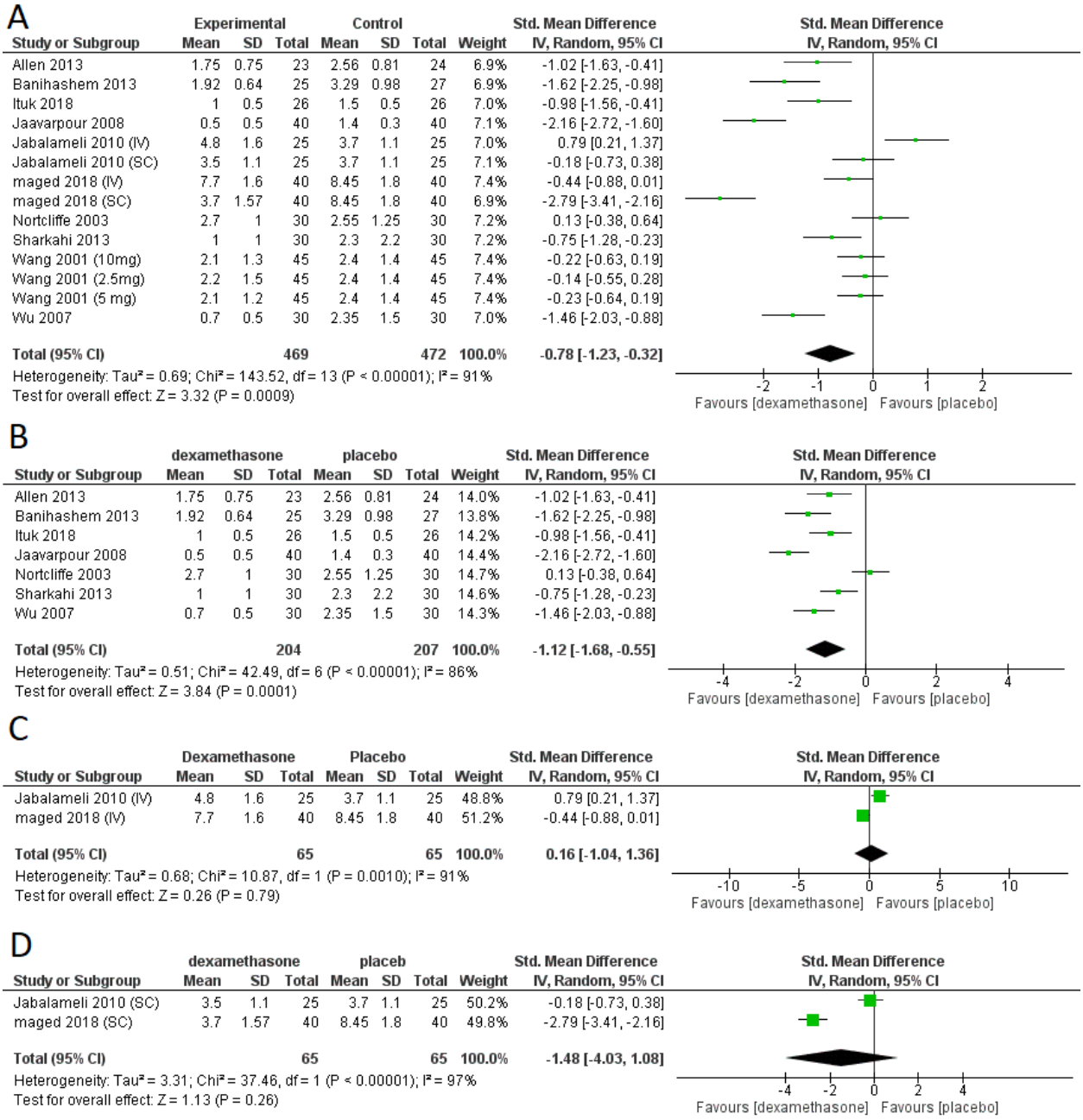

Figure 7. Effect of dexamethasone on relieving rest pain

Figure 7A. Overall analysis of all doses of dexamethasone on relieving rest pain
Figure 7B. Analysis result of 8 mg IV dexamethasone on relieving rest pain
Figure 7C. Analysis result of 16 mg IV dexamethasone on relieving rest pain
Figure 7D. Analysis result of 16 mg SC dexamethasone on relieving rest pain

In general, differences in pain scores for the dexamethasone groups did not vary widely from those for placebo. However, there was variation based on dosage given. For example, pain scores were significantly decreased for 8mg of IV dexamethasone as compared with placebo (SMD = -1.12, 95% CI (-1.68, -0.55), P = 0.0001).[11,20,21,27,31,32,35] (Figure 7B) However, the SMD was not significantly different with 16 mg of IV or SC dexamethasone, (SMD = 0.16, 95% CI (-1.04, 1.36), P = 0.79 and SMD = -1.48, 95% CI (-4.03, 1.08), P = 0.26) respectively.[36,37] (Figures 7C, 7D) Similarly, there was no significant difference between 2.5, 5 or 10 mg of IV dexamethasone and placebo.[38]

Nausea

In this research, 17 out of 24 studies reported outcomes for the occurrence of nausea. [11,13,20,24,25,27,28,30-36,38,40,41] Ituk et al. did not report data eligible for meta-analysis. They found no significant difference between dexamethasone and placebo groups with regard to nausea severity scores across the following periods: (1) from 6 to 12 hours, p = 0.82, (2) from 12 to 24 hours, p = 0.67, or (3) from 0 to 6 hours, p = 0.10.[31] Selzer et al. also found no significant difference between the two groups at 48 hours.[34]

Findings for the remaining 15 studies indicated that the relative risk (RR) of the occurrence or severity of nausea was significantly more likely in the dexamethasone group (RR = 0.57, 95% CI (0.47, 0.69), P < 0.00001). Pooled results were homogeneous (P = 0.14, I^2 = 27%). (Figure 8A) In studies in which 8 mg IV dexamethasone was administered, the RR most significantly favored the dexamethasone group (RR = 0.55, 95%CI (0.42, 0.72), P < 0.001), indicating decreased occurrence or severity of nausea. (Figure 8B)

The incidence of nausea was significantly lower in groups that received 2.5, 5 and 10 mg of IV dexamethasone as compared with those who received placebo.[38] Nausea incidence significantly decreased with a16 mg IV dose, and there were no significant differences between groups that received 16 mg SC dexamethasone and those who were given placebo.[36] Relative risk of nausea was also not significant among those given 0.6 mg/Kg of IV dexamethasone.[40]

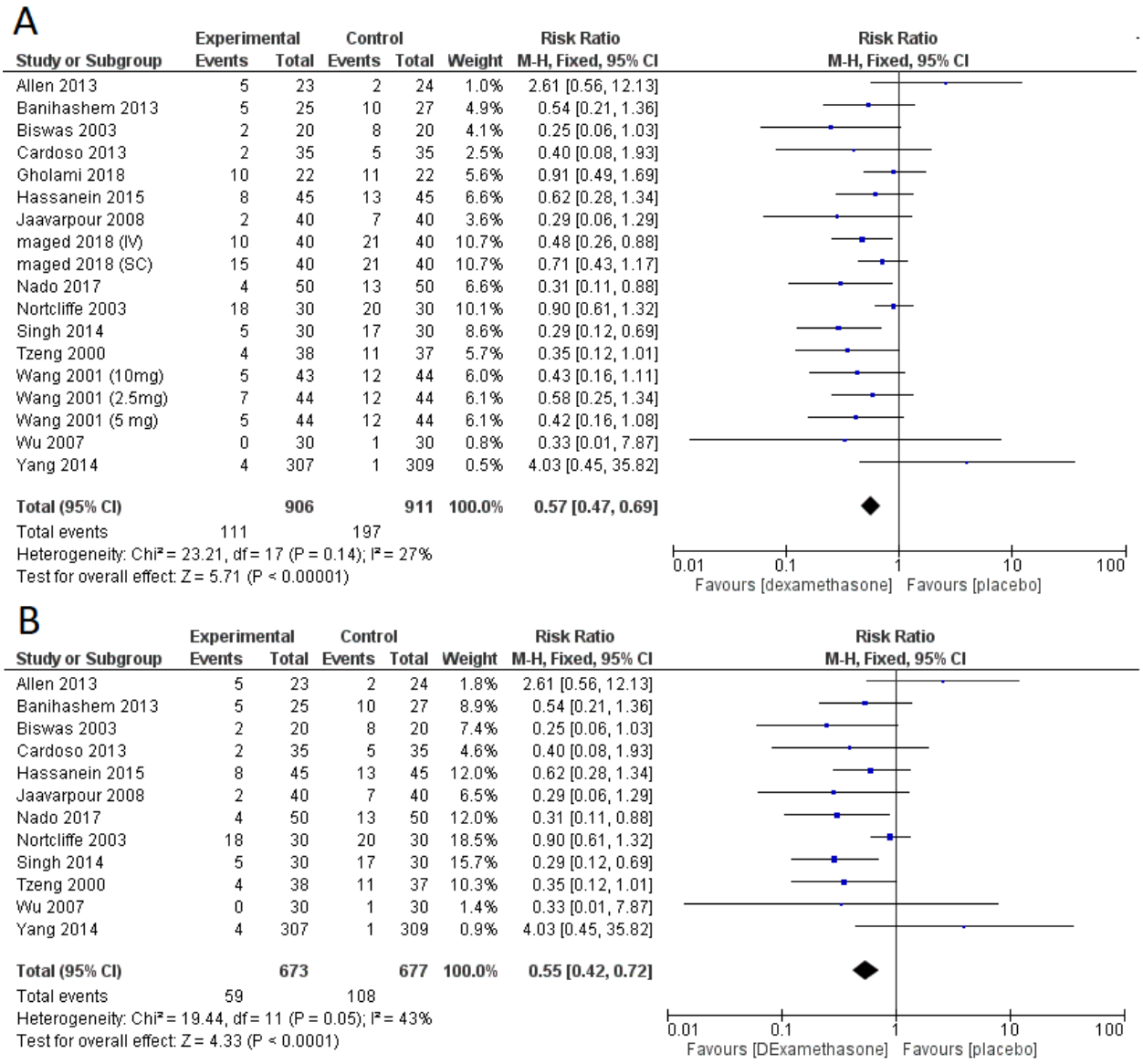

Figure 8. Effect of dexamethasone on decreasing nausea incidence

Figure 8A. Overall analysis of all doses of dexamethasone on decreasing nausea
Figure 8B. Analysis result of 8 mg IV dexamethasone on decreasing nausea

Vomiting

Seventeen studies used in this research reported outcomes for occurrence of vomiting.[11,13,20,21,24-28,30-35,38,39] Four studies did not provide sufficient data for analysis. Sharkahi et al. reported a significant difference in vomiting severity

upon recovery room entrance between the dexamethasone and placebo groups, P < 0.001.[21] However, there were no significant reported differences during the remaining period of the Sharkahi study.[21] Yousefshafhi et al. reported no significant difference in the incidence of nausea and vomiting between the two groups, where n = 99 (54.4%) in the dexamethasone group and n = 92 (51.7%) in the placebo group and P = 0.673.[26] Modir et al. reported no significant difference in intraoperative and postoperative vomiting VAS scores between dexamethasone and placebo groups.[39] Selzer et al. reported that the incidence of postoperative nausea and vomiting at 48 hours was higher in the dexamethasone group, where n = 29 (52.7%) than the incidence in the placebo group, where n = 24 (45.3%).[34] However, this was not a significant difference. For the 13 remaining studies,[11,13,20,24,25,27,28,30-33,35,38] overall relative risk significantly favored the use of dexamethasone (RR =0.57, 95% CI (0.44, 0.73), P<0.001). In addition, pooled results were homogeneous (P= 0.32, I^2 =12%). (Figure 9A) The RR in studies using 8 mg IV dexamethasone significantly favored the use of dexamethasone for the reduction of vomiting (RR = 0.61, 95%CI (0.46, 0.81), P < 0.001). (Figure 9B) Meanwhile, the incidence of nausea and vomiting was significantly lower for groups given 2.5, 5 and 10 mg of IV dexamethasone compared as with those given placebo.[38]

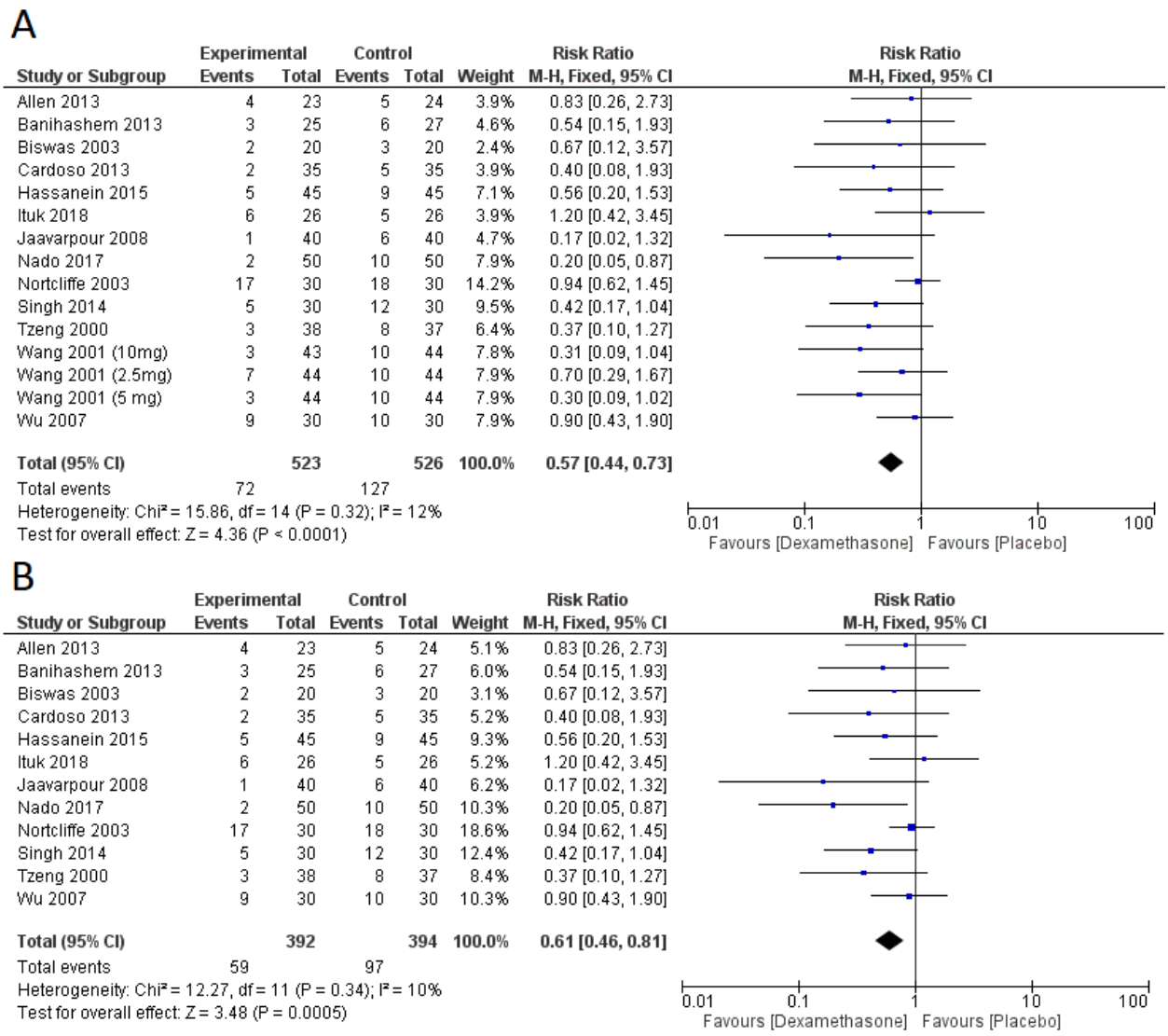

Figure 9. Effect of dexamethasone on decreasing vomiting

Figure 9A. Overall analysis of all doses of dexamethasone on decreasing vomiting
Figure 9B. Analysis result of 8 mg IV dexamethasone on decreasing vomiting

Headache

In this research, five studies reported outcomes for the incidence of headaches.[23,26,29,40,41] The total RR did not show a significant difference between either of the two groups (RR = 0.92, 95% CI (0.37, 2.31), P = 0.86). Pooled results were heterogeneous (P = 0.0008, I^2 = 79%) (Figure10A). Neither

leave-one-out or subgroup analysis according to dose, administration route, the drug used for anesthesia or country of residence of study participants could be used to resolve these differences across these studies. The RR was not significantly different between 8 mg and 0.6 mg doses of IV dexamethasone (RR = 0.98, 95% CI (0.31, 3.05), P = 0.86).[40] (Figure 10B)

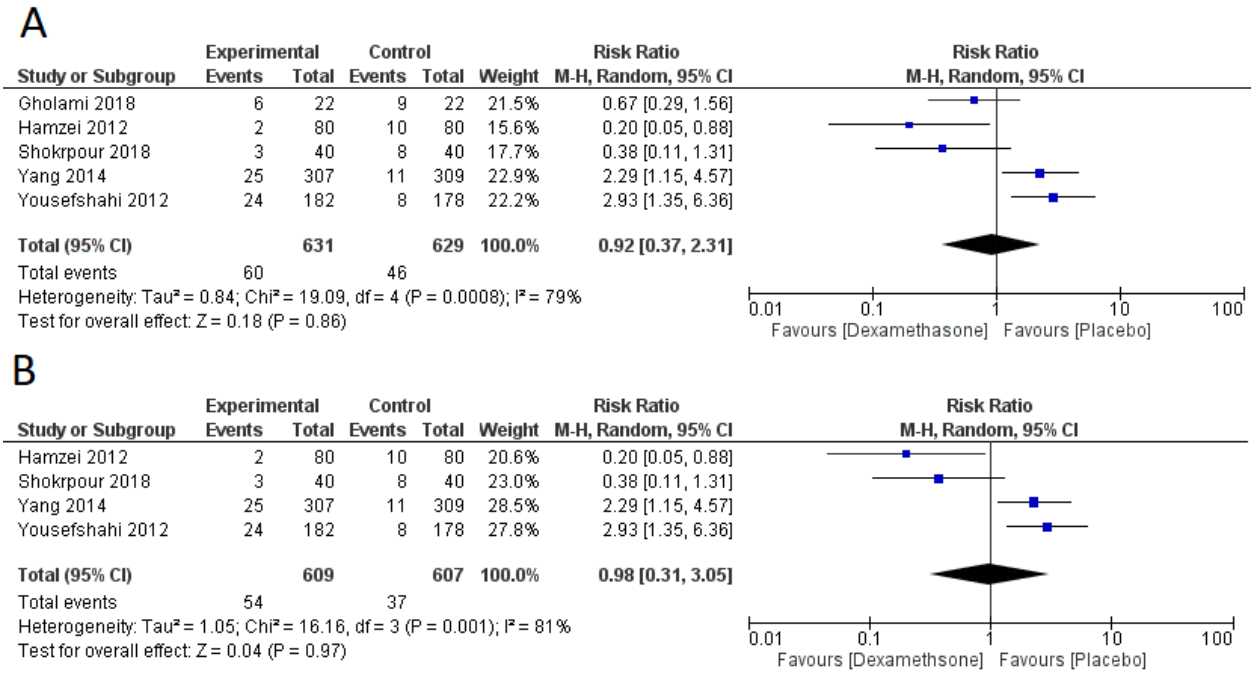

Figure 10. Effect of dexamethasone on decreasing headache

Figure 10A. Overall analysis of all doses of dexamethasone on decreasing headache
Figure 10B. Analysis result of 8 mg IV dexamethasone on decreasing headache

Pruritus

Four studies reported outcomes for the occurrence of pruritus.[11,20,25,27] The total RR of pruritus incidence did not favor any group (RR = 0.96, 95% CI (0.80, 1.14), P = 0.61). Pooled results were homogeneous (P = 0.95, I^2 = 0%). (Figure 11)

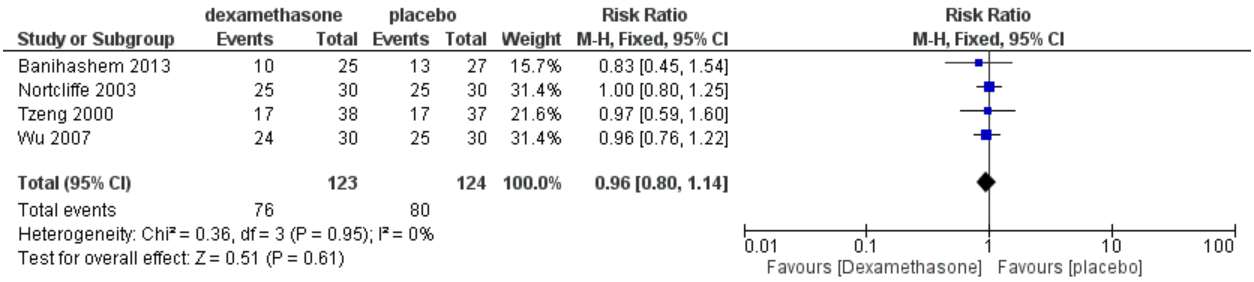

Figure 11. Effect of dexamethasone on decreasing pruritus

Postoperative rescue analgesia

Six studies reported outcomes involving a need for post-operative rescue analgesic.[11,20,25,34,36,38] However, Selzer et al. found no significant difference in the amount of analgesic drugs used in 48 hours between the two groups, and therefore it was not eligible for use in our meta-analysis.[34] The total RR of the remaining five studies favored dexamethasone significantly (RR = 0.70, 95% CI (0.59, 0.84), P < 0.001).[11,20,25,34,36,38] (Figure 12A) Pooled results were homogeneous (P = 0.83, I^2 = 0%). The RR was not significant for 8 mg of IV dexamethasone (RR = 0.78, 95% CI (0.55, 1.11), p = 0.16).[9,18,23] (Figure 12B). The incidence of requests for analgesic drugs was different but not significant for 2.5, 5 10 and 16 mg doses of IV dexamethasone as compared with placebo.[38] It was also not significantly different from the IV 16 mg dose. However, the need for analgesic drugs was significantly reduced for a16 mg SC dose.[36]

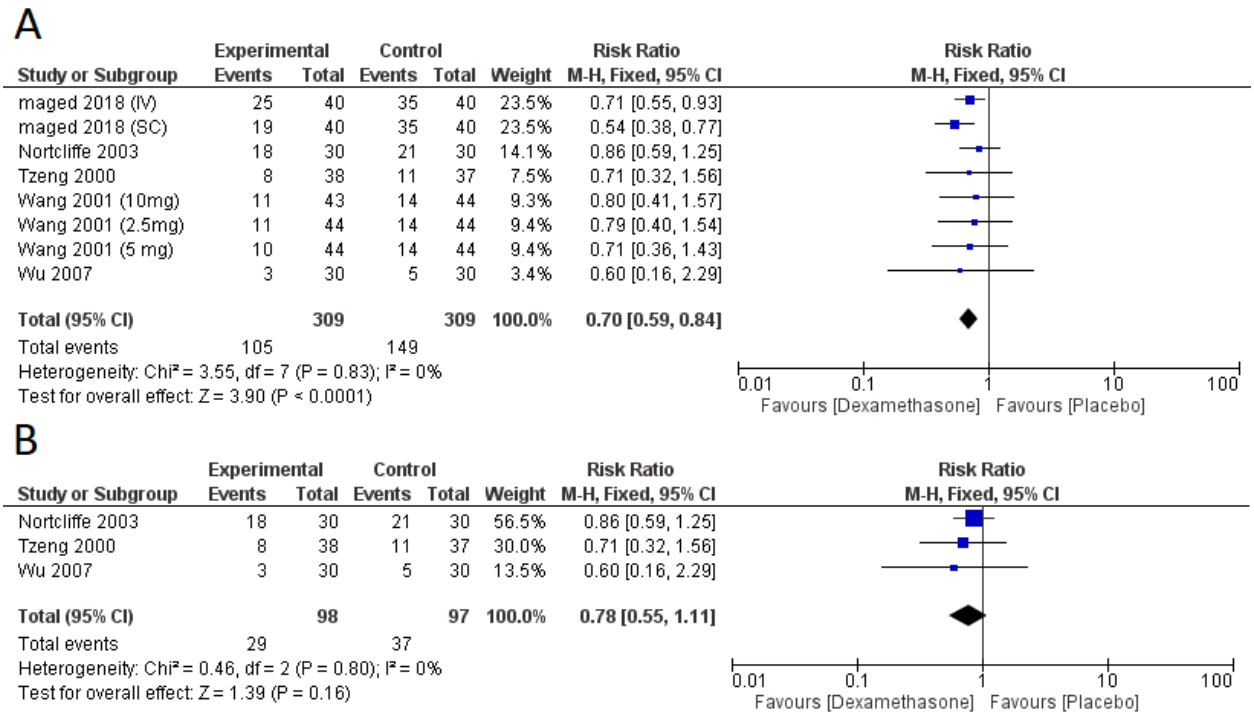

Figure 12. Effect of dexamethasone on decreasing analgesic drug using

Figure 12A Overall analysis of all doses of dexamethasone on decreasing analgesic drug using.
Figure 12B.: Analysis result of 8 mg IV dexamethasone on decreasing analgesic drug using.

Postoperative rescue antiemetic

There were ten studies that reported outcomes where post-operative rescue antiemetics were needed.[11,20,24-26,30,31,34,35,38] Selzer et al. reported that the outcome during the first 48 hours did not favor any group and, hence, was not eligible for meta-analysis.[34] However, the rest of the studies reported the need for antiemetics during 24 hours postoperative, and the total RR significantly favored findings for groups receiving dexamethasone (RR=0.65, 95% CI (0.47, 0.90), P=0.01). Pooled results were heterogeneous (P=0.0005, I2=68%).[11,20,24-26,30,31,35,38] (Figure 13A) Heterogeneity could not be resolved by the leave-one-out method or subgroup analysis based on dose, route of administration, the drug used for anesthesia, or country where the RTC was conducted. The RR for 8 mg IV was not significant (RR=0.76, 95% CI (0.55, 1.06), P = 0.11)[11,20,24-26,30,31,35] (Figure 13B) The incidence of requests for antiemetic drug significantly decreased with 5 and 10 mg IV doses of dexamethasone, while there was no significant difference between 2.5 mg IV dexamethasone and placebo.[38]

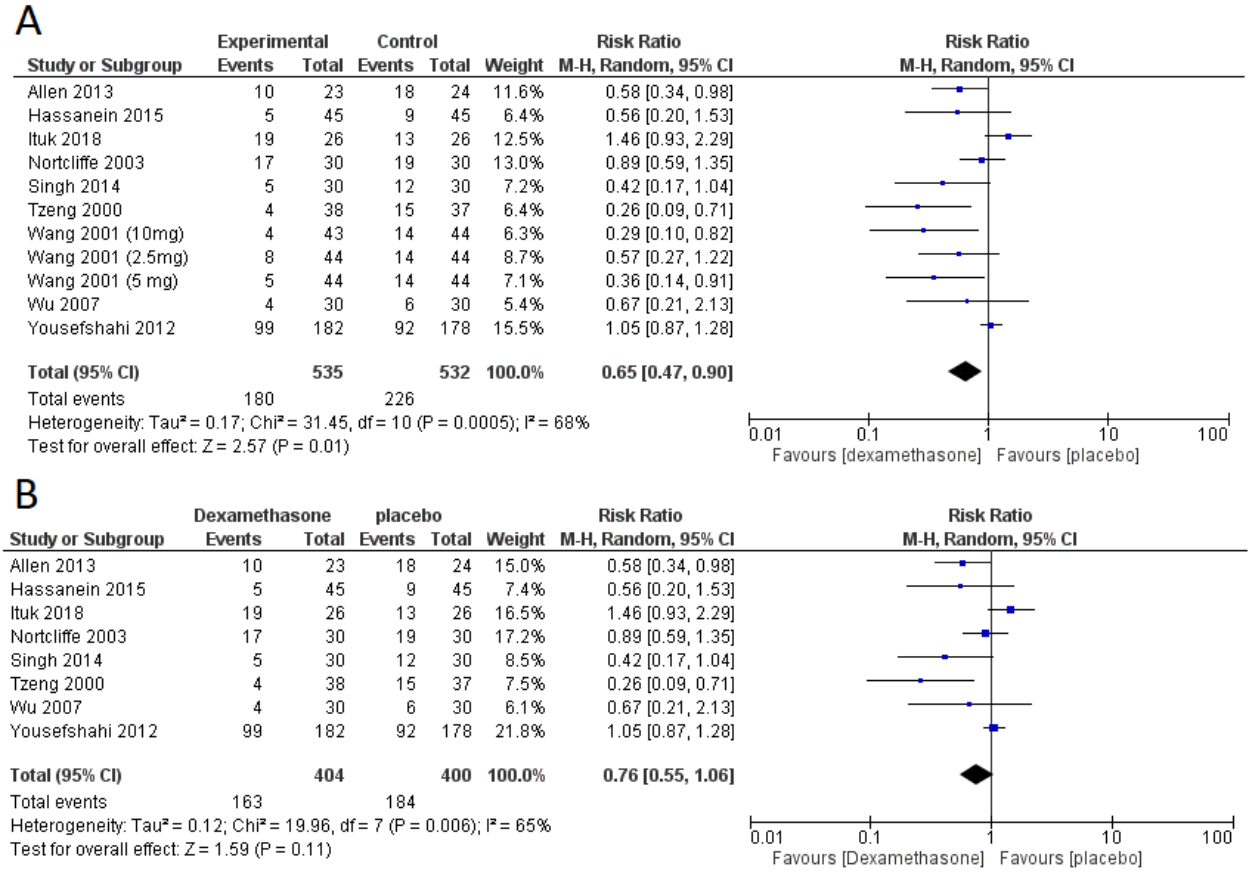

Figure 13. Effect of dexamethasone on decreasing antiemetic drug using

Figure 13A. Overall analysis of all doses of dexamethasone on decreasing antiemetic drug using.
Figure 13B. Analysis result of 8 mg IV dexamethasone on decreasing antiemetic drug using.

Discussion

The present meta-analysis found that dexamethasone appears to significantly reduce pain associated with CS. Moreover, dexamethasone administration leads to a significant decrease in nausea and vomiting in patients. Outcomes for the incidence of headache and pruritus were equal in both arms. Requests for both postoperative rescue antiemetic and

rescue analgesic, as well as the occurrence of retching were significantly lower in the dexamethasone arm.

Our findings are similar to those found in the current literature for other types of surgeries. For example, in a recent meta-analysis, dexamethasone was found to decrease pain after spinal anesthesia.[42] In addition, IV administration of dexamethasone was shown to reduce morphine consumption in the first 24 postoperative hours.[42] Another study found that, because dexamethasone has been found to pair well with many adjunctive interventions to decrease pain, the combination of dexamethasone and mepivacaine led to significantly longer duration of analgesia.[43] Yet another study showed increased analgesia time for bupivacaine administration with dexamethasone as an adjunctive therapy.[44]

A large, systematic review and meta-analysis by Allen et al. concluded that dexamethasone administration exerts significant antiemetic properties.[15] In addition, this study shows that dexamethasone helped reduce postoperative analgesia usage by patients. However, the same study reported that dexamethasone was not effective for preventing neuraxial morphine-induced pruritus.[15] The use of dexamethasone is widespread in different surgical interventions. In addition, a study found that the drug helps in prophylaxis against nausea and vomiting following thyroidectomy.[45] Another study found that nausea and vomiting were significantly lower in patients administered dexamethasone before cholecystectomy.[46]

The results of previous trials, reviews and meta-analyses support our study. Dexamethasone has been widely used for reducing postoperative pain, nausea and vomiting. This resulted in a large number of trials that could be included in our review. The resulting heterogeneity in our analysis could be used to call into question the accuracy of some of our results. However, the fact that we used 27 multi-national trials implies a certain level of anticipated heterogeneity, given the diversity in each trial's methodology. Nor did we find significant homogeneity when subgroups were re-evaluated based on dose or route of administration, or by country in which the RCT was performed. We can say, however, that the findings in our study were consistent with those found across available literature.

The main strength of our meta-analysis is that it includes a large number of fair-sized clinical trials. We had 27 studies, with a total of 2966 participants. As far as we know, we included all previously published, relevant clinical trials, as our data bases were searched twice to make sure that no additional, supporting information was missed. Another strong point in our analysis is that there is low total risk of bias, as most of the included studies were adequately designed, which provided more precise, stronger evidence.

The main limitation of our study is the presence of heterogeneity. For example, we were unable to account for the cause of large, heterogeneous results for outcomes involving pain. Another limitation is the presence of publication bias in two of our outcomes. This indicates that our results may have been affected by heterogeneity or missing data, which was another limitation that we encountered. Although we reported

nearly all outcomes, some studies reported outcomes in a way that was inconsistent with the other data used in this research. For example, pain scores were dichotomized in four studies. This inconsistency was also noted in other primary outcomes, which may have led to the masking of correct results.

In conclusion, dexamethasone administration appears to be effective in reducing pain associated with CS. In addition, its use seems to lead to lower incidence of nausea, vomiting, retching, postoperative analgesia requests and postoperative antiemetic needs.

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References

1. Vogel JP, Betrán AP, Vindevoghel N, Souza JP, Torloni MR, Zhang J, Tunçalp Ö, Mori R, Morisaki N, Ortiz-Panozo E, Hernandez B, Pérez-Cuevas R, Qureshi Z, Gülmezoglu AM, Temmerman M; WHO Multi-Country Survey on Maternal and Newborn Health Research Network. Use of the Robson classification to assess caesarean section trends in 21 countries: a secondary analysis of two WHO multicountry surveys. Lancet Glob Health. 2015 May;3(5):e260-70. https://doi.org/10.1016/S2214-109X(15)70094-X. Epub 2015 Apr 9. PMID: 25866355.

2. O'Donovan C, O'Donovan J. Why do women request an elective cesarean delivery for non-medical reasons? A systematic review of the qualitative literature. Birth. 2018 Jun;45(2):109-119. https://doi.org/10.1111/birt.12319 Epub 2017 Nov 6. PMID: 29105822.

3. Schonfeld, T., Cesarean Delivery on Maternal Request: Ethical Considerations. Postgraduate Obstetrics & Gynecology: 2013 Jan 31;33(2):1-7. https://doi.org/10.1097/01.PGO.0000427521.55429.b0

4. Fuchs F, Benhamou D. Césarienne et post-partum. Recommandations pour la pratique clinique [Post-partum management after cesarean delivery. Guidelines for clinical practice]. J Gynecol Obstet Biol Reprod (Paris). 2015 Dec;44(10):1111-7. French. https://doi.org/10.1016/j.jgyn.2015.09.020. Epub 2015 Oct 31. PMID: 26527019.

5. Liu K, Hsu CC, Chia YY. Effect of dexamethasone on postoperative emesis and pain. Br J Anaesth. 1998 Jan;80(1):85-6. https://doi.org/10.1093/bja/80.1.85 PMID: 9505784.

6. Alemnew EF, Lemma DT, Abate SM, Regassa BA. Effectiveness of intravenous dexamethasone on fascia iliaca compartment block with bupivacaine as part of postoperative multimodal analgesia for an open reduction and internal fixation surgery of femoral fracture in Hawassa Comprehensive Referral Hospital, Ethiopia, 2019: a randomized controlled trial. International Journal of Surgery Open, 2020;25:24-28. https://doi.org/10.1016/j.ijso.2020.06.007

7. Teshome D, Fenta E, Hunie M. Intravenous dexamethasone and peripheral nerve blocks: a systemic review and meta-analysis of randomized controlled trials. International Journal of Surgery Open, 2020;26:86-96. https://doi.org/10.1016/j.ijso.2020.08.014

8. Aminmansour B, Khalili HA, Ahmadi J, Nourian M. Effect of high-dose intravenous dexamethasone on postlumbar discectomy pain. Spine. 2006 Oct 1;31(21):2415-7. https://doi.org/10.1097/01.brs.0000238668.49035.19 PMID:17023848.

9. Kaan MN, Odabasi O, Gezer E, Daldal A. The effect of preoperative dexamethasone on early oral intake, vomiting and pain after tonsillectomy. Int J Pediatr Otorhinolaryngol. 2006 Jan;70(1):73-9. https://doi.org/10.1016/j.ijporl.2005.05.013. Epub 2005 Jun 24. PMID: 15979735.

10. Kardash KJ, Sarrazin F, Tessler MJ, Velly AM. Single-dose dexamethasone reduces dynamic pain after total hip arthroplasty. Anesth Analg. 2008 Apr;106(4):1253-7. https://doi.org/10.1213/ANE.0b013e318164f319. PMID: 18349202.

11. Wu JI, Lo Y, Chia YY, Liu K, Fong WP, Yang LC, Tan PH. Prevention of postoperative nausea and vomiting after intrathecal morphine for Cesarean section: a randomized comparison of dexamethasone, droperidol, and a combination. Int J Obstet Anesth. 2007 Apr;16(2):122-7. https://doi.org/10.1016/j.ijoa.2006.11.004. Epub 2007 Feb 1. PMID: 17275282.

12. Movafegh A, Soroush AR, Navi A, Sadeghi M, Esfehani F, Akbarian-Tefaghi N. The effect of intravenous administration of dexamethasone on postoperative pain, nausea, and vomiting after intrathecal injection of meperidine. Anesth Analg. 2007 Apr;104(4):987-9. https://doi.org/10.1213/01.ane.0000257926.07491.55 PMID: 17377120.

13. Cardoso MM, Leite AO, Santos EA, Gozzani JL, Mathias LA. Effect of dexamethasone on prevention of postoperative nausea, vomiting and pain after caesarean section: a randomised, placebo-controlled, double-blind trial. Eur J Anaesthesiol. 2013 Mar;30(3):102-5. https://doi.org/10.1097/EJA.0b013e328356676b. PMID: 23022704.

14. Jokela RM, Ahonen JV, Tallgren MK, Marjakangas PC, Korttila KT. The effective analgesic dose of dexamethasone after laparoscopic hysterectomy. Anesth Analg. 2009 Aug;109(2):607-15. https://doi.org/10.1213/ane.0b013e3181ac0f5c PMID: 19608838.

15. Allen TK, Jones CA, Habib AS. Dexamethasone for the prophylaxis of postoperative nausea and vomiting associated with neuraxial morphine administration: a systematic review and meta-analysis. Anesth Analg. 2012 Apr;114(4):813-22. https://doi.org/10.1213/ANE.0b013e318247f628 Epub 2012 Feb 17. PMID: 22344239.

16. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336-41. https://doi.org/10.1016/j.ijsu.2010.02.007 Epub 2010 Feb 18. Erratum in: Int J Surg. 2010;8(8):658. PMID: 20171303.

17. Higigns JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons, 2008.

18. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005 Apr 20;5:13. https://doi.org/10.1186/1471-2288-5-13 PMID: 15840177; PMCID: PMC1097734.

19. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997 Sep 13;315(7109):629-34. https://doi.org/10.1136/bmj.315.7109.629. PMID: 9310563; PMCID: PMC2127453.

20. Nortcliffe SA, Shah J, Buggy DJ. Prevention of postoperative nausea and vomiting after spinal morphine for Caesarean section: comparison of cyclizine, dexamethasone and placebo. Br J Anaesth. 2003 May;90(5):665-70. https://doi.org/10.1093/bja/aeg120 PMID: 12697596.

21. Shahraki AD, Feizi A, Jabalameli M, Nouri S. The effect of intravenous Dexamethasone on post-cesarean section pain and vital signs: A double-blind randomized clinical trial. J Res Pharm Pract. 2013 Jul;2(3):99-104. https://doi.org/10.4103/2279-042X.122370. PMID: 24991614; PMCID: PMC4076920.

22. Shalu PS, Ghodki PS. To Study the Efficacy of Intravenous Dexamethasone in Prolonging the Duration of Spinal Anesthesia in Elective Cesarean Section. Anesth Essays Res. 2017 Apr-Jun;11(2):321-325. https://doi.org/10.4103/0259-1162.194537. PMID: 28663614; PMCID: PMC5490098.

23. Shokrpour M, Homayuni S, Kamali A, Pazuki S. Comparing the prophylactic effect of ondansetron and dexamethasone in controlling headaches caused by spinal anesthesia among women candidated for caesarean A randomized controlled trial. Electron J Gen Med. 2018;15(4):em64. https://doi.org/10.29333/ejgm/93132

24. Singh G, Patil PB. A Study of Single Dose Dexamethasone in Reducing Postoperative Sore Throat, Nausea and Vomiting in Patients Receiving General Anaesthesia for Caesarean Section. J of Evolution of Med and Dent Sci. 2014 Dec 18; 3(71):15026-15038. https://doi.org/10.14260/jemds/2014/4022

25. Tzeng JI, Wang JJ, Ho ST, Tang CS, Liu YC, Lee SC. Dexamethasone for prophylaxis of nausea and vomiting after epidural morphine for post-Caesarean section analgesia: comparison of droperidol and saline. Br J Anaesth. 2000 Dec;85(6):865-8. https://doi.org/10.1093/bja/85.6.865 PMID: 11732521.

26. Yousefshahi F, Dahmardeh AR, Khajavi M, Najafi A, Khashayar P, Barkhordari K. Effect of dexamethasone on the frequency of postdural puncture headache after spinal anesthesia for cesarean section: a double-blind randomized clinical trial. Acta Neurol Belg. 2012 Dec;112(4):345-50. https://doi.org/10.1007/s13760-012-0065-6 Epub 2012 Apr 20. PMID: 22527786.

27. Banihashem N, Hasannasab B, Alereza H. Does dexamethasone prevent subarachnoid meperidin-induced nausea, vomiting and pruritus after cesarean delivery? Saudi J Anaesth. 2013 Apr;7(2):138-41. https://doi.org/10.4103/1658-354X.114057 PMID: 23956711; PMCID: PMC3737687.

28. Biswas BN, Rudra A, Das SK, Nath S, Biswas SC. A comparative study of glycopyrrolate, dexamethasone and metoclopramide in control of post-operative nausea and vomiting after spinal anaesthesia for caesarean delivery. Indian J Anaesth. 2003; 47(3):198-200.

29. Hamzei A, Basiri-Moghadam M, Pasban-Noghabi S. Effect of dexamethasone on incidence of headache after spinal anesthesia in cesarean section. A single blind randomized controlled trial. Saudi Med J. 2012 Sep;33(9):948-53. PMID 22964805.

30. Hassanein A, Mahmoud E. Effect of low dose ketamine versus dexamethasone on intraoperative nausea and vomiting during cesarean section under spinal anesthesia. Egyptian Journal of Anaesthesia. 2015 Jan;31(1):59-63. https://doi.org/10.1016/j.egja.2014.09.005

31. Ituk U, Thenuwara K. The effect of a single intraoperative dose of intravenous dexamethasone 8 mg on post-cesarean delivery analgesia: a randomized controlled trial. Int J Obstet Anesth. 2018 Aug;35:57-63. https://doi.org/10.1016/j.ijoa.2018.03.008 Epub 2018 Mar 26. PMID: 29773484.

32. Jaafarpour M, Khani A, Dyrekvandmoghadam A, Khajavikhan J, Saadipour K. The effect of dexamethasone, on nausea, vomiting and pain in parturients undergoing caesarean delivery. JCDR J Clin Diagn Res. 2008 Jun;2(3):854-858.

33. Nado H, Singh N R, Laithangbam P, Shanti Devi R K, Alemwapang O, Gangmei FL. A comparative study between propofol and propofol plus dexamethasone as antiemetic during cesarean section under spinal anesthesia. J Med Soc 2017;31:174-7. https://doi.org/10.4103/0972-4958.211102

34. Selzer A, Pryor KO, Tangel V, O'Connell K, Kjaer K. The effect of intravenous dexamethasone on postoperative nausea and vomiting after Cesarean delivery with intrathecal morphine: a randomized-controlled trial. Can J Anaesth. 2020 Jul;67(7):817-826. English. https://doi.org/10.1007/s12630-020-01582-y Epub 2020 Jan 27. PMID: 31989472.

35. Allen T. Dexamethasone for post-cesarean delivery pain. ClinicalTrials.gov/NCT01812057, 2017. https://clinicaltrials.gov/ct2/show/study/NCT01812057

36. Maged AM, Deeb WS, Elbaradie S, Elzayat AR, Metwally AA, Hamed M, Shaker A. Comparison of local and intra venous dexamethasone on post operative pain and recovery after caeseream section. A randomized controlled trial. Taiwan J Obstet Gynecol. 2018 Jun;57(3):346-350. https://doi.org/10.1016/j.tjog.2018.04.004 PMID: 29880162.

37. Jabalameli M, Saryazdi H, Massahipour O. The effect of subcutaneous dexamethasone added to bupivacaine on postcesarean pain: a randomized controlled trial. Iran J Med Sci. 2010 Mar;35(10): 21-26.

38. Wang JJ, Ho ST, Wong CS, Tzeng JI, Liu HS, Ger LP. Dexamethasone prophylaxis of nausea and vomiting after epidural morphine for post-Cesarean analgesia. Can J Anaesth. 2001 Feb;48(2):185-90. https://doi.org/10.1007/BF03019733 PMID: 11220429.

39. Modir H, Moshiri E, Kamali A, Shokrpour M, Shams N. Prophylatic efficacy of dexamethasone, ketamine and dexmedetomidine against intra- and postoperative nausea and vomiting under spinal anesthesia. Formosan Journal of Surgery. 2019;52(1):17-23. https://doi.org/10.4103/fjs.fjs_37_18

40. Gholami H, Moradi Y, Khazaei Z, Tehrani, S. A comparison of the effect of dexamethasone and pethidine for prevention of shivering after spinal anesthesia in caesarean section: randomization clinical trial. Biomedical Research and Therapy. 2018;5(9):2646-2650. https://doi.org/10.15419/bmrat.v5i9.473

41. Yang B, Li DL, Dong P, Zhang XY, Zhang L, Yu JG. Effect of dexamethasone on the incidence of post-dural puncture headache after spinal anesthesia: a randomized, double-blind, placebo-controlled trial and a meta-analysis. Acta Neurol Belg. 2015 Mar;115(1):59-67. https://doi.org/10.1007/s13760-014-0307-x Epub 2014 May 28. PMID: 24865592.

42. Heesen M, Rijs K, Hilber N, Eid K, Al-Oweidi A, Rossaint R, Klimek M. Effect of intravenous dexamethasone on postoperative pain after spinal anaesthesia – a systematic review with meta-analysis and trial sequential analysis. Anaesthesia. 2019 Aug;74(8):1047-1056. https://doi.org/10.1111/anae.14666 Epub 2019 May 6. PMID: 31058317.

43. Parrington SJ, O'Donnell D, Chan VW, Brown-Shreves D, Subramanyam R, Qu M, Brull R. Dexamethasone added to mepivacaine prolongs the duration of analgesia after supraclavicular brachial plexus blockade. Reg Anesth Pain Med. 2010 Sep- Oct;35(5):422-6. https://doi.org/10.1097/AAP.0b013e3181e85eb9 PMID: 20814282.

44. Holte K, Werner MU, Lacouture PG, Kehlet H. Dexamethasone prolongs local analgesia after subcutaneous infiltration of bupivacaine microcapsules in human volunteers. Anesthesiology. 2002 Jun;96(6):1331-5. https://doi.org/10.1097/00000542-200206000-00011. PMID: 12170044.

45. Ahmad R, Changeez M, Tameez Ud Din A, Iftikhar A, Ahmad HB, Mujtaba A, Khan JS, Malik MN. Role of Prophylactic Dexamethasone Before Thyroidectomy in Reducing Postoperative Pain, Nausea and Vomiting. Cureus. 2019 May 23;11(5):e4735. https://doi.org/10.7759/cureus.4735. PMID: 31355094; PMCID: PMC6649885.

46. Rajnikant K, Bhukal I, Kaloria N, Soni SL, Kajal K. Comparison of Palonosetron and Dexamethasone with Ondansetron and Dexamethasone to Prevent Postoperative Nausea and Vomiting in Patients Undergoing Laparoscopic Cholecystectomy. Anesth Essays Res. 2019 Apr-Jun;13(2):317-322. https://doi.org/10.4103/aer.AER_21_19. PMID: 31198253; PMCID: PMC6545955.