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META-ANALYSIS

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Dexamethasone Reduces Nausea and Vomiting but not Pain after Thyroid Surgery: A Meta-Analysis of Randomized Controlled Trials

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Postoperative nausea and vomiting (PONV) is a common complication after thyroidectomy. The aim of this article was to evaluate the efficacy of dexamethasone for prevention of PONV and pain in patients undergoing thyroidectomy.

Material/Methods: We performed this meta-analysis based on the QUORUM (Quality of Reporting of Meta-analyses) guidelines. Our study included randomized controlled trials (RCTs) that compared preoperative single-dose administration of dexamethasone with no dexamethasone in patients undergoing thyroidectomy. The primary outcome was occurrence and severity of PONV, and the secondary outcomes included pain, use of analgesics, and steroid-related complications.

Results: Seven RCTs were included, with a total of 611 patients. A statistically and clinically significant difference in the incidence and severity of PONV was found in favor of dexamethasone (SMD, 0.23; 95% CI, 0.13–0.41; P<0.00001; SMD, 0.53; 95% CI, –1.03 to –0.03; P=0.04). However, there was no significant difference in reduction of pain severity and analgesic consumption in using dexamethasone (SMD, –0.83; 95% CI, –1.85 to 0.18; P=0.14; SMD, –0.19; 95% CI, –0.43 to 0.04; P=0.10). No steroid-related complications were noted.

Conclusions: A single preoperative administration of dexamethasone reduced the incidence and severity of PONV but not pain severity and analgesic consumption in patients undergoing thyroidectomy. Further studies with a larger sample size are needed to further explore the efficacy of dexamethasone on postoperative pain severity and analgesic consumption.

MeSH Keywords: Anesthesiology • Dexamethasone • Thyroidectomy

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Background

Thyroidectomies are one of the most common elective surgical procedures all over the world [1]. After thyroidectomy the incidence of postoperative nausea and vomiting (PONV), which is less than 30% in other surgical interventions [2], is 70–80% when no prophylactic antiemetic therapy is given [3,4]. PONV might be the main source of discomfort after thyroidectomy, and repeated or vigorous vomiting can lead to postoperative bleeding with subsequent airway obstruction and potential need for reparative surgery [5]. Apfel et al. found that patients were more afraid of PONV than postoperative pain, which substantiated the importance of avoiding PONV events [6]. Numerous antiemetics have been studied for the prevention and treatment of PONV following thyroidectomy, including tropisetron and dexamethasone [7,8]. Most published trials indicated improved prophylaxis against PONV by using effective antiemetic therapy in patients scheduled for thyroid surgery [1].

Postoperative pain and PONV are separate outcomes; however, it is well-recognized that pain can result in anxiety, which can be associated with nausea [9]. Interestingly, several studies have also shown that preoperative administration of steroids reduced postoperative pain after oral, orthopedic, spinal, and laparoscopic surgery [10–12].

Dexamethasone, an adrenocortical steroid, is effective in preventing the nausea and vomiting associated with cancer chemotherapy [13,14] and has shown efficacy against postoperative nausea in several studies [15–20]. Previous meta-analyses concluded that dexamethasone prophylactic use of steroids for patients undergoing thyroidectomy was safe and should be considered for routine clinical practice [21]. However, it failed to show the efficacy of dexamethasone on severity of PONV, and the data on pain relief was insufficient. In addition, a recent randomized trial by Barros et al. showed that dexamethasone did not have any effects on incidence of PONV [22]. Hence, the results reported on the use of dexamethasone for patients undergoing thyroidectomy are still variable and controversial. The objective of this study was to perform a meta-analysis to assess the overall effect of dexamethasone on PONV and pain after thyroidectomy.

Material and Methods

We performed this meta-analysis based on the QUORUM guidelines (Quality of Reporting of Meta-analyses) [23] and the recommendations of the Cochrane Collaboration [24].

Data sources and searches

The electronic databases screened were PubMed (1990 to February 2014), EMBASE (1990 to February 2014), and the Cochrane Library (Issue 1 of 12, Jan 2014), including the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), and Health Technology Assessments (HTA). The search terms were: "thyroidectomy" or "thyroid surgery" AND "dexamethasone" or "steroid". Searches were limited to randomized controlled trials in English and were performed for all types of publications. We also screened the references of retrieved articles and contacted the authors to request additional data when key information relevant to the meta-analysis was missing. The full search strategy was developed from PubMed and was adapted for the other electronic databases (Figure 1).

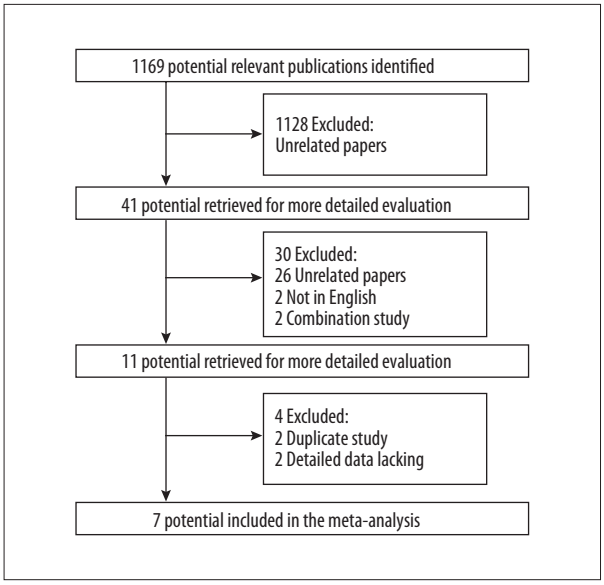

Figure 1. Flow chart of included studies.

Data extraction

Two of us (BS Lv and W Wang) independently screened the titles and abstracts of potentially eligible studies. The full text articles were examined independently by 2 of us (BS Lv and W Wang) to determine whether they met the inclusion criteria. Two of us (BS Lv and W Wang) independently extracted data (study characteristics and results) using data extraction forms, and then the collected data were entered into RevMan 5.1 using the double-entry system. Point estimates for selected variables were extracted and checked by the other 2 reviewers. All discrepancies were rechecked and consensus was achieved by discussion. A record of reasons for excluding studies was kept. We selected PONV and pain symptoms as outcome measures for dexamethasone therapy. The primary outcome was occurrence and severity of PONV, and the secondary outcomes included pain, use of analgesics, and steroid-related complications. The Jadad test (5 items) [25] was applied for assessing methodological quality as high (score 5), moderate (score 4), or low (scores 1–3).

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Table 1. Characteristics of the trials included in the meta-analysis.

Source	De dose	Sample dize	Anesthetic technique	Additional drug administration	Method quality Jadad score	Outcome measures used for meta-analysis
Wang 1999 (Taiwan)	10 mg	38 De 38 P	Propofol 2.0–2.5 mg/kg, glycopyrrolate 0.2 mg, fentanyl 2.0 µg/kg IV maintained with isoflurance in oxygen	Analgesia: diclofenac 75 mg IM Antiemetics: ondansetron 4 mg IV	5	Incidence of PONV Pain Score
Lee 2001 (Taiwan)	8 mg *vs.* 5 mg	88 De 44 P	Glycopyrrolate 0.2 mg, fentanyl 2.0 µg/kg, thiopental 5 mg IV maintained with desflurance in oxygen	Analgesia: ketorolac 15 mg IV Antiemetics: droperidol 1.25 mg IV	5	Incidence of PONV Pain Score
Fujii 2007 (Japan)	8 mg *vs.* 4 mg	50 De 25 P	Propofol 2.0 mg/kg, fentanyl 2.0 µg/kg, vecuronium 0.1 mg/kg IV maintained with 1–3% sevoflurance in oxygen	Analgesia: indomethacin 50 mg rectally Antiemetics: oral ranitidine 150mg	4	Incidence of PONV Severity of nausea
Worni 2008 (Switzeland)	8 mg	37 De 35 P	Propfol/thiopental, atracurium, isoflurance, or sevoflurance and fentanyl (5–10 µg/kg)	Analgesia: acetaminophen 4 g/day Antiemetics: ondansetron 4mg IV	5	Incidence of PONV Severity of nausea Pain score Analgesic consumption
Feroci 2011 (Italy)	8 mg	51 De 51 P	Propofol 2 mg/kg, fentanyl 2 µg/kg, vecuronium 0.1 mg/kg IV maintained with sevoflurance in oxygen	Analgesia: paracetamol 1,000 mg IV q8 h, ketorolac 30 mg IV Antiemetics: metoclopramide 10 mg IV	5	Incidence of PONV Severity of nausea Pain score Analgesic consumption
Doksrod 2012 (Norway)	0.3 mg/kg *vs.* 0.15 mg/kg	80 De 40 P	Propofol, fentanyl, vecuronium IV maintained with desflurance in oxygen	Analgesia: fentanyl 0.5 µg/kg IV Antiemetics: metoclopramide 20 mg IV	5	Incidence of PONV Pain score Analgesic consumption
Barros 2013 (Portugal)	4 mg	17 De 17 P	Propofol 2 mg/kg, fentanyl 2 µg/kg, ciatracurium 0.15 mg/kg IV maintained with sevoflurance in oxygen	Analgesia: ketorolac 30 mg IV Antiemetics: ondansetron 4 mg IV	5	Incidence of PONV Severity of nausea Pain score Analgesic consumption

De – dexamethasone; P – placebo; IV – intravenous; IM – intramuscular; PONV – postoperative nausea and vomiting; A – analgesia.

Data collection and analysis

The following data and information were collected:

1. General study information such as title, authors, contact address, publication source, publication year, country, and study sponsor.
2. Characteristics of the study: design, study setting, inclusion and exclusion criteria, quality criteria (e.g., randomization method, allocation procedure, blinding of patients, caregivers and outcome assessors, withdrawals and dropouts, and intention-to-treat (ITT) analysis whenever necessary).
3. Characteristics of the study population (e.g., age, weight, height, sex, BMI).
4. Characteristics of the intervention, such as treatment comparators and duration of therapy.
5. Outcome measures as mentioned above.
6. Outcome measures at the end of the controlled phase, and any summary measures with standard deviations, confidence intervals, and P values, where given, dropout rate, and reasons for withdrawal.

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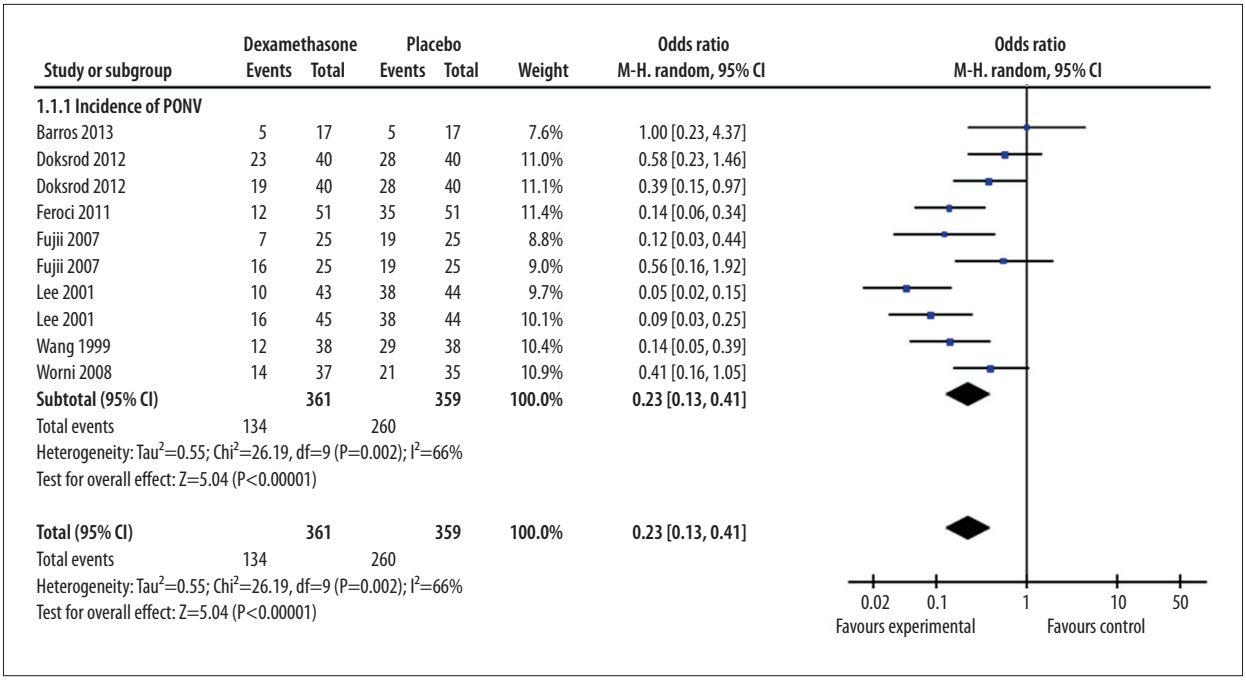

Figure 2. Forest plot of comparison: dexamethasone *vs.* control. Outcome: incidence of postoperative nausea and vomiting (PONV). M-H – Mantel-Haenszel method; CI – confidence interval.

For all included studies, the main outcome of PONV and pain were scored according to VRS and VAS. Because most outcomes were presented as continuous data (mean value or mean changes), we used the standardized mean difference (SMDs) as effect measures. Because they were determined in different trials using different scales, odds ratio (OR) was used in evaluating incidence of PONV. To calculate SMDs, we used means and change scores and their standard deviations. When these values were shown in a graph without any description of absolute value, we first tried to contact the authors. Measurements from the graph were used if we could not get data from the authors. It was converted into standard deviation only when the standard error was reported.

I^2 statistics were used to measure heterogeneity of the RCTs. If the I^2 value was less than 50%, a fixed-effects meta-analysis was applied. If the I^2 value was 50% or more, the random-effects meta-analysis was used [26]. We used the following descriptors to classify meta-analysis results [27]: "strong" indicated consistent findings in multiple (at least 2) high- or moderate-quality RCTs, "moderate" indicated consistent findings in multiple low-quality RCTs or 1 high- or moderate-quality RCT, "limited" indicated 1 low-quality RCT, and "conflicting" indicated inconsistent findings among multiple RCTs.

Visual assessment of the funnel plot calculated by RevMan Analyses software was used to investigate the potential publication bias (the association of publication probability with the statistical significance of study results). Publication bias may lead to asymmetrical funnel plots [28].

Result

Flow chart

The literature search yielded 1169 citations. Initially, 41 publications met our inclusion criteria. On more detailed review, an additional 30 papers were excluded for the following reasons: unrelated papers, not in English, and combination study. Four more publications were further excluded because of duplicate study and detailed data lacking. The remaining 7 studies met our selection criteria and were included in the meta-analysis [15–20,22] (Figure 1).

Included studies characteristics

Table 1 shows the doses of dexamethasone, sample sizes, anesthetic technique, additional drug administration, and Jadad score of the studies. There were 611 study participants in the beginning, of which 361 patients received dexamethasone therapy, and 250 received placebo treatment. Two of 7 studies were conducted in Taiwan and the other 5 were conducted in Japan, Switzerland, Italy, Norway, and Portugal. There were 6 studies with high methodological quality (score 5) and 1 with moderate quality (score 4). The dosage of dexamethasone ranged from 5 mg to 10 mg.

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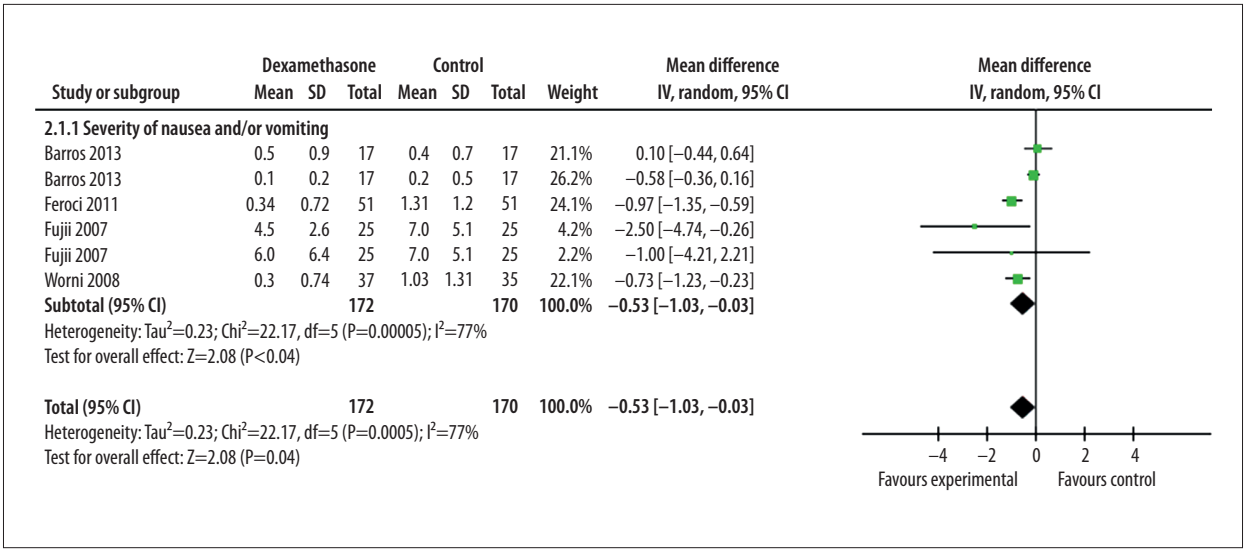

Figure 3. Forest plot of comparison: dexamethasone *vs.* control. Outcome: severity of postoperative nausea and vomiting (PONV). V – inverse variance method; SD – standard deviation.

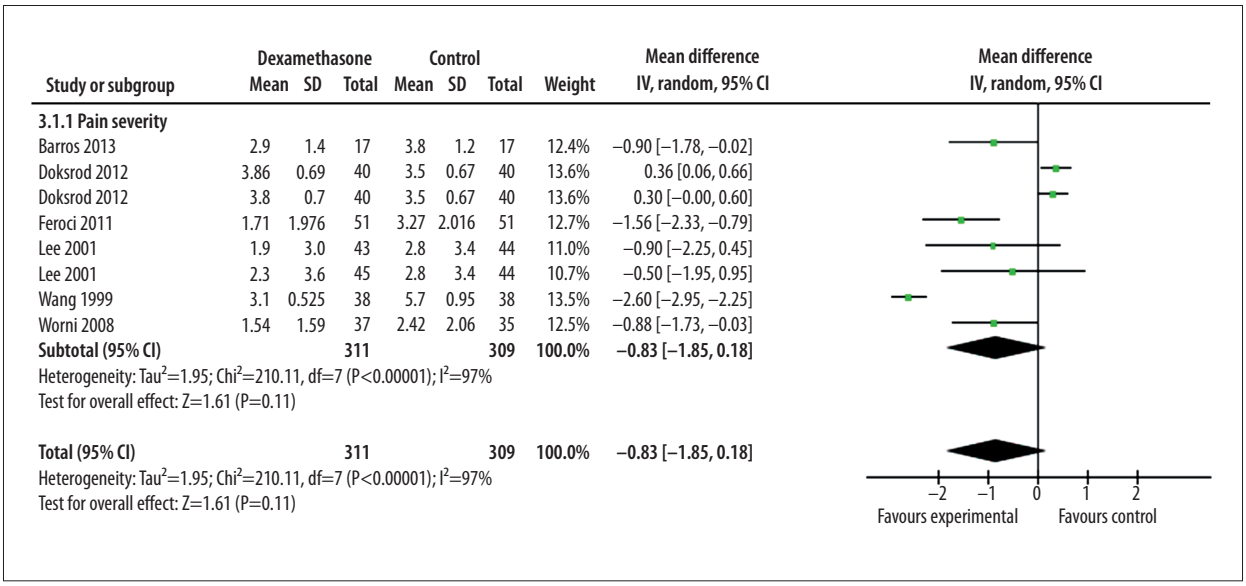

Figure 4. Forest plot of comparison: dexamethasone *vs.* control. Outcome: pain severity.

Incidence of PONV

According to χ^2 test of heterogeneity (I^2=66%), a random-effects model was used to evaluate the incidence of PONV. Based on Cohen categories for evaluating the magnitude of effect sizes, there was strong evidence for reducing incidence of PONV in using dexamethasone (SMD, 0.23; 95% CI, 0.13 to 0.41; P<0.00001) (Figure 2).

PONV severity

According to χ^2 test of heterogeneity (I^2=77%), a random-effects model was used to evaluate the severity of PONV. There was strong evidence for a reduction of PONV severity in using dexamethasone (SMD, 0.53; 95% CI, –1.03 to –0.03; P=0.04) (Figure 3), based on Cohen categories for evaluating the magnitude of effect sizes.

Pain severity

According to χ^2 test of heterogeneity (I^2=97%), a random-effects model was used to evaluate the severity of pain. Based on Cohen categories for evaluating the magnitude of effect sizes, there was no significant difference for a reduction of pain severity in using dexamethasone (SMD, –0.83; 95% CI, –1.85 to 0.18; P=0.14) (Figure 4).

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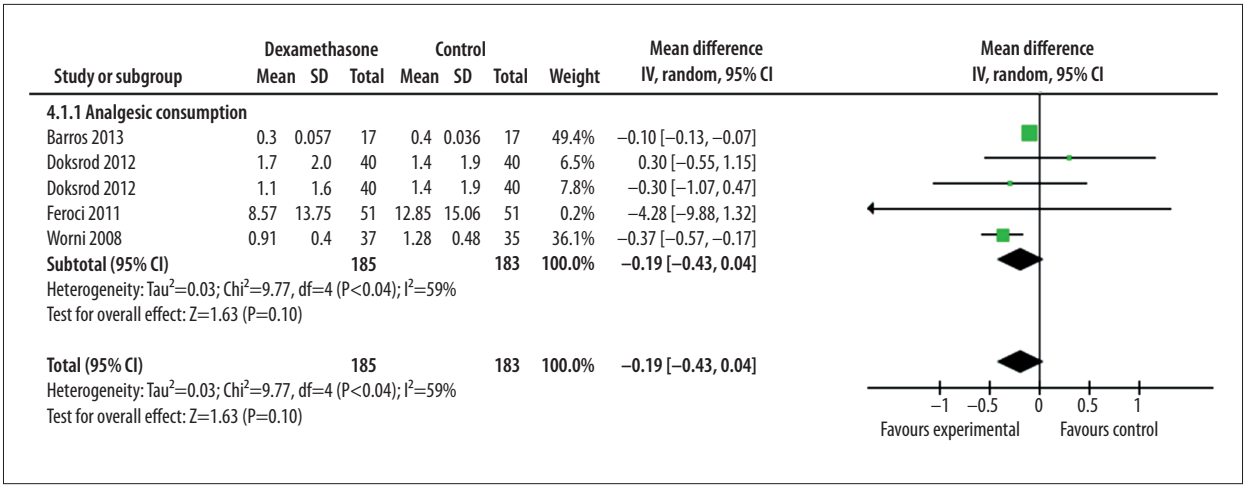

Figure 5. Forest plot of comparison: dexamethasone *vs.* control. Outcome: analgesic consumption (patient number at 24 h).

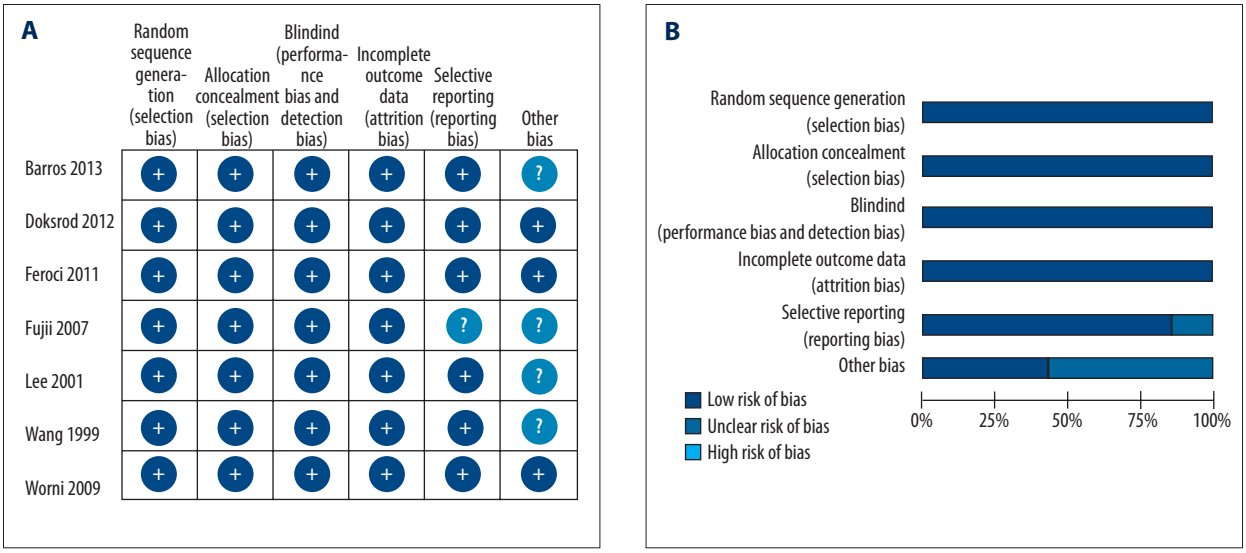

Figure 6. (**A**) Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies. (**B**) Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Analgesic consumption

According to χ^2 test of heterogeneity (I^2=59%), a random-effects model was used to evaluate the severity of pain. There was no significant difference in reduction of analgesic consumption in using dexamethasone (SMD, –0.19; 95% CI, –0.43 to 0.04; P=0.10) (Figure 5), based on Cohen categories for evaluating the magnitude of effect sizes.

Adverse events with dexamethasone therapy

No postoperative wound infections or steroid-related adverse events were noted in any of the included studies.

Risk of bias in included studies

Assessment tables of the risk of bias are presented in Figure 6A and Figure 6B. There was only 1 study, by Fujii et al., with moderate quality (score 4) because of the unclear reporting bias [17]. Sensitivity analysis was applied by excluding the study of Fujii et al. Based on Cohen categories for evaluating the magnitude of effect sizes, there was strong evidence for reducing incidence of PONV in using dexamethasone (SMD, 0.22; 95% CI, 0.12 to 0.43; P<0.00001) (Figure 7).

Discussion

In 2012, the systematic review conducted by Chen et al. showed that a single preoperative administration of dexamethasone

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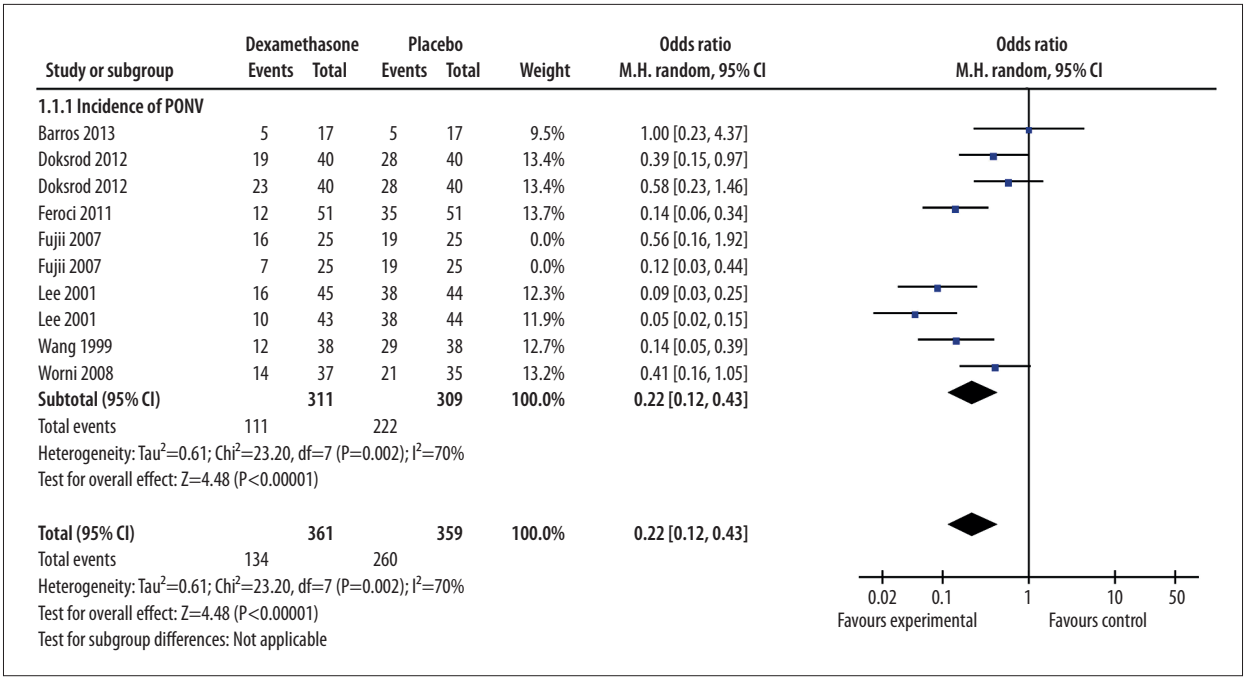

Figure 7. Forest plot of comparison: dexamethasone *vs.* control. Outcome: incidence of PONV (Fujii [16] is excluded).

reduced the incidence of PONV and analgesic requirements in patients undergoing thyroidectomy [21]. However, the subsequent randomized trial by Doksrød et al. noted that dexamethasone had no analgesic or opioid-sparing effect in patients after thyroid surgery [20]. Our systematic review is remarkably different from the previous one and we assessed that: i) In addition to the previous meta-analysis, we have paid more attention to evaluating the severity of PONV; and ii) We included more studies, which included sufficient data on pain relief. Our current data showed that a single preoperative administration of dexamethasone reduced the incidence and severity of PONV but not pain severity and analgesic consumption in patients undergoing thyroidectomy.

PONV is an unpleasant experience after thyroidectomy, which might be perceived as the main source of discomfort in postoperative recovery [29]. However, the exact etiology of PONV after thyroidectomy is not clearly understood. It is assumed that several factors, including age, sex, and the intense of preoperative vagal stimulation might be related to PONV [30]. Other factors, including obesity, menstruation, smoking, and anesthetic technique, are considered to influence the frequency of PONV [31]. However, in all of the included randomized control trials the above factors were similar between experimental and control groups. Therefore, the difference in frequency of PONV among groups can be attributed to the drug tests.

Wang et al. did the first randomized controlled trial and showed efficacy against PONV in women undergoing thyroidectomy. To date, 7 randomized control trials have been published investigating the effects of a single-dose application of dexamethasone during thyroidectomy [15–20,22], and most of them support the use of dexamethasone.

Pain after thyroidectomy is another major cause of discomfort, and all patients experienced throat pain without other relevant pain. The recent review by De Oliveira et al. concluded that dexamethasone at doses more than 0.1 mg/kg is an effective adjunct in multimodal strategies to reduce post-operative pain and opioid consumption after surgery [32]. Furthermore, Chen et al. found evidence that dexamethasone significantly reduced the severity of postoperative pain and was more effective than placebo for reducing the use of analgesics [21]. However, 2 more recent RCTs by Doksrød et al. and Barros et al. reported no beneficial effect of a preoperative single dexamethasone dose on decreasing tramadol requirement after thyroid surgery [20,22], perhaps due to low sensitivity of the pain model or because pain after thyroid surgery responds poorly to glucocorticoid therapy [20]. In addition, Barros et al. concluded that their study results did not support the hypothesis that a preoperative single dexamethasone dose decreases tramadol requirement, possibly because the dexamethasone dose (4 mg) was too low [22]. Thus, they suggested that larger studies using a higher dexamethasone dose (8 mg) to analyze its beneficial effect on tramadol consumption are needed for further investigation [22].

In the present meta-analysis, the dosage of dexamethasone from included studies ranged from 5 mg to 10 mg. The study

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by Wang et al. showed no further effect by increasing the total dose from 5 mg to 10 mg [15], which is also confirmed by a meta-analysis by Henzi et al. [33]. The possible reason is that the maximal anti-emetic effect of dexamethasone reaches a ceiling at a lower dosing level. However, the studies by Lee et al. and Fuji et al. concluded that higher doses of dexamethasone are more effective at reducing symptoms than are lower doses (8 mg *vs.* 5 mg; 8 mg *vs.* 4 mg) [15,17]. Because of the limited number of included RCTs, we did not apply a further layer of analysis for the effect of different dosage of dexamethasone.

In our included studies, no postoperative wound infections or steroid-related adverse events were noted. A previous study evaluated the complications of preoperative administration of dexamethasone, and found no harm to patients [34]. Furthermore, several studies evaluating the administration of corticosteroid for other (oral or orthognathic) surgery found no significant difference in the risk of wound infection [35,36]. Thus, single-dose administration of dexamethasone seems to be safe in otherwise healthy patients undergoing thyroidectomy.

Limitation

Our meta-analysis has several limitations. First, there was significant heterogeneity in the results for the incidence and severity of PONV, as well as pain severity. Because of the small size effect and limited number of included studies, we did not apply a further layer of analysis and only performed the random-effects model analysis. Secondly, some statistical methods used in our study may be limited, such as using I^2 to assess the amount of heterogeneity in random-effects meta-analysis [37] and visual assessment of the funnel plot for excluding publication bias. Thirdly, although we made our best effort to get the full text of all published studies, there were still some studies that were not included in our meta-analysis due to the lack of detailed data.

Conclusions

This systematic review and meta-analysis suggests the following: i) A single preoperative administration of dexamethasone in patients undergoing thyroidectomy is safe and reduces the incidence and severity of PONV; ii) Pain severity and analgesic consumption cannot be reduced by a single preoperative administration of dexamethasone; and iii) The effect of different dosage of dexamethasone is unclear, so further studies with a larger sample size using a higher dexamethasone dose are needed to analyze its beneficial effect on postoperative pain severity and analgesic consumption.

Statement

No current funding sources for this study.

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