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MISCELLANEOUS

The use of steroids to reduce complications after tonsillectomy: a systematic review and meta-analysis of randomized controlled studies

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Abstract

Objectives To systemically review and compare the efficacy of intravenous, local, and oral steroids in decreasing post-tonsillectomy pain, nausea, and vomiting, and its risk of causing hemorrhage.

Methods We searched electronic databases (PubMed, Scopus, Cochrane Library) and additional sources. The date of the most recent search was June 20th, 2018. We selected RCTs of steroids in all routes of administration, in all age groups who underwent tonsillectomy or adenotonsillectomy and studied the results of nausea/vomiting, pain, and hemorrhage. Data analysis was done using Review Manager 5.3.5 software.

Results We included 64 studies (6,327 participants) with variety quality assessed by the Cochrane Handbook for Systematic Reviews of Interventions. IV steroids statistically and clinically significant decrease post-tonsillectomy nausea/vomiting in children and adult, with superior effect to local steroids (Children: OR 0.21; 95% CI 0.15–0.30; $P < 0.001$, $I^2 = 67\%$, Adult: OR 0.32; 95% CI 0.16–0.67; $P = 0.002$, $I^2 = 40\%$). In the analysis of local steroids studies, there was only evidence in children that local steroids decrease post-tonsillectomy nausea/vomiting (OR 0.54; 95% CI 0.33–0.88; $P = 0.01$, $I^2 = 32\%$). IV and local steroids statistically significant decrease immediate post-operative pain severity. Local steroids had extended effect in reducing pain scores on the first day after tonsillectomy. However, the clinical significance of pain relief had to be concerned due to decreasing VAS only about 1 out of 10. Adding oral steroids to IV steroids gave no difference in effect from IV steroids alone. There are very few local steroids studies in adults and oral steroids studies to show the significant effects. Steroids have no statistically significant effect in reducing pain severity after a 1-day period. Steroids in all routes had no statistically significant effects on post-operative hemorrhage (primary hemorrhage: OR 0.96; 95% CI 0.55–1.67; $P = 0.88$, $I^2 = 0\%$; secondary hemorrhage: OR 1.05; 95% CI 0.74–1.51; $P = 0.79$, $I^2 = 0\%$).

Conclusion Intravenous steroids statistically significantly decrease post-tonsillectomy nausea/vomiting, and immediate pain scores (< 24 h) in children and adults. There is evidence in only children that local steroids statistically significantly decreases post-tonsillectomy nausea/vomiting, and pain scores during the 0-h to 1-day period.

Keywords Tonsillectomy · Steroids · Nausea · Bleed · Pain · Meta-analysis

Introduction

Tonsillectomy is a common surgical procedure, especially in children. Post-tonsillectomy morbidities include pain, nausea, vomiting, hemorrhage, delayed diet, dehydration, intra-operative soft tissue injury, pulmonary edema, velopharyngeal insufficiency, nasopharyngeal stenosis, atlantoaxial subluxation, and death [1]. Post-tonsillectomy pain, nausea and vomiting are common complications, which may prolong hospital stay and decrease patient quality of life. Better pain relief and reduced nausea and vomiting are worthy goals.

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Corticosteroids have been studied to reduce post-tonsillectomy complications. The anti-inflammatory effect of steroids reduces tissue edema, decreases pain nerve terminal sensitization, reduces irritation to pharyngeal muscles, and finally relieves post-operative pain [2]. In contrast, the mechanism of the anti-emetic effect of steroids is not well understood. In theory, steroids decrease nausea and vomiting by action on the emetic center in the brain stem, decreasing neuro-transmitters associated with vomiting and reducing the triggering of parasympathetic nervous system at operating site [3].

Steroids are currently given intravenously. Meta-analysis studies about the efficacy of intravenous steroids have showed statistically significant reductions of post-operative nausea/vomiting [2, 4–7] and pain in 24 h after tonsillectomy [2, 4, 5, 8]. Steroids can be used not only as an intravenous injection but also local injection, and oral ingestion. However, systematic reviews of the efficacy of local and oral steroids have not been adequately studied.

Local steroids may be more advantageous than intravenous steroids in achieving a higher localized drug concentration without loss due to distribution or the onset of elimination [9]. Local steroids are statistically significantly better than intravenous steroids in decreasing pain scores in 1–16 h after tonsillectomy in Gao's study [10], and in the first 3 days after tonsillectomy in Basuni's study [11], but had no difference in anti-emetic effect in both studies. Post-operative oral steroids may have advantage over a single dose of intra-operative, intravenous steroids in decreasing late complications.

Post-tonsillectomy hemorrhage is rare but has severe complications. In an animal model study, steroids cause post-operative bleeding by delaying wound healing, due to decreasing collagen and fibrin deposition, suppressing epidermal growth factor [12, 13], and inhibiting platelet function [14]. The use of steroids should include increased patient risk consideration for post-tonsillectomy hemorrhage, especially when used locally.

This meta-analysis aimed to systemically review and compare the efficacy of intravenous, local, and oral steroids in decreasing post-tonsillectomy pain, nausea, and vomiting, and its risk of causing hemorrhage.

Materials and methods

Search strategy

Three authors (T.C., K.P., and S.K.) independently conducted searches for published, unpublished, and ongoing RCTs from electronic databases, via PubMed, Scopus, and the Cochrane library. The date of the last search was June 20th, 2018. Search terms used were "(tonsillectomy OR adenotonsillectomy) AND (steroids OR prednisolone OR dexamethasone OR triamcinolone)." We manually searched other sources from the Chulalongkorn Medical Library and those existing primary researches in previous meta-analyses.

Selection of studies

The inclusion criteria were articles relating to: (1) patients in all age groups who underwent tonsillectomy or adenotonsillectomy; (2) steroids administered intravenously, locally, or orally, all dose ranges, and all types of synthetic pharmaceutical drugs; (3) comparisons of steroids versus non-steroids, which were normal saline, placebo tablets, or no medication; (4) at least one of the outcome measures mentioned below was reported: (4.1) post-operative pain severity, in 4 durations after surgery: <24 h, 1 day, 3 days, and 7 days, measured by pain scores, assessed by patients or caregivers, (4.2) nausea and/or vomiting events, (4.3) post-operative primary hemorrhage (bleeding in first 24 h after surgery), and secondary hemorrhage (bleeding in > 24 h after surgery) events; (5) randomized controlled trials. Articles with the following exclusion criteria were eliminated if: (1) report data were incorrect or incomplete and could not provide outcome studies, (2) repeated published literature, and (3) on-going or terminated trials which results were not reported.

Three authors (TC, KP, and SK) independently reviewed titles and abstracts of all studies, and selected the studies that met the selection criteria. We obtained the full texts of the articles, arranged translation accordingly, and if necessary, contacted the investigators for any insufficient data. Discrepancies were resolved by discussion or through a fourth investigator (HP).

Quality assessment

Three authors (TC, KP, and SK) independently assessed the methodological quality of included studies according to the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 recommended by Cochrane Collaboration. Evaluation included seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each item was judged as "low risk", "unclear risk", and "high risk." Discrepancies were resolved by discussion or through a fourth investigator (H.P.).

Data extraction

Two authors (TC and KP) independently extracted and recorded data onto record forms. Patient information included patient age, surgical technique, steroids route, steroids dosage, placebo, follow-up time, severity of pain,

number of patients with post-operative nausea/vomiting, and number of patients with post-operative hemorrhage.

Statistical analysis

We measured treatment effects using a standardized mean difference (SMD) for the pain severity score and odds ratio (OR) for nausea/vomiting and hemorrhage events. Data were analyzed using Review Manager version 5.3.5. We assessed the presence of heterogeneity using the I^2 statistic with statistical heterogeneity at $P < 0.1$. Review Manager analyzed data using the fixed-effects method for data without heterogeneity and the random-effects method for data with heterogeneity. We also conducted a subgroup analysis for route of steroids administration, adult/children patients, and dosage of steroids. We performed sensitivity analysis based the following: high methodological quality study, exclusion of studies that caused heterogeneity, and exclusion of studies with different pain score systems.

Results

Study selection

We retrieved a total of 393 references. After titles and abstract review, 296 studies were excluded. 97 studies were considered possible inclusion, and full papers were further reviewed. Of these, 64 met the selection criteria and were included in the meta-analysis (Fig. 1).

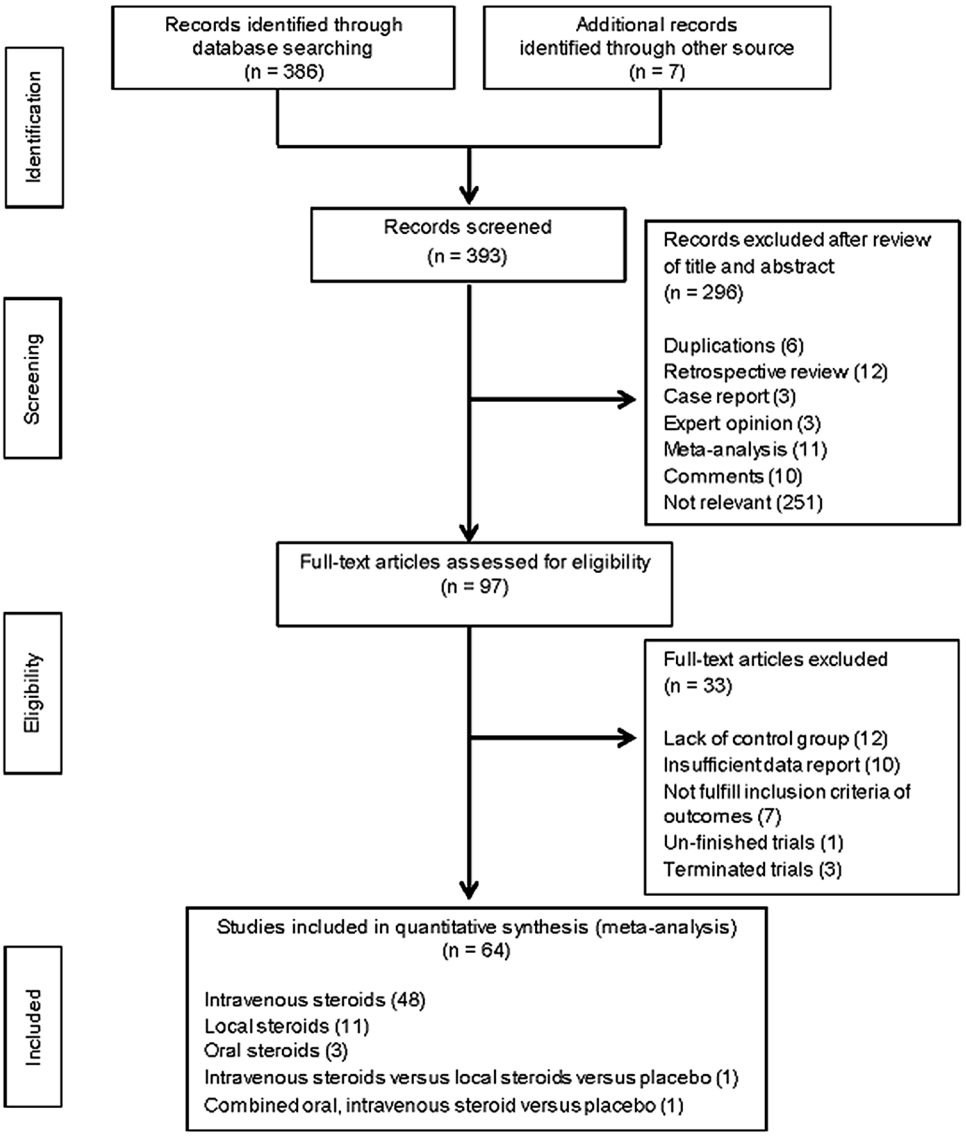

Fig. 1 PRISMA flow diagram of study searching strategy

Quality assessment

A summary of quality evaluation results for included studies is presented in Figs. 2 and 3. About 50% of the included studies had low risk of randomization. 70% of the included studies had adequate concealment of allocations. Three studies had high risk of selection bias due to using non-random component in the sequence generation process and inadequate concealment of allocations prior to assignment. All studies had no detection bias because outcome measurement was not influenced by lack of blinding the outcome assessors. Most of studies had low risk of performance bias, and two studies had high risk of performance bias due to lack of blinding the participants that may influence the pain severity outcome. More than half of the included studies did not mention drop-out participants or missing data. Six studies had high risk of attrition bias due to a large proportion of drop-out participants without explanation. All of the studies had low risk of reporting bias.

Characteristics of included studies

64 studies were included in this meta-analysis (6327 participants) [10, 15–77]. Characteristics of the included studies are shown in Table 1. 47 studies used intravenous steroids injection (dexamethasone dose ranging from 0.05 to 1 mg/kg). 11 studies used local steroids injection, of which 8 studies used dexamethasone ranging from 0.3 to 1 mg/kg, 1 study used triamcinolone acetonide 10 mg, 1 study used deposteroids 20 md, and 1 study did not mention details of steroids and dosage. Three studies used oral steroids (prednisolone dose ranging from 0.25 to 0.5 mg/kg/day for 5–7 days following tonsillectomy). One study compared intravenous dexamethasone, or local dexamethasone to placebo. Two studies used combination of intravenous dexamethasone plus oral prednisolone. Of 64 studies, 61 studies were published in English. Three studies were published in other languages, which were Korean, Chinese, and Hebrew.

From all studies, 42 studies were conducted in children (33 studies used intravenous steroids, 6 studies used local steroids, 1 study used oral steroids, 1 study compared intravenous to local steroids, and 1 study combined intravenous with oral steroids). 18 studies were conducted in adults (13 studies used intravenous steroids, 4 studies used local steroids, and 1 study combined intravenous with oral steroids). 3 studies were conducted in both children and adults (1 study used intravenous steroids, and 2 studies used oral steroids). 1 study did not mention about age of participants.

Effects of interventions

Nausea and/or vomiting

46 studies (4,784 participants) were included in this analysis. Results showed a statistically significant OR, favoring steroids (OR 0.31; 95% CI 0.24–0.40; $P < 0.001$). High heterogeneity regarding the odds ratio was noted ($I^2 = 82.6\%$; $P < 0.001$). The result is shown in Fig. 4.

Subgroup analysis (Nausea and/or vomiting): routes of administration From 46 studies about nausea and/or vomiting outcome, 35 studies used IV steroids, 7 studies used local steroids, 3 studies used oral steroids, and 2 studies used IV-oral steroids combination.

The analysis of IV and local steroids studies showed a statistical difference in the OR of nausea/vomiting events, favoring steroids (IV steroids: OR 0.24; 95% CI 0.18–0.33; $P < 0.0001$, $I^2 = 65\%$, Local steroids: OR 0.56; 95% CI 0.36–0.87; $P = 0.009$, $I^2 = 22\%$). A test of subgroup differences comparing IV to local steroids showed

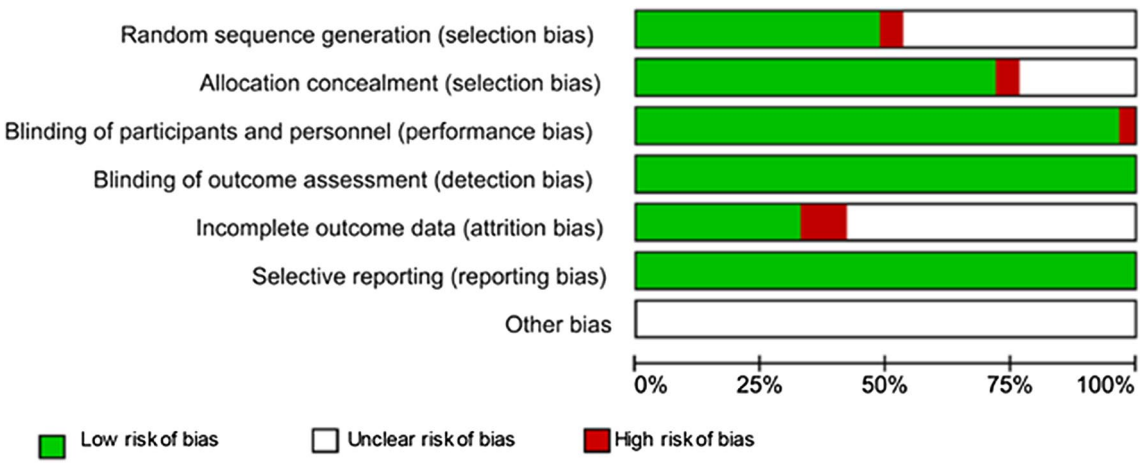

Fig. 2 Quality assessment summary for included studies: risk of bias graph

A; Random sequence generation (selection bias), B; Allocation concealment (Selection bias), C; Blinding of participants and personnel (Performance bias), D; Blinding of outcome assessment (Detection bias), E; Incomplete outcome data (Attrition bias), F; Selective report (Reporting bias), G; Other bias

Fig. 3 Methodology quality assessment for each included study

a statistically significant difference, favoring IV steroids ($\chi^2 = 9.32$, $P = 0.002$).The analysis of oral steroids studies did not show a statistical difference. Meanwhile, the analysis of IV-oral steroids combination studies showed a statistical difference, favoring steroids. (oral steroids: OR 0.85; 95% CI 0.53–1.35; $P = 0.49$, $I^2 = 0\%$, IV-oral steroids combination: OR 0.38; 95% CI 0.21–0.7; $P = 0.002$, $I^2 = 0\%$). However, adding oral to IV steroids did not show any statistically significant difference in the subgroup difference testing when compared to IV steroids alone ($\chi^2 = 1.72$, $P = 0.19$).

In conclusion, IV or local steroids statistically significantly decreases post-tonsillectomy nausea/vomiting. IV steroids were superior to local steroids. Oral steroids gave no statistically significant effect. The result of subgroup analysis according to the route of steroids administration is shown in Fig. 4.

Table 1 Characteristics of included studies

Authors	Year	Sample size		Range of age (years)	Follow-up	Experimental interventions	Control interventions	Outcome measures						
		Steroids	Control					N/V	Pain				PB	SB
									< 24 h	D1	D3	D7		
IV steroids														
Lakhan [15]	2017	60	60	6–12	8 h	IV dexamethasone 0.15 mg/kg	No treatment		+					
Amin [16]	2014	30	30	4–6	18 h	IV dexamethasone 0.15 mg/kg with oral gabapentin 10 mg/kg	Oral gabapentin 10 mg/kg	+	+					
Khalili [17]	2012	35	35	3–7	1 h	IV dexamethasone 0.2 mg/kg	IV NSS 0.05 ml/kg		+					
Gallagher [18]	2012	157	157	3–18	14 days	IV dexamethasone 0.5 mg/kg, max 20 mg	IV NSS equivalent volume						+	+
Hermans [19]	2012	100	44	2–8	2 days	IV dexamethasone 0.15 or 0.5 mg/kg	IV NSS 0.5 ml/kg	+						
Hashimi [20]	2012	50	50	4–12	1 day	IV dexamethasone 0.5 mg/kg, max 8 mg	IV NSS equivalent volume	+	+	+				
Buland [21]	2012	30	30	10–40	12 h	IV dexamethasone 0.15 mg/kg	No treatment		+					
Safavi [22]	2012	30	30	2–12	1 day	IV dexamethasone 0.5 mg/kg, max 8 mg	IV NSS equivalent volume	+	+	+				
Khan [23]	2012	50	50	6–30	8 h	IV dexamethasone 0.5 mg/kg	No treatment		+					
Thimmasettaiah [24]	2012	25	25	> 15	1 day	IV dexamethasone 0.5 mg/kg	IV NSS equivalent volume	+	+	+				
Islam [25]	2011	50	50	3–40	1 day	IV dexamethasone 8 mg with IV granisetron 40 mcg/kg	IV granisetron 40 mcg/kg	+						
Viaman [26]	2011	30	30	18–29	1 day	IV dexamethasone 20 mg	Placebo (no detail)			+				
Vaiman [27]	2011	30	30	18–34	1 day	IV dexamethasone 20 mg	Placebo (no detail)			+				
Mathiesen [28]	2011	43	45	18–50	14 days	IV dexamethasone 8 mg with oral pregabalin 300 mg	Oral pregabalin 300 mg	+	+	+				
Ammar [29]	2009	30	30	5–41	5 days	IV dexamethasone 10 mg for adult IV dexamethasone 5 mg for children	Vitamin C			+	+			+
Karaman [30]	2009	100	50	3–11	1 day	IV dexamethasone 0.2 or 0.7 mg/kg, max 25 mg	No treatment	+						
Mohamed [31]	2009	50	50	2–12	1 day	IV dexamethasone 0.15 mg/kg, max 8 mg with local 0.5% bupivacaine 3 ml	Local 0.5% bupivacaine 3 ml		+					
Bhattacharya [32]	2009	50	50	6–15	1 day	IV dexamethasone 8 mg	IV NSS 2 ml	+						
Khani [33]	2009	33	33	4–12	8 h	IV dexamethasone 8 mg	IV NSS equivalent volume	+	+					
Czarnetzki [34]	2008	159	54	2–17	10 days	IV dexamethasone 0.05 or 0.15 or 0.5 mg/kg, max 20 mg	IV NSS equivalent volume	+					+	+

Table 1 (continued)

Authors	Year	Sample size		Range of age (years)	Follow-up	Experimental interventions	Control interventions	Outcome measures						
		Steroids	Control					N/V	Pain				PB	SB
									< 24 h	D1	D3	D7		
Lachance [35]	2008	41	61	18–45	7 days	IV dexamethasone 8 mg	Placebo (no detail)		+	+	+	+		
Alajmi [36]	2008	42	38	5–18	16 days	IV dexamethasone 1 mg/kg	IV NSS 5 ml	+						+
Rujirojindakul [37]	2008	25	25	15–60	7 days	IV dexamethasone 20 mg	IV NSS equivalent volume	+	+	+			+	+
Liechti [38]	2007	45	45	Children	2 days	IV dexamethasone 0.15 mg/kg, max 6 mg with IV tropisetron 0.1 mg/kg	IV tropisetron 0.1 mg/kg	+						
Fazel [39]	2007	50	50	5–15	1 day	IV dexamethasone 0.5 mg, max 8 mg	IV NSS equivalent volume	+						
Kaan [40]	2006	32	30	4–12	1 day	IV dexamethasone 0.5 mg, max 16 mg	IV NSS equivalent volume	+	+					
Mohammad [41]	2006	25	25	3–18	3 days	IV dexamethasone 1 mg/kg, max 12 mg	No treatment	+	+				+	+
Kaufmann [42]	2006	101	103	2–16	7 days	IV dexamethasone 0.5 mg	No treatment	+	+				+	+
McKean [43]	2006	24	22	16–70	7 days	IV dexamethasone 10 mg	IV NSS 2 ml	+	+	+	+	+		
Malde [44]	2005	45	45	> 3	7 days	IV dexamethasone 0.15 mg/kg	IV NSS 5 ml	+	+	+			+	+
Al-Shehri [45]	2004	15	15	18–35	14 days	IV dexamethasone 6 mg intra-operative then at 8, 16 h after surgery	IV NSS equivalent volume	+		+		+		
Samarkandi [46]	2004	29	31	2–12	1 day	IV dexamethasone 0.5 mg/kg	IV NSS equivalent volume	+						
Hanasano [47]	2004	106	113	9–12	3 days	IV dexamethasone 1 mg/kg, max 50 mg	IV NSS equivalent volume	+		+			+	+
Elhakim [48]	2003	55	55	4–11	2 days	IV dexamethasone 0.5 mg/kg, max 8 mg	IV NSS equivalent volume	+	+	+			+	+
Giannoni [49]	2002	25	25	3–15	10 days	IV dexamethasone 1 mg/kg, max 16 mg	IV NSS equivalent volume	+	+	+	+			+
Aouad [50]	2001	53	53	2–12	1 day	IV dexamethasone 0.5 mg/kg, max 8 mg	IV NSS equivalent volume	+						
Holt [51]	2000	64	56	2–14	5 days	IV dexamethasone 0.5 mg/kg, max 8 mg with IV tropisetron 0.1 mg/kg	IV NSS with IV tropisetron 0.1 mg/kg	+					+	
Carr [52]	1999	15	14	Adult	10 days	IV dexamethasone 20 mg	IV NSS equivalent volume			+	+	+	+	+
Vosdoganis [53]	1999	22	19	2–12	1 day	IV dexamethasone 0.4 mg/kg, max 8 mg	IV NSS equivalent volume	+	+	+				
Pappas [54]	1998	65	63	2–12	1 day	IV dexamethasone 1 mg/kg, max 25 mg	IV NSS equivalent volume	+						

Table 1 (continued)

Authors	Year	Sample size		Range of age (years)	Follow-up	Experimental interventions	Control interventions	Outcome measures						
		Steroids	Control					N/V	Pain				PB	SB
									< 24 h	D1	D3	D7		
Splinter [55]	1996	63	70	2–12	1 day	IV dexamethasone 0.15 mg/kg, max 8 mg	IV NSS equivalent volume	+						
Fujii [56]	1996	30	30	4–10	1 day	IV dexamethasone 4 mg with granisetron 40 mcg/kg	IV NSS with granisetron 40 mcg/kg	+						
Tom [57]	1996	26	32	1–18	10 days	IV dexamethasone 1 mg/kg, max 10 mg	Placebo (no detail)	+					+	
April [58]	1996	41	39	3–15	10 days	IV dexamethasone 1 mg/kg, max 10 mg	IV NSS equivalent volume	+					+	+
Ohlms [59]	1995	34	35	3–18	10 days	IV dexamethasone 0.5 mg/kg, max 12 mg	Placebo (no detail)	+	+	+	+	+		
Tewary [60]	1993	40	42	16–34	2 days	IV dexamethasone 4 mg	No treatment			+				
Catlin [61]	1991	10	15	4–12	7 days	IV dexamethasone 8 mg/m^2	IV NSS equivalent volume							+
Local steroids														
Topal [62]	2017	20	20	3–13	1 day	Local dexamethasone 0.3 mg/kg	Local NSS equivalent volume	+	+	+			+	+
Bayram [63]	2015	20	20	18–60	7 days	5% levobupivacaine hydrochloride 4 ml (5 mg/ml) + dexamethasone sodium phosphate 2 ml (4 mg/ml)	Local NSS 6 ml	+	+	+	+	+	+	
Aysenur [64]	2014	20	20	children	7 days	Local dexamethasone 1 mg/kg, max 25 mg	Local NSS equivalent volume	+	+	+	+	+	+	+
Ju [65]	2013	95	94	4–10	1 day	Local dexamethasone 0.5 mg/kg with 0.2% ropivacaine 1 mg/kg	Local NSS with 0.2% ropivacaine 1 mg/kg	+	+	+				
Montazeri [66]	2009	31	31	3–15	8 h	Local dexamethasone 0.5 mg/kg, max 12 mg	Local NSS equivalent volume	+	+					
Kerekarnjanarong [67]	2007	50	50	11–40	7 days	Right tonsil : 10 mg of triamcinolone acetonide aqueous suspension	Left tonsil: No treatment			+	+	+		
Kim [68]	2004	40	40	15–30	7 days	Local dexamethasone 0.5 mg/kg, max 20 mg	Local NSS equivalent volume			+	+	+	+	+
Kaygusuz [69]	2003	20	20	6–14	7 days	Local dexamethasone 1 mg/kg	NSS spray			+	+	+		
Egeli [70]	1997	25	27	14–34	7 days	Local dexamethasone 0.5 mg/kg, max12mg with lidocaine hidroklorid, epinephrine	Local NSS with lidocaine hidroklorid, epinephrine						+	+
Anderson [71]	1975	65	60	NA	7 days	Local deposteroid 20 mg/side	Local NSS							+

Table 1 (continued)

Authors	Year	Sample size		Range of age (years)	Follow-up	Experimental interventions	Control interventions	Outcome measures						
		Steroids	Control					N/V	Pain				PB	SB
									< 24 h	D1	D3	D7		
Rundle [72]	1967	100	100	children	3 days	Penicillin-steroid-xylocaine mixture 2–4 Ml/Side Both	No treatment	+					+	+
Oral steroids														
Park [73]	2015	99	99	> 4	14 days	Prednisolone 0.25 mg/kg/d for 7 days	No treatment	+		+		+		+
Mccassey [74]	2012	91	102	3–16	8 days	Prednisolone syrup 0.5 mg/kg up to a maximum of 20 mg/d for 5 days	Placebo syrup	+		+	+			+
Palme [75]	2000	25	25	> 5	14 days	Prednisolone 10 mg per day in patients aged 5–11 y, 0.5 mg/kg in those aged > 12 years For 7 days	Placebo tablet	+		+	+			+
Compare IV, local steroid, placebo														
Gao [10]	2015	78	79	5–10	1 day	Local dexamethasone 0.5 mg/kg, max 24 mg and IV NSS 10 mL Local NSS 10 mL saline and IV dexamethasone 0.5 mg/kg, max 24 mg	IV NSS 10 ml with local NSS 10 ml	+	+	+				
Combine IV and oral steroids														
Bahammam [76]	2015	50	50	5–20	14 days	IV dexamethasone 0.15 mg/kg followed by oral Prednisolone 0.25 mg/kg/day for 7 days then tapering for next 7 days	IV NSS No placebo tablet	+						+
Stewart [77]	2002	64	68	> 16	10 days	IV dexamethasone 8 mg intraoperative then oral dexamethasone 2 mg on the evening, twice daily for 4 days With oral piroxicam 10 mg preop then on the evening, twice daily for 4 days	Oral piroxicam 10 mg preop then on the evening, twice daily for 4 days	+						+

Max maximum dose, *IV* intravenous, *NSS* normal saline, *< 24 h* immediate pain severity < 24 h after surgery, *D1* pain severity 1 day after surgery, *D3* pain severity 3 day after surgery, *D7* pain severity 7 day after surgery, *N/V* nausea and/or vomiting, *PB* primary bleeding events within 24 h after surgery, *SB* secondary bleeding events 24 h after surgery

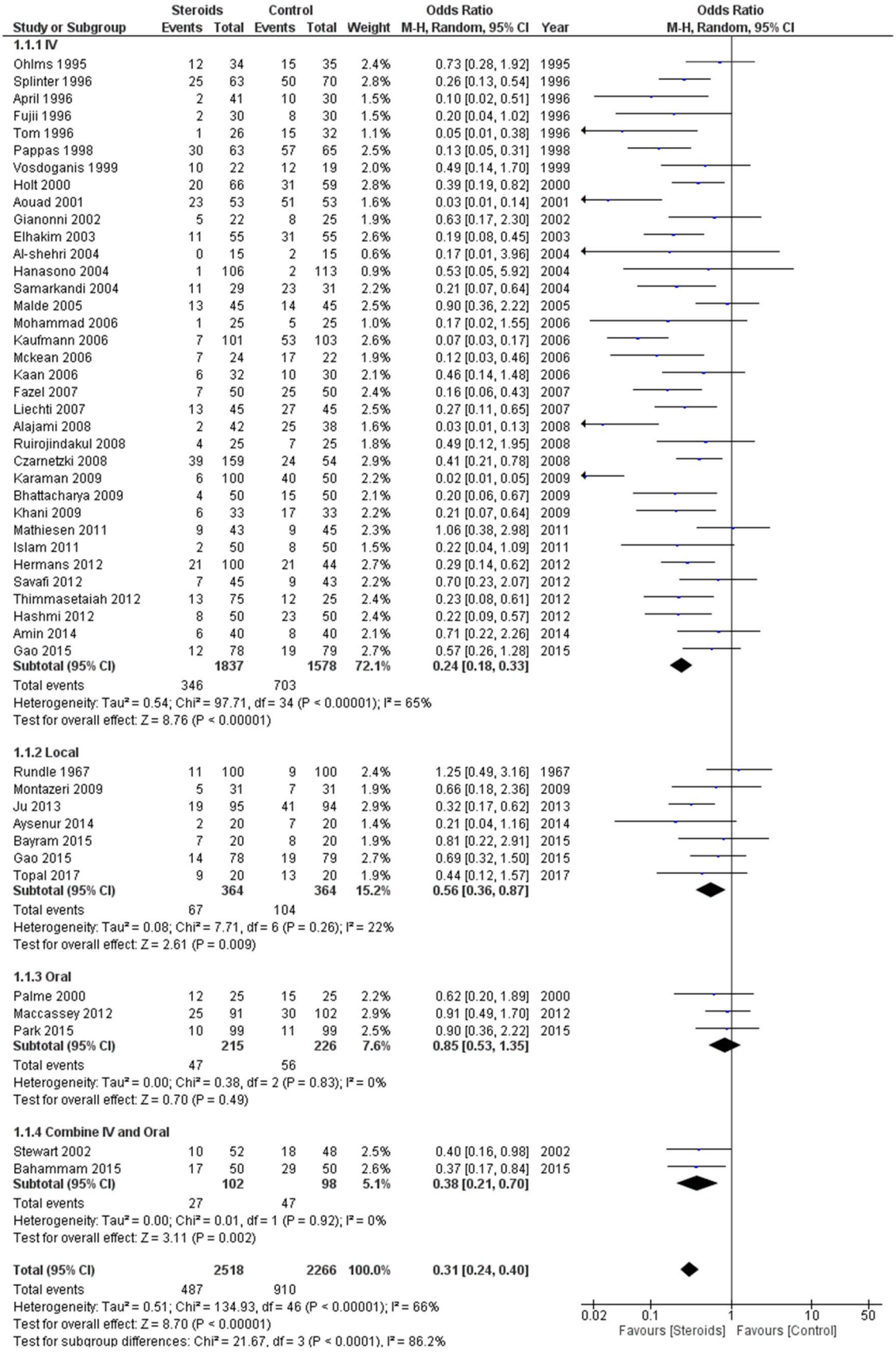

Fig. 4 Nausea/vomiting, odds ratio (OR), steroids versus control: random-effect model

Pain severity 41 studies (3477 participants) were included in the analysis. Results showed a statistical difference of SMD of pain scores favoring steroids in all 4 periods (< 24 h, 1 day, 3 days, 7 days) after tonsillectomy (< 24 h: SMD −0.74; 95% CI −1.02 to −0.53; $P<0.001$; $I^2=69\%$, Day 1: SMD −0.99; 95% CI −1.32 to −0.67; $P<0.001$; $I^2=92\%$, Day 3: SMD −0.62; 95% CI −1.05 to −0.19; $P<0.001$; $I^2=89\%$, Day 7: SMD −0.46; 95% CI −0.75 to −0.18; $P<0.001$; $I^2=78\%$). The analysis showed peak effect of steroids on the first day. These results are shown in Figs. 5, 6, 7 and 8.

Subgroup analysis (pain severity): routes of administration In 28 studies about immediate post-operative (< 24 h) pain severity outcome, there were studies that used IV and local steroids. There was no oral steroids study measured immediate post-operative pain outcome. The analysis of IV and local steroids studies showed a statistical difference in SMD of pain scores, favoring steroids, with high heterogeneity (IV steroids: SMD −0.78; 95% CI −1.09 to −0.48; $P<0.001$; $I^2=90\%$, local steroids: SMD −0.77; 95% CI −1.12 to −0.42; $P<0.001$; $I^2=69\%$). A test of subgroup differences comparing IV to local steroids showed no statistically significant difference ($\chi^2=0$, $P=0.95$).

In 26 studies about pain severity outcome on the first day after surgery, there were studies that used IV and local steroids. There was no oral steroids study measured pain outcome on the first day. The analysis of IV and local steroids studies showed a statistical difference in SMD of pain scores, favoring steroids, with high heterogeneity (IV steroids: SMD −0.97; 95% CI −1.38 to −0.56; $P<0.001$; $I^2=92\%$, local steroids: SMD −1.12; 95% CI −1.77 to −0.48; $P<0.001$; $I^2=90\%$). A test of subgroup differences comparing IV to local steroids showed no statistically significant difference ($\chi^2=0.16$, $P=0.69$).

In 13 studies about pain severity outcome on the 3rd day after tonsillectomy, there were studies that used IV, local, and oral steroids. Only local steroids studies also

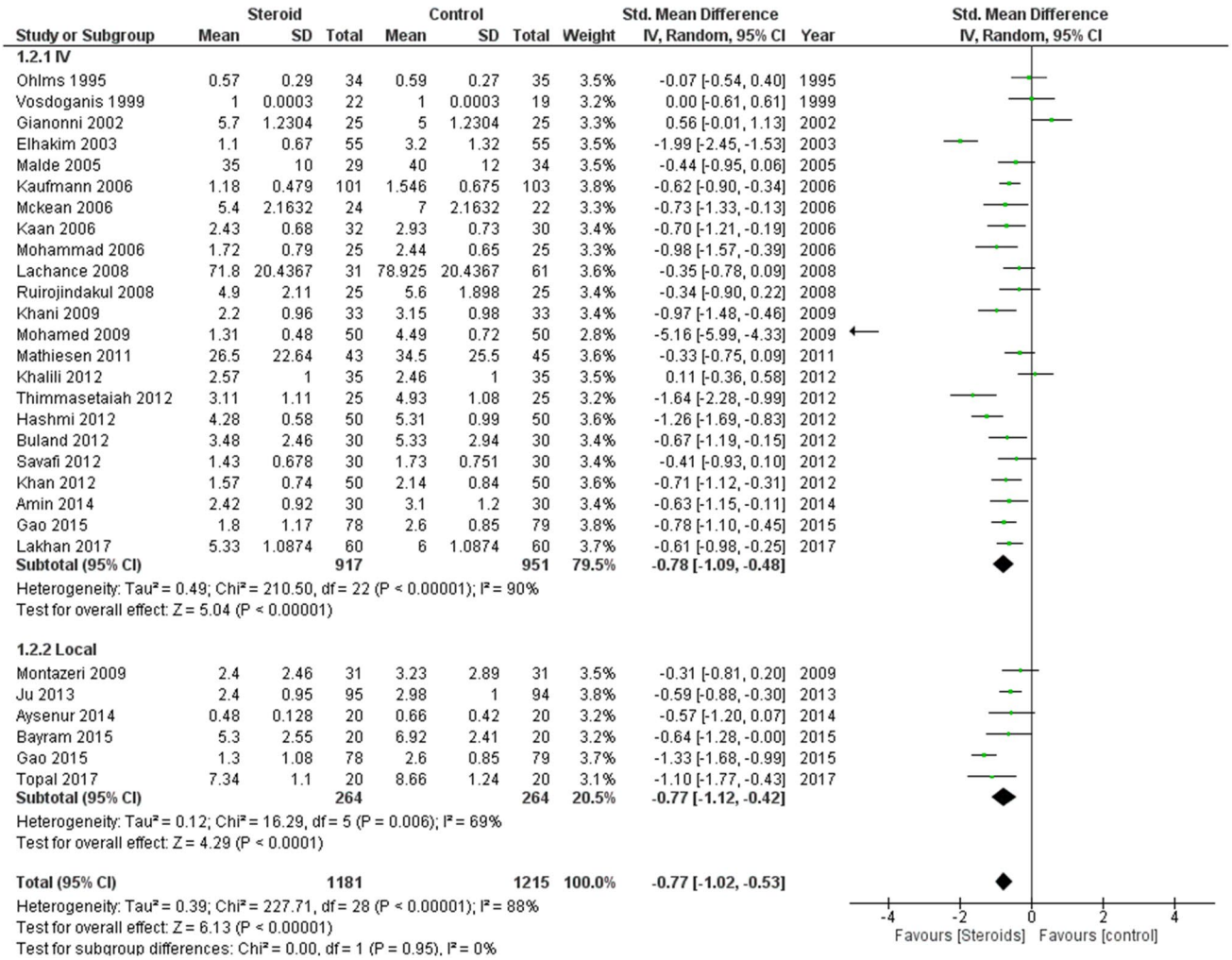

Fig. 5 Immediate pain severity (< 24 h after tonsillectomy), standardized mean difference (SMD), steroids versus control: random-effect model

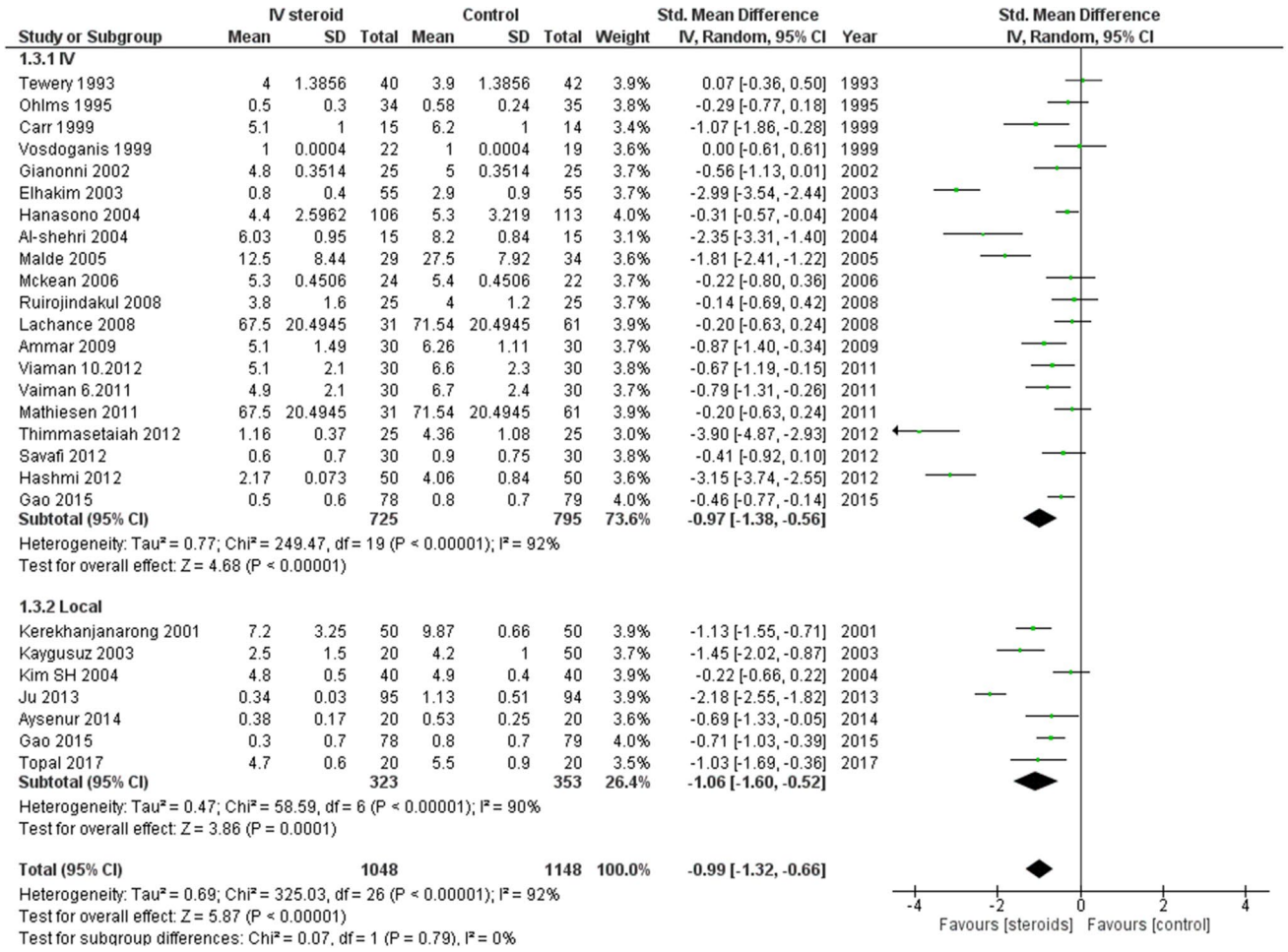

Fig. 6 Pain at day 1 after tonsillectomy, standardized mean difference (SMD), steroids versus control: random-effect model

showed a statistical difference, favoring steroids. The analysis of IV and oral steroids showed no statistical difference (IV steroids: SMD −0.30; 95% CI −1.05 to −0.19; $P=0.21$; $I^2=77\%$, local steroids: SMD −0.94; 95% CI −1.80 to −0.07; P = 0.03; $I^2=91\%$, oral steroids: SMD −0.78; 95% CI −2.05 to −0.05; $P=0.23$; $I^2=94\%$). A test of subgroup differences comparing route of steroids administration showed no statistically significant difference ($\chi^2=1.85$, $P=0.40$).

In 13 studies about pain severity outcome on the 7th day after tonsillectomy there were studies that used IV, local, and oral steroids. Although the analysis of all routes of administration showed a statistical difference favoring steroids, the subgroup analysis of each routes showed no statistical difference in SMD of pain scores on the 7th after tonsillectomy (IV steroids: SMD −0.40; 95% CI −0.89 to 0.10; $P=0.12$; $I^2=72\%$, local steroids: SMD −0.59; 95% CI −1.20 to 0.03; P = 0.06; $I^2=84\%$, oral steroids: SMD −0.36; 95% CI −0.77 to 0.06; $P=0.09$; $I^2=76\%$). A test of subgroup differences comparing route of steroids administration showed no statistically significant difference ($\chi^2=0.38$, $P=0.83$).

In conclusion, IV or local steroids statistically significantly decreases pain severity during the 0-h to 1-day period. Only local steroids showed statistically significant effect on the third day. Oral steroids gave no statistically significant effect. The result of subgroup analyses according to the route of steroids administration is shown in Figs. 5, 6, 7 and 8.

Hemorrhage

15 studies (1,736 participants) about primary hemorrhage outcome were included in this analysis. Results showed no statistically significant OR of primary hemorrhage events (OR 0.96; 95% CI 0.55–1.67; $P=0.88$). No heterogeneity regarding the OR was noted ($I^2=0\%$; $P=0.86$). The results are shown in Fig. 9.

23 studies (2440 participants) about secondary hemorrhage outcome were included in this analysis. Results showed no statistically significant OR of secondary

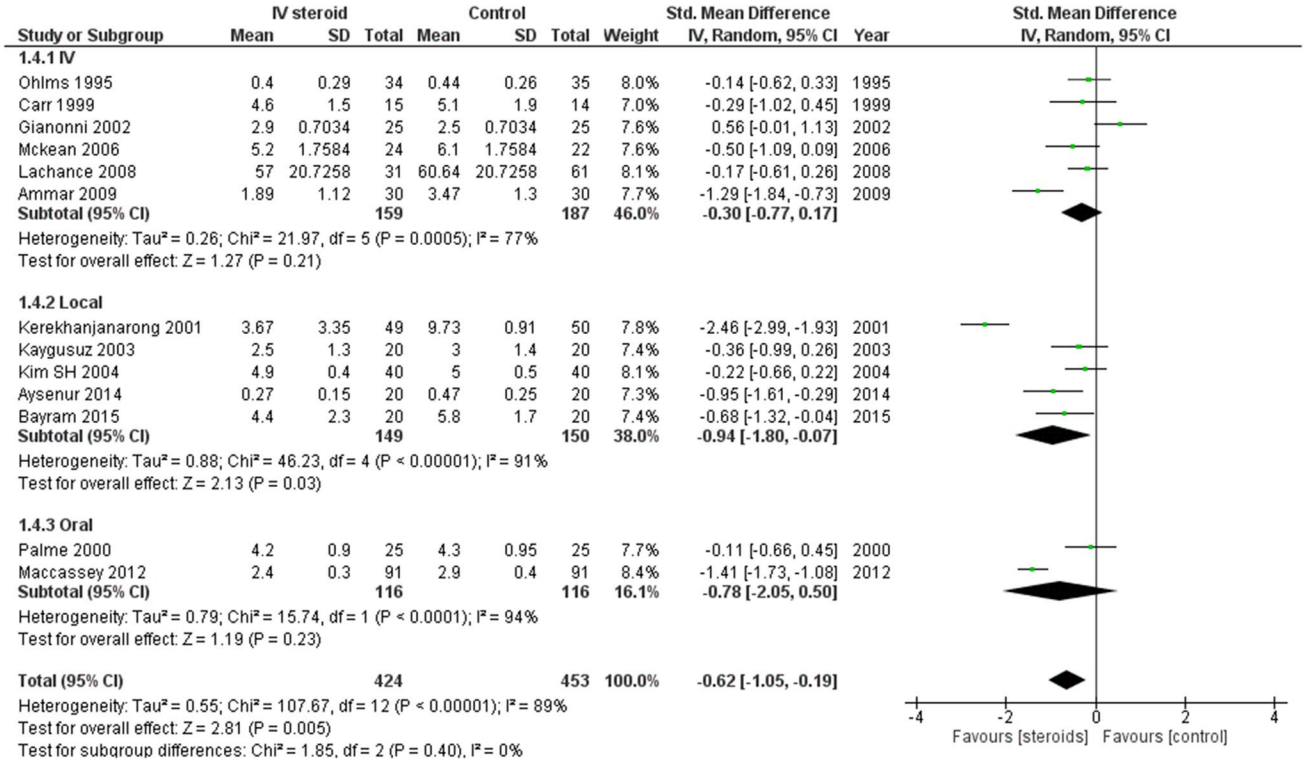

Fig. 7 Pain at day 3 after tonsillectomy, standardized mean difference (SMD), steroids versus control: random-effect model

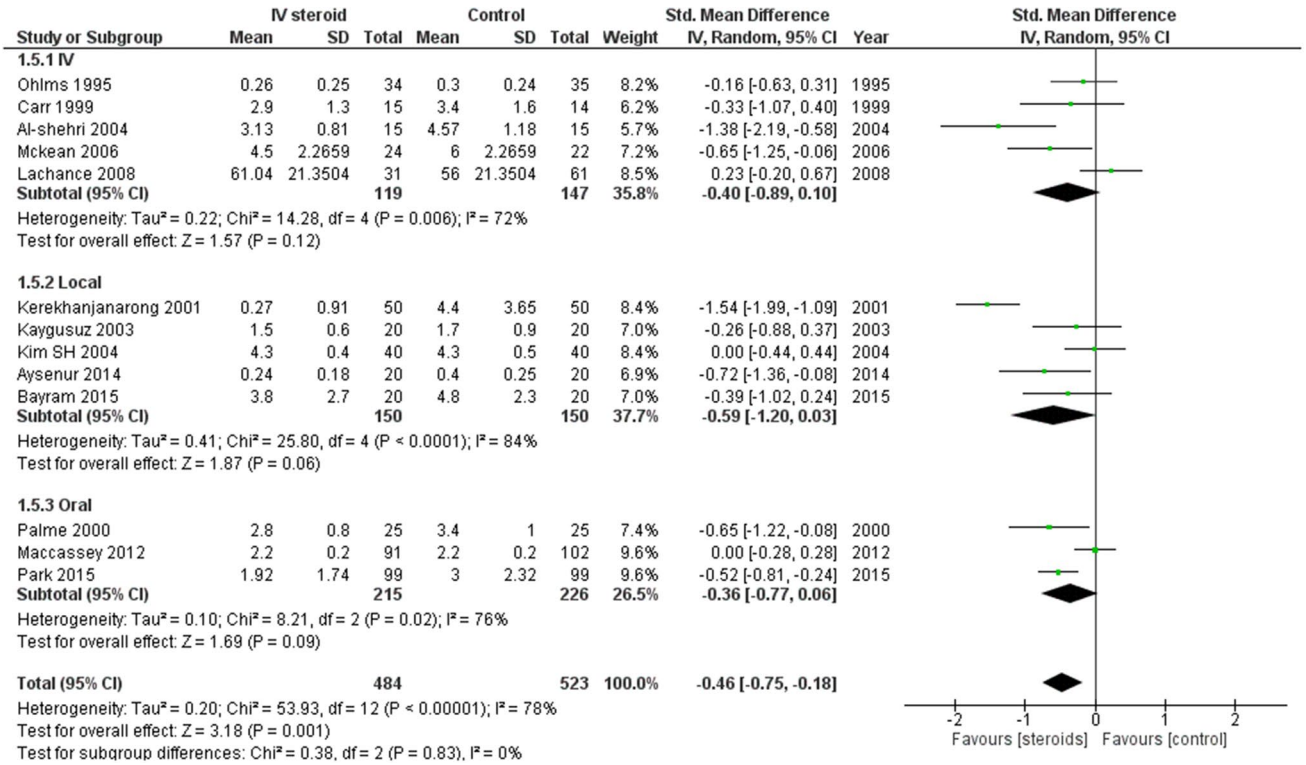

Fig. 8 Pain at day 7 after tonsillectomy, standardized mean difference (SMD), steroids versus control: random-effect model

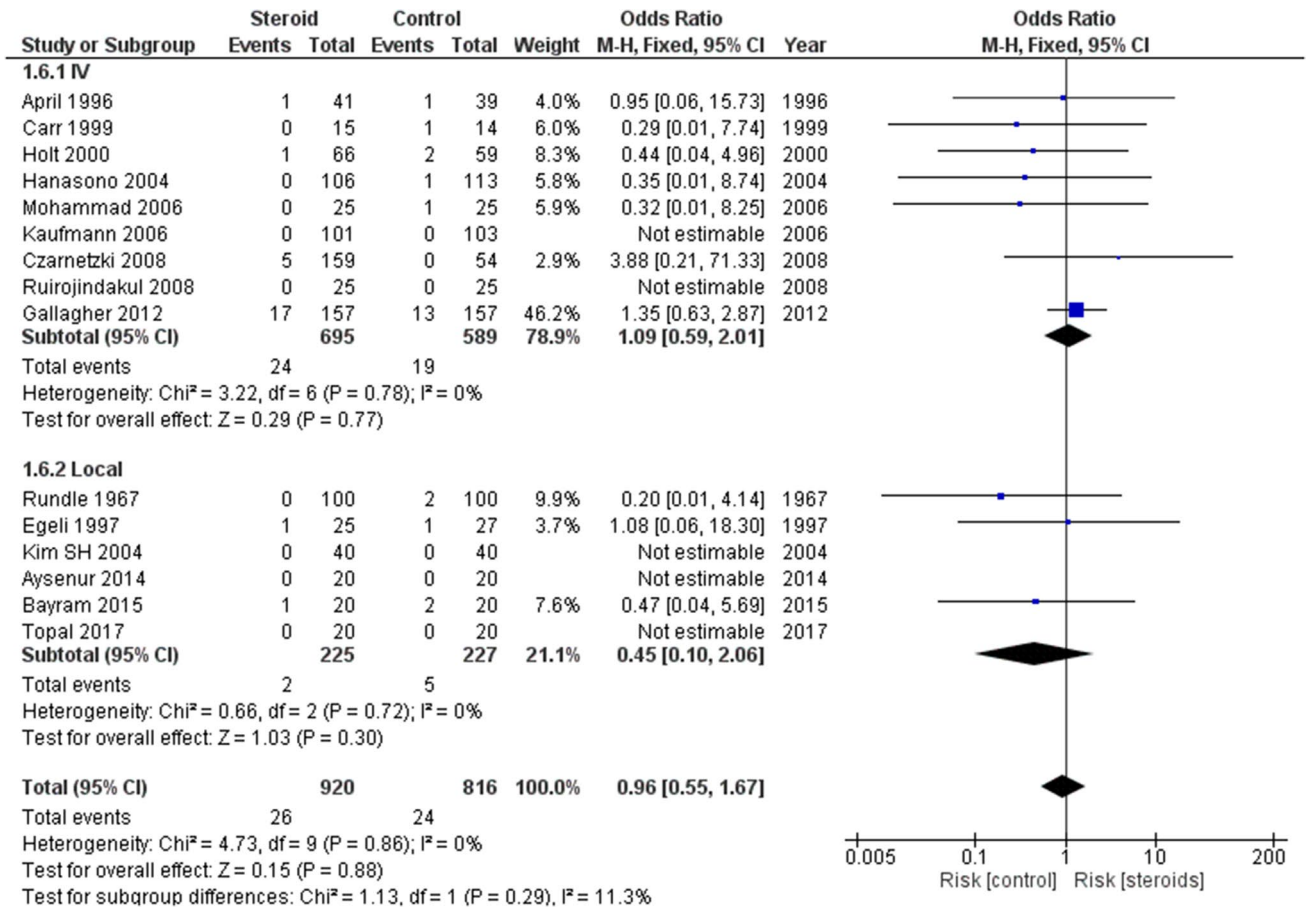

Fig. 9 Primary hemorrhage, odds ratio (OR), steroids versus control: fixed-effect model

hemorrhage events (OR 1.05; 95% CI 0.74–1.51; $P=0.79$). No heterogeneity regarding the OR was noted ($I^2=0\%$; $P=0.72$). The results are shown in Fig. 10.

Subgroup analysis (hemorrhage): routes of administration In 15 studies about primary hemorrhage outcome, there were studies that used IV, and local steroids. The analysis showed no statistical difference in the OR of primary hemorrhage events (IV steroids OR 1.09; 95% CI 0.59–2.06; $P=0.80$, $I^2=0\%$, local steroids: OR 0.48; 95% CI 0.10–2.38; $P=0.37$, $I^2=0\%$). A test of subgroup differences comparing route of steroids administration did not show a statistically significant difference ($\chi^2=1.13$, $P=0.29$).

In 23 studies about secondary hemorrhage outcome, there were studies that used IV, local, oral, and IV-oral steroids combination. The analysis showed no statistical difference in the OR of secondary hemorrhage events (IV steroids: OR 1.21; 95% CI 0.75–1.96; $P=0.44$, $I^2=0\%$, local steroids: OR 1.29; 95% CI 0.48–3.51; $P=0.62$, $I^2=0\%$, oral steroids: OR 0.90; 95% CI 0.36–2.22; $P=0.82$, I^2 NA, combination of oral and IV steroids: OR 0.60; 95% CI 0.23–1.57; $P=0.30$, I^2 NA). A test of subgroup differences comparing route of steroids administration did not show any statistically significant difference ($\chi^2=1.89$, $P=0.60$).

In conclusion, steroids in all route of administration had no statistically significant effect in increasing primary and secondary hemorrhage events. Results of these subgroup analyses according to the route of steroids administration are shown in Figs. 9 and 10.

Subgroup analysis: age of participants and doses of steroids administration The analysis of IV steroids in children and adult showed a statistical difference in OR of nausea/vomiting events, and SMD of immediate pain severity within 1 day after surgery, favoring steroids. Test of subgroup differences did not show any statistically significant differences in all results.

The analysis of local steroids in children showed a statistical difference in OR of nausea/vomiting events, and SMD of immediate pain severity within 3 day after surgery, favoring steroids. However, there were small numbers of studies that used local steroids in adult with analyses showing no statistical differences in all results. Results are shown in e-figures 1–5 in the electronic supplement.

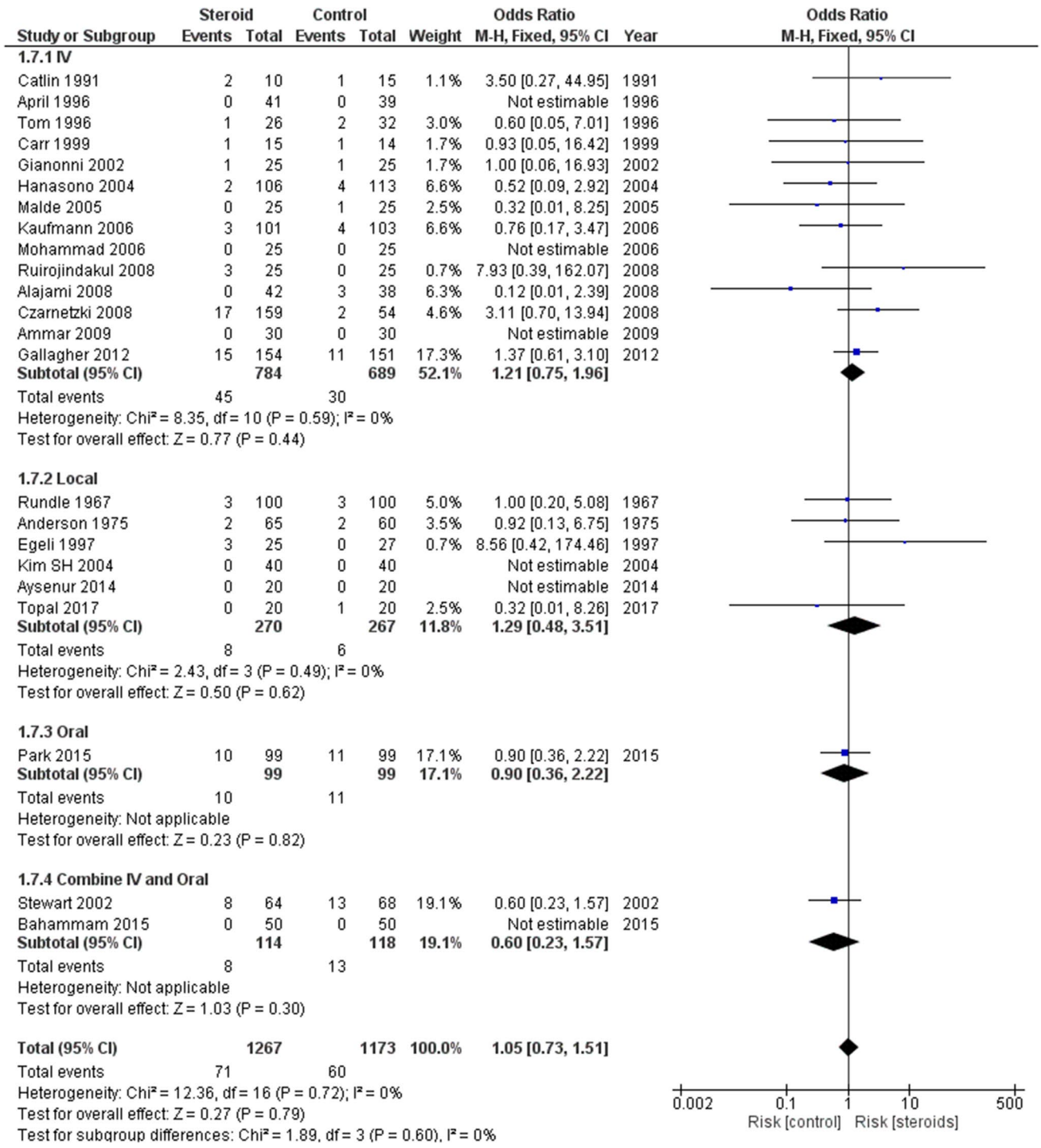

Fig. 10 Secondary hemorrhage, odds ratio (OR), steroids versus control: fixed-effect model

In the analysis of IV and local steroids doses in children, dexamethasone at 0.5 mg/kg dose showed statistical difference in odds ratio of nausea/vomiting events, and SMD of pain severity, favoring steroids. Meanwhile, other doses had small numbers of studies or showed a statistical difference in only some outcomes.

There was a variation of doses of IV dexamethasone studies in adults, which were 0.15 mg/kg/dose, 0.5 mg/kg/dose, 6 mg/dose, 8 mg/dose, 10 mg/dose, and 20 mg/dose. There were too few numbers of studies to analyze.

A subgroup analysis was not conducted in the studies that used oral steroids, and IV-oral steroids combination due to

small numbers of the studies. Moreover, most of the studies were conducted in both children and adults without separation of results for each age group.

Sensitivity analysis

We performed a sensitivity analysis based on methodological characteristics. The analysis of high quality studies showed statistically significant OR of nausea/vomiting events, favoring steroids, in both IV and local steroid administration. However, the analysis of high-quality studies showed statistically significant SMD of pain scores, favoring steroids, in only < 24 h period in IV steroid studies, and in < 24 h and day 1 period in local steroid studies. Results are shown in e-figures 8–11 in the electronic supplement.

We detected significant heterogeneity in the meta-analysis of nausea/vomiting and pain severity outcome. We therefore, performed a sensitivity analysis by excluding the studies that contributed the most to the I^2. From the sensitivity analysis, we found a consistency of results.

In conclusion, the sensitivity analysis showed a statistically significant anti-emetic effect. Meanwhile, IV steroids reduced pain severity in only < 24 h period, and local steroids reduced pain severity during the 0 h to 1-day period.

In the studies about pain severity outcome, there was variation in the types of pain score. The most frequent pain scored used was visual analog scale (VAS), ranging from 0 to 10. We performed sensitivity analysis in the studies that used VAS 0–10, and used the mean difference in those statistical analyses. We found that steroids can decrease VAS to about 1 out of 10 in both IV and local steroids administration. Results are shown in **e**-figures 12–14 in the electronic supplement.

Publication bias

Nausea/vomiting events, pain score, and hemorrhage event funnel plots revealed that the distribution of the studies was reasonably symmetrical, suggesting no evidence of publication bias. The funnel plots are shown in e-figures 15–21 in the electronic supplement.

Discussion

From our meta-analysis, we found that IV or local dexamethasone, at 0.5 mg/kg dose, could statistically significantly decrease post-tonsillectomy nausea/vomiting, and immediate pain scores (< 24 h) in children. Local steroids had extended effect in reducing pain scores on the first day after tonsillectomy. Similarly, IV steroids, at variety doses, can statistically significantly decrease post-tonsillectomy nausea/vomiting, and immediate pain scores in adult. However, there were too few local steroids studies in adult to show significant effects. The subgroup analysis found IV steroids superior to local steroids in decreasing nausea/vomiting events.

From the existing studies, oral steroids had no significant effect on nausea and pain severity outcome. Adding oral steroids to IV steroids had no different effect from IV steroids alone in the subgroup analysis. Steroids had no statistically significant effect in reducing pain severity after 1-day period.

The effects of steroids on post-tonsillectomy hemorrhage cannot be concluded in both children and adult patients, due to a low number of events. An analysis of IV steroids studies did not show statistically significant results but had a tendency to increase the risk of primary and secondary hemorrhage. Therefore, the use of IV steroids should include consideration of increased patient risk of post-operative hemorrhage.

Although IV and local steroids showed a statistical difference in reducing nausea/vomiting events, the clinical significance had to be considered. The sensitivity analysis excluding studies, which did not use 10-point pain scale, showed a decrease in only 1 out of the 10-point pain score. Steroids had a clinically significant anti-emetic effect. IV steroids could reduce about 70–80% of nausea/vomiting events with a NNT of 3 in children, and 6 in adult. Local steroids could reduce about 50% of nausea/vomiting events with a NNT of 9 in children.

Our study is the first meta-analysis including studies used steroids in all routes, including participants in all age groups, comparing each route of administration, and comparing doses of steroids. Moreover, our analysis includes primary studies without excluding non-English studies. The funnel plots show low publication bias.

The limitation of our study includes the heterogeneity of the meta-analysis due to pooling data from studies with different patient populations, surgical techniques, anesthetic techniques, dexamethasone dosages, and outcome measurement tools. We accepted the inherent heterogeneity and used a random-effects model for analysis. We performed a sensitivity analysis, excluding the studies that caused heterogeneity. The analysis showed a consistency of results.

Our results are in-line with the previous five meta-analyses performed by Diakos, Steward, Afman, Bolton, and Goldman [2, 4, 6, 7, 78], which found that IV steroids can decrease nausea/vomiting and immediate post-operative pain within 24 h.

The analysis of local steroids studies also showed a consistency with previous meta-analysis performed by Vlok [79], which found that local medications (dexamethasone, magnesium, pethidine, tramadol) can decrease post-tonsillectomy pain, and only dexamethasone can decrease nausea/vomiting. However, Volk's meta-analysis included one improper study, which was Basuni's study [11] comparing

local to IV dexamethasone, contaminated by bupivacaine HCL, without placebo.

As well as other meta-analyses, our study still cannot conclude the effect of steroids to post-tonsillectomy hemorrhage [2, 80–83]. Plante et al. [81] found that intravenous steroids increase the rate of reintervention to treat post-tonsillectomy bleeding with a statistical significance. Post-tonsillectomy hemorrhage does not frequently occur, thus low event rates were found in the pooling studies of our review. Further study conducted in RCTs with larger sample size or non-RCTs are needed to detect bleeding events.

As for clinical implications, this meta-analysis suggests that IV dexamethasone, at 0.5 mg/kg dose during tonsillectomy in all age groups, is helpful in reducing nausea/vomiting. Local steroids also reduce nausea/vomiting events in children with inferior effect to IV steroids. Steroids had no clinically significant effect in reducing post-operative pain severity. No significant risk of causing hemorrhage was found.

Future researches including local steroids study in adults, RCTs about hemorrhage outcome with larger sample size, and non-RCTs about hemorrhage outcome would help shed more light on the subject.

Conclusions

Intravenous steroids could statistically significantly decrease post-tonsillectomy nausea/vomiting, and immediate pain scores (< 24 h) in all age group. There was evidence only in children that local steroids could statistically significantly decrease post-tonsillectomy nausea/vomiting, and pain scores during the 0-h to 1-day period. From the subgroup analysis, intravenous steroids were superior to local steroids in decreasing nausea/vomiting events.

Adding oral steroids to IV steroids gave no different effect from IV steroids alone. There were too few local steroids studies in adults and oral steroids studies to show significant effects. Steroids had no statistically significant effect in reducing pain severity after 1-day period.

The effects of steroids on post-tonsillectomy hemorrhage cannot be concluded in both children and adult patients, due to a low number of events.

Compliance with ethical standards

Conflict of interest The authors declared no conflicts of interest and received no financial support for the research, authorship, and/or publication of this article.

Research involving human participant and/or animals This study does not involve human participants or animals.

Informed consent Not applicable.

Ethical approval No evaluation of an Ethical Committee was necessary because this study was designed as a meta-analysis.

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