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The efficacy and safety of perioperative administration of dexamethasone: a systematic review and meta-analysis

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Abstract

Background Perioperative prophylactic dexamethasone is commonly administered to reduce postoperative nausea and vomiting (PONV) and pain after surgery. In this study, we aimed to systematically review the efficacy and adverse effects of perioperative dexamethasone administration.

Methods We conducted a systematic search until January 2023 in scientific databases, including PubMed, Scopus, Embase, Web of Science, and Google Scholar. After assessing the methodological quality of relevant studies, we synthesized those focusing on PONV, oral food intake tolerance, impaired wound healing, major postoperative complications, and postoperative infections following the perioperative administration of dexamethasone.

Results A total of 27 studies were included in this systematic review and meta-analysis. The dexamethasone group showed decreased PONV (OR = 0.19; 95% CI 0.06–0.55), increased oral food intake tolerance (OR = 7.38; 95% CI 1.07–51.11), increased risk of impaired wound healing (OR = .48; 95% CI 0.52–4.21), decreased probability of postoperative infection (OR = 0.61; 95% CI 0.51–0.72), and increased risk of major postoperative complications (OR = 1.27; 95% CI 0.68–2.39) compared to the controls.

Conclusions The results of our pooled data analysis showed that dexamethasone was superior to the control in terms of PONV, oral food intake tolerance, and postoperative infections.

Keywords Dexamethasone, Intraoperative, Perioperative, Nausea, Vomiting

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Background

Dexamethasone is often used as a premedication for anesthesia due to its anti-inflammatory properties that can help with airway manipulation, prevention of skin and drug reactions, and reduction of nausea and vomiting. Additionally, it has analgesic properties that can aid in pain management (Polderman et al. 2018). Postoperative nausea and vomiting (PONV) and pain are the side effects of this medication that can lead to patient discomfort, decreased satisfaction with surgery, and delayed functional improvement of patients undergoing surgery (Cui et al. 2015). Glucocorticoids can not only relieve pain by reducing inflammation at the wound site (Bahammam et al. 2017) but also may be used perioperatively to



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reduce PONV due to their antiemetic effects (Gan et al. 2007).

Meanwhile, due to induced peripheral resistance to insulin and the immunosuppressive effects of glucocorticoids, there are debates on the preoperative administration of dexamethasone (Kwon et al. 2013; Jules-Elysee et al. 2011). In this regard, Backes et al. reported side effects, such as reduced sleep quality, high risk of infection, and early postoperative hyperglycemia following the application of preoperative dexamethasone (Backes et al. 2013). It should be noted that these side effects are associated with long-term treatment using glucocorticoids (Schimmer BP, Funder JW. ACTH 2011), while it remains controversial whether a single perioperative dose of glucocorticoids is associated with an increased risk of adverse effects.

Overall, the use of dexamethasone during surgery to reduce PONV remains a topic of debate. Therefore, we aimed to conduct this systematic review and meta-analysis of the available evidence to investigate the efficacy and adverse effects of perioperative and intraoperative administration of dexamethasone in all healthy individuals undergoing different types of surgery.

Methods

In this systematic review and meta-analysis, we used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

Search strategy

To identify relevant published studies, we conducted a systematic search until January 2023 in scientific databases, including PubMed, Scopus, Embase, Web of Science, and Google Scholar, using related keywords provided in the Additional file 1 (Supplementary file S1). A medical librarian supervised the search strategy. We also manually searched the reference lists of all eligible studies and previous reviews for additional relevant research.

Population

All healthy individuals undergoing different types of surgery were included in our study with no restrictions on age, sex, nationality, ethnicity, race, or geographic location.

Intervention

In this review, we evaluated any formulation or dose of dexamethasone, administered perioperatively or intraoperatively through various routes, alone or in combination therapy.

Comparator

Other treatment regimens or controls with either placebo or other antiemetic agents were the comparators in this study.

Outcome

The effects of dexamethasone on the prevention of PONV and oral food intake tolerance were the outcomes of this study. Also, other outcomes of interest were the adverse effects of dexamethasone, including impaired wound healing, major postoperative complications, and postoperative infections.

Inclusion and exclusion criteria

Studies based on the Population, Intervention, Comparator, Outcomes (PICO) framework were included in this systematic review. In studies where dexamethasone implant was used in ocular surgeries, the outcomes of interest were not reported, and studies with incomplete or unidentified data were excluded. Also, animal, in vitro, or in vivo studies, non-English articles, publications without accessible full-text manuscripts in English, case reports, case series, literature reviews, letters to the editor, theses, book sections, conference proceedings, and preprints were excluded.

Data extraction

After collecting records from the online databases, duplicated records were removed in Endnote Version 20, and the rest of the duplicates were deleted manually. Three authors independently extracted data, including the first author, publication date, study type, study location, total sample size, age, sex, dose, main outcomes, and adverse effects. In case of disagreement between the authors, the senior author provided guidance and advice to help resolve the issue. In studies with incomplete data, the corresponding author was contacted if possible. The extracted data were organized in Microsoft Excel 2019.

Quality assessment

Three independent investigators evaluated the quality of all studies, using the Joanna Briggs Institute (JBI) critical appraisal technique. Generally, JBI has proposed nine, 11, and 13 criteria for evaluating the quality of quasi-experimental studies, cohorts, and randomized controlled trials (RCTs), respectively.

Statistical analysis (meta-analysis)

Data are presented using descriptive statistics (mean \pm SD) for continuous variables. Frequency and percentage are also measured for categorical variables. Dichotomous data are expressed as pooled odds ratio (OR) and 95% confidence intervals (95% CI). The

mean difference (MD) and 95% CIs were calculated for continuous outcomes. Moreover, a random-effects meta-analysis of the available data was conducted. Heterogeneity between studies was assessed based on the I^2 and P value of Cochran's Q test; $I^2 > 50\%$ and P < 0.05were considered statistically significant. Additionally, funnel plots were used to investigate publication bias. All statistical analyses were performed in Stata Version 14.2 (StataCorp LLC, College Station, TX, USA).

Results

Search results

A total of 202 articles were identified in the scientific databases, 55 of which were found to be duplicates. After

removing duplicates, 82 articles were excluded based on the title and abstract, and 65 articles were evaluated for the availability of their full-text manuscripts. A total of 57 full-text articles were found and screened. After screening the full-text manuscripts, 27 articles were included in the qualitative synthesis and meta-analysis, based on the inclusion criteria (Fig. 1).

The included articles were as follows: 16 RCTs, nine cohorts, one non-randomized experimental study, and one case–control study. Most studies were conducted in the USA (n=9) and the Netherlands (n=5), followed by China (n=2) and then, Turkey, Scotland, Ukraine, Germany, Korea, Brazil, Russia, Pakistan, Thailand, Georgia, and Canada, each with one study.



Fig. 1 Flowchart of studies included in the systematic review

Demographic characteristics

In the reviewed studies, a total of 31,048 cases were examined for the efficacy and adverse effects of dexamethasone administered perioperatively or intraoperatively through various routes. In studies where sex was reported, 18,872 of the subjects (61%) were male, while 11,715 (39%) were female. The sample size of the included studies ranged from 41 to 7910 participants. The mean \pm SD age of the patients was 51.1 ± 9.2 years, ranging from 2 months to 88 years. In 17 studies, the administration of dexamethasone was reported to be effective. Two of the included studies (Karaman et al. 2009a; Tkachenko and Pyasetska 2019) each included two intervention groups with different characteristics; therefore, they were entered separately into Table 1 and meta-analysis. The characteristics of the reviewed studies are presented in Table 1.

PONV

The pooled data of eight eligible studies reported an OR of 0.19 in the meta-analysis (95% CI 0.06–0.55), which indicated that perioperative or intraoperative dexameth-asone administration could be effective in decreasing PONV (Fig. 2).

Oral food intake tolerance

The pooled data of four eligible studies indicated an OR of 7.38 in the meta-analysis (95% CI 1.07–51.11), suggesting that perioperative or intraoperative dexamethasone increased the oral food intake tolerance (Fig. 3).

Impaired wound healing and postoperative infection

The meta-analysis of three eligible studies indicated that dexamethasone increased the risk of impaired wound healing (OR=1.48; 95% CI 0.52–4.21) (Fig. 4). On the other hand, in the meta-analysis of three other eligible studies, dexamethasone decreased the probability of postoperative infection (OR=0.61; 95% CI 0.51–0.72) (Fig. 5).

Major postoperative complications

The pooled OR of four eligible studies indicated that dexamethasone increased the risk of major postoperative complications, including shock, hemorrhage, deep vein thrombosis (DVT), and pulmonary embolism (PE) (OR = 1.27; 95% CI 0.68–2.39) (Fig. 6).

Quality assessment and publication bias of studies

The JBI critical appraisal score was six for both quasiexperimental (out of 9 points) and case-control (out of 10 points) studies. It also ranged from five to eight (out of 11 points) for cohorts and from six to 10 (out of 13 points) for RCTs included in this review. The quality assessment tools varied based on the study design; consequently, the scores could not be directly compared (Supplementary file S2, Table S1–4). However, the funnel plot analysis showed a mild asymmetry due to possible publication bias or heterogeneity (Figs. 7, 8, 9, 10 and 11).

Discussion

In this PRISMA-compliant systematic review and metaanalysis, we aimed to investigate the efficacy and adverse effects of perioperative or intraoperative administration of dexamethasone in all healthy individuals undergoing any type of surgery. Dexamethasone, due to its antiemetic and analgesic effects, is the first intervention to reduce PONV associated with general anesthesia and relieve pain following various surgeries. However, the efficacy of this medication in preventing PONV is still controversial (Fan et al. 2018). Feelings of discomfort, shame, dissatisfaction with the surgery outcome, as well as fear of a new surgery, are some psychiatric problems following PONV (Jolley 2013). In this regard, Apfel et al. showed that the patients' fear of PONV was more significant than their fear of postoperative pain (Apfel et al. 2004). Therefore, evidence-based studies are necessary to help anesthesiologists make accurate clinical decisions.

The present review indicated that perioperative or intraoperative dexamethasone administration could effectively decrease PONV. Three recent systematic reviews reported that prophylactic dexamethasone decreased the incidence of PONV after mastectomy (Xu et al. 2020), total hip arthroplasty (Fan et al. 2018), and thyroidectomy (Chen et al. 2012) relative to the placebo. Evidence suggests that the central antiemetic effects of dexamethasone reduced the incidence of PONV (Lunn and Kehlet 2013). On the other hand, in three RCTs conducted by Corcoran et al. (Corcoran et al. 2017), Ituk et al. (Ituk and Thenuwara 2018), and Kleif et al. (Kleif et al. 2017), it was found that dexamethasone did not effectively relieve PONV after different types of surgery.

This systematic review revealed that prophylactic dexamethasone increased the oral food intake tolerance of the patients in the dexamethasone group compared to the placebo group. Consistent with our results, Pappas et al. showed that administration of prophylactic dexamethasone in children undergoing tonsillectomy improved their postoperative oral intake (Pappas et al. 1998). The beneficial anti-nausea and vomiting effects of dexamethasone persisted until about three days after surgery and facilitated early oral intake (PO) (Karaman et al. 2009b).

The possible adverse effects of dexamethasone are impaired wound healing, hyperglycemia, and increased

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	Author, year	Country	Study design	Sample size	Gender (<i>n</i>)	Age range (year)	Type of operation	Dosage	Forms of drug use	Effectivness
-	Snall (2013)	Finland	Single-blinded RCT	4	M:40 F:1	18-51	Open reduction/osthe- osynthesis of mandibu- lar fractures	30 mg	IV 10 mg/IM 20 mg	Q
5	Karaman et al. (2009a)	Turkey	Single-blinded RCT	100	NR	NR	Adenotonsillectomy/ tonsillectomy	0.2 mg/kg	≥	Yes
\sim	Karaman et al. (2009b)	Turkey	Single-blinded RCT	100	NR	NR	Adenotonsillectomy/ tonsillectomy	0.7 mg/kg	≥	Yes
4	Newhook et al. (2021b)	USA	Retrospective cohort	373	M:210 F:163	35–88	Pancreatic ductal adenocarci- noma resection	4–10 mg	≥	Q
Ŝ	Jacob et al. (2015a)	Netherlands	Double-blinded RCT	4465	M:3248 F:1217	NR	Cardiac surgery with CPB	1 mg/kg	≥	Yes
9	Dieleman et al. (2012)	Netherlands	Double-blinded RCT	4482	M:3250 F:1232	NR	Cardiac surgery with CPB	1 mg/kg	≥	Yes
\sim	Zhang et al. (2019)	China	Double-blinded RCT	214	M:51 F:163	18–65	Thyroid	0.1 mg/kg	≥	Yes
00	Pappas et al. (1998)	USA	Double-blinded RCT	128	NR	2-12	Ambulatory tonsil- lectomy	1 mg/kg	≥	Yes
6	Shakeel et al. (2010)	Scotland	Retrospective cohort	333	M:157 F:176	NR	Tonsillectomy	NR	NR	Yes
10	Tkachenko and Pyaset- ska (2019)	Ukraine	Double-blinded RCT	83	M:0 F:83	18–36	Cesarean section	4 mg	Intrathecal	Yes
=	Tkachenko and Pyaset- ska (2019)	Ukraine	Double-blinded RCT	82	M:0 F:82	18–36	Cesarean section	8 mg	≥	No
12	Blume et al. (2018b)	Germany	Retrospective cohort	49	M:32 F:17	NR	Cervical spondylotic myelopathy	40 mg	2	No
13	Ituk and Thenuwara (2018)	USA	Double-blinded RCT	52	NR	NR	Post-cesarean delivery analgesia	8 mg	2	No
4	Lim et al. (2011)	Korea	RCT	80	M:47 F:33	NR	Gallbladder resection	8 mg	≥	Yes
15	Hatfield (2017)	USA	Case-control	200	M:100 F:100	18–64	Laparoscopic cholecys- tectomy	4–8 mg	≥	Yes
16	Jacob et al. (2015b)	Netherlands	Double-blinded RCT	62	M:47 F:15	>18	Cardiac surgery	1 mg/kg	2	No
17	Sauër et al. (2014)	Netherlands	Double-blinded RCT	737	M:480 F:257	>18	Isolated CABG, valve surgerv	1 mg	≥	No

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	Author, year	Country	Study design	Sample size	Gender (<i>n</i>)	Age range (year)	Type of operation	Dosage	Forms of drug use	Effectivness
100	Corcoran et al. (2017)	10 countries-ENIGMA II Trial Post hoc	Double-blinded RCT	5499	M:3559 F:1940	> 45	Uralogy, neuralogy, gastrointestinal, liver, ENT, Orthopedic, plastics, gynecological, vascular, colorectal	NR NR	R	°Z
19	Klement et al. (2018)	USA	Retrospective cohort	7910	M:3649 F:4261	NR	Total joint arthroplasty	NR	\geq	Yes
20	Lomivorotov et al. (2020)	China, Brazil, Russia	Double-blinded RCT	394	M:186 F:208	- V	Cardiac surgery	1 mg	\geq	No
21	Samona et al. (2017)	USA	Retrospective cohort	102	M:44 F:58	> 18	Total knee arthroplasty	NR	\geq	Yes
22	Sandini et al. (2018b)	USA	Retrospective cohort	562	M:322 F:357	NR	Pancreaticoduodenec- tomy	NR	\geq	Yes
23	Osch et al. (2015)	Netherlands-DECS trial post hoc	Double-blinded RCT	4482	M:3250 F:1232	> 18	Cardiac surgery	1 mg	\geq	No
24	Khan and Iqbal (2012)	Pakistan	Quasi experiment	100	M:66 F:34	6_30	Tonsillectomy	0.5 mg/kg	\geq	Yes
25	Thongrong et al. (2018)	Thailand	Double-blinded RCT	54	M:17 F:37	29–74	Microvascular decom- pression	4 mg	\geq	No
26	Bateman et al. (2006)	USA	Retrospective cohort	65	NR	2–120 months	Cleft palate	4 mg	≥	Yes
27	Foulkes (1990)	Georgia	Retrospective cohort	45	M:30 F:15	24–87	Lumbar hemilaminec- tomy/micro diskec- tomy	16 mg	NR	Yes
28	Splinter and Roberts (1996)	Canada	Double-blinded RCT	133	NR	2-12	Tonsillectomy	150 pg/kg	\geq	Yes
29	Egan et al. (2019b)	USA	Retrospective cohort	121	M:87 F:34	27–87	Diabetic patients who underwent surgery due to cutaneous burns	10-4 mg	≥	N

M male, F female, IV intravenous, NR not reported

Treatment Control						Odds ratio					
Study	Yes	No	Yes	No					with 95% CI	(%)	
Karaman M 2009	4	46	40	10	_	-			0.02 [0.01, 0.07]	12.12	
Karaman M 2009	2	48	40	10					0.01 [0.00, 0.05]	11.04	
Pappas A 1998	19	45	40	24					0.25 [0.12, 0.53]	13.48	
Tkachenko R 2019	8	34	25	16		-			0.15 [0.06, 0.41]	12.83	
Tkachenko R 2019	18	23	25	16				_	0.50 [0.21, 1.21]	13.14	
ltuk U 2018	5	21	4	22					- 1.31 [0.31, 5.55]	11.46	
Thongrong C 2018	8	19	10	17				\vdash	0.72 [0.23, 2.23]	12.42	
William M. Splinter 1996	25	38	50	20			_		0.26 [0.13, 0.54]	13.51	
Overall						-			0.19 [0.06, 0.55]		
Heterogeneity: $\tau^2 = 2.14$,	l ² = 89.	19%,	$H^2 =$	9.25							
Test of $\theta_i = \theta_j$: Q(7) = 42.1	6, p =	0.00									
Test of θ = 0: z = -3.03, p	= 0.00										
					1/256	1/32	1/4	2	-		

Random-effects REML model

Fig. 2 Forest plots for comparison of dexamethasone effectiveness in decreasing postoperatively nausea and vomiting between intervention and control groups



Random-effects REML model

Fig. 3 Forest plots for comparison of dexamethasone effectiveness in increasing tolerability to start taking oral foods between intervention and control groups

	Interv	ention	Co	ontrol					Odds ra	atio	Weight
Study	Yes	No	Yes	No					with 95%	6 CI	(%)
Snall J 2013	7	13	6	15					1.35 [0.36,	5.04]	62.43
Blume C 2017	5	20	0	24			-		— 13.15 [0.69,	252.16]	12.45
Klement 2018	1	1,292	8	6,609		-	_		0.64 [0.08,	5.12]	25.12
Overall									1.48 [0.52,	4.21]	
Heterogeneity: T	.00%,	$H^2 = 1.00$									
Test of $\theta_i = \theta_j$: Q	(2) = 2	.75, p =	0.25								
Test of θ = 0: z =	= 0.74,	p = 0.46	6								
					1/8	1	8	64	_		

Random-effects REML model

Fig. 4 Forest plots for comparison of dexamethasone effectiveness in increasing the risk of wound healing impairment between intervention and control groups

major/infectious complications (Kwon et al. 2013; Bartlett and Hartle 2013). Adverse effects, such as impaired wound healing and increased anastomotic drainage, often occur following chronic dexamethasone administration (Bartlett and Hartle 2013; Eriksen et al. 2014). Our meta-analysis showed that dexamethasone increased the risk of impaired wound healing. Blume et al. also observed a significantly higher rate of wound

	Trea	atment	Co	ontrol						Odds ra	atio	Weight
Study	Yes	No	Yes	No						with 95%	6 CI	(%)
Dieleman J.M 2012	212	2,023	333	1,914						0.60 [0.50,	0.72]	87.81
Blume C 2017	5	20	0	24	_					13.15 [0.69,	252.16]	0.34
Sandini 2018	22	95	160	402						0.58 [0.35,	0.96]	11.85
Overall					٠					0.61 [0.51,	0.72]	
Heterogeneity: $\tau^2 = 0$.00, I ²	= 0.00%	5, H ² =	: 1.00								
Test of $\theta_i = \theta_j$: Q(2) =	4.20,	p = 0.12	2									
Test of θ = 0: z = -5.7	′2, p =	0.00										
					1/2	2	8	32	128			

Random-effects REML model

Fig. 5 Forest plots for comparison of dexamethasone effectiveness in decreasing the probability of postoperative infection between intervention and control groups



Random-effects REML model

Fig. 6 Forest plots for comparison of dexamethasone effectiveness in increasing the risk of major postoperative complications between intervention and control groups



Fig. 7 Funnel plot for publication bias of studies which reported dexamethasone effectiveness in decreasing postoperatively nausea and vomiting



Fig. 8 Funnel plot for publication bias of studies which reported dexamethasone effectiveness in increasing tolerability to start taking oral foods



Fig. 9 Funnel plot for publication bias of studies which reported dexamethasone effectiveness in increasing the risk of wound healing impairment

infection following the administration of high-dose (0.4–0.8 mg/kg/day) prophylactic dexamethasone in cervical spondylotic myelopathy surgery (Blume et al. 2018a). In another study on mandibular surgeries, no significant difference was observed in the incidence of impaired wound healing between the dexamethasone and control groups (Snäll et al. 2013).

In the present study, dexamethasone decreased the risk of postoperative infection. According to a study by Sandini et al., a single intraoperative dose of dexamethasone was associated with a lower probability of post-pancreaticoduodenectomy sepsis (Sandini et al. 2018a). A meta-analysis by Dan et al. demonstrated that intraoperative dexamethasone did not significantly increase the risk of infection (Dan et al. 2010). Nevertheless, it is worth mentioning that the prescription of dexamethasone could increase blood sugar by increasing peripheral insulin resistance. Meanwhile, the risk of developing infections after surgery increased in patients with uncontrolled blood sugar (Kwon et al. 2013), and dexamethasone exerted well-known immunosuppressive effects, which might increase the risk of infectious complications.



Fig. 10 Funnel plot for publication bias of studies which reported dexamethasone effectiveness in decreasing the probability of postoperative infection



Fig. 11 Funnel plot for publication bias of studies which reported dexamethasone effectiveness in increasing the risk of major postoperative complications

The pooled data of our meta-analysis indicated that dexamethasone increased the risk of major postoperative complications. There are conflicting reports regarding the effect of intraoperative glucocorticoids on postoperative complications. Diabetic burn patients receiving intraoperative steroids showed increased rates of major complications, especially partial graft loss compared to the control group (Egan et al. 2019a). However, another study reported that prophylactic dexamethasone was not associated with any differences in postoperative major/infectious complications compared to the control group (Newhook et al. 2021a). In some evaluated studies, the score of the verbal analogue scale for pain was significantly lower in patients who received perioperative prophylactic dexamethasone compared to the control group (Lim et al. 2011; Hatfield 2017; Samona et al. 2017; Khan and Iqbal 2012; Thongrong et al. 2018). Nonetheless, due to a lack of sufficient data, we were unable to conduct a meta-analysis on this subject.

The major limitation of the present study was the lack of a subgroup analysis based on different types of surgery, anesthesia techniques, and characteristics of patients, such as sex or age. Also, we did not compare the efficacy of dexamethasone with that of other antiemetics. Despite these limitations, our study is the most recent meta-analysis evaluating the efficiency and safety of prophylactic administration of dexamethasone.

Conclusions

The results of this meta-analysis suggested that prophylactic administration of dexamethasone not only decreased the incidence of PONV and the probability of postoperative infection in all healthy individuals undergoing surgery but also increased their tolerance to start oral food intake. However, dexamethasone administration increased the risk of impaired wound healing and major postoperative complications. Since the advantages of dexamethasone outweigh its disadvantages, the perioperative administration of prophylactic dexamethasone can benefit the patients.

Abbreviations

PONV Postoperative nausea and vomiting

- OR Odds ratio
- MD Mean difference
- CI Confidence interval
- SD Standard deviation
- DVT Deep vein thrombosis
- RCT Randomized controlled trials
- PO Per Os
- PE Pulmonary embolism

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s42077-023-00376-w.

Additional file 1: Supplementary file S1. Relevant published studies

Additional file 2: Supplementary file S2. Table 1. Quality Assessment of Cohort Studies. Table 2. Quality Assessment of Randomized Controlled Trial Studies. Table 3. Quality Assessment of Non-Randomized Experimental Studies. Table 4. Quality Assessment of Case Control Studies.

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Authors' contributions

NN and PN designed the study, MJN, MOS and, MS collected data, MJN wrote the first draft of the paper, MH contributed to the writing and revision of the manuscript. NN designed the Meta-analysis. All authors contributed to finalizing the manuscript.

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Nil.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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