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Review

A systematic review and meta-analysis on the safety and efficacy of premedication prior to elective intubation in neonates

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Abstract

Objective: Endotracheal intubation, as an emergent but also as an elective procedure, can be stressful and painful, causing hypoxemia, bradycardia, acidosis or increased intracranial pressure. We aimed to investigate the safety and efficacy of premedication prior to elective intubation in order to contribute to the development of a more standardized strategy.

Method: A systematic review and meta-analysis was conducted. The PubMed database was searched using the PICO method and keywords according to MeSH terms were used. Only studies with control groups were included (randomized controlled trials, prospective observational and case-control studies).

Results: Our search procedure yielded 722 potentially eligible studies. Finally, 26 studies were included for qualitative and quantitative analysis. Blood pressure during intubation was found lower for neonates that received premedication compared to controls (SMD = -1.27; 95% CI [-2.59; 0.05]; $p < 0.01$). Heart rate change was found higher in the control group (SMD = -0.26; 95% CI [-1.07; 0.55]; $p = 0.54$). Intervention groups were found to have higher odds for bradycardia (OR = 1.13; 95% CI [0.79; 1.62]; $p = 0.51$), and less odds for desaturation compared to control groups (OR = 0.69; 95% CI [0.33; 1.45]; $p = 0.33$). The odds for adverse events were found 3 times lower in the intervention group, in relation to controls (OR = 0.71; 95% CI [0.55; 0.73]; $p = 0.012$). Intubation time for the intervention groups was lower than controls (SMD = -0.59; 95% CI [-1.06; -0.11]; $p < 0.02$). Intubation attempts were found marginally increased in the intervention group (ROM = 1.10; 95% CI [0.79; 1.53]; $p = 0.57$). No difference was found regarding mortality rate between groups.

Conclusion: Most Neonatal Intensive Care Units should consider premedication prior to intubation for vigorously and active term and preterm

infants as a safe and efficient procedure that buffers serious physiological responses and assures better procedural conditions.

Keywords

Intubation, premedication, neonates, sedatives, anesthesia, pain.

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Introduction

Laryngoscopy and intubation are invasive, usually difficult and stressful procedures, affecting central nervous and cardiorespiratory system [1, 2]. Published data show vastly different, low rating use of sedatives and/or muscle relaxants, along with lack of non-written policy in Neonatal Intensive Care Units (NICUs) within and among countries. Ziegler and Todres since 1992 reported in United States NICU premedication use of 23% to 43% [3]. More recently, in UK, written policy for premedication before elective (non-emergent) intubation reached an impressive 90%, although the variety of drugs used reflects lack of standardization of care [4, 5]. Still, concern remains for premedication safety and effectiveness during elective intubation for newborns in relation to their age/maturity and medical status [6].

Intubation in non-adequately sedated patients is considered causal for serious cardiovascular stress, pain, intracranial pressure (ICP) increase, systemic blood pressure (BP) increase, bradycardia, oxygen saturation drop (desaturation), acidosis and even tracheal injury or laryngospasm [7-9]. In an unsedated newborn infant, intubation could also provoke bronchospasm, pulmonary hypertension and trauma [10]. Finally, responses to laryngoscopy in non-adequately sedated newborns could be choking, gagging, coughing, laryngospasm and increased ICP [11].

Concerns about the beneficial role of sedation and analgesia for premedication in intubation still arise. Implemented premedication is used mainly for term rather than preterm neonates and usually includes potent opiates, benzodiazepines, muscle relaxants or anaesthetic drugs [12]. Whyte et al. reported that, in 1998, premedication was administered in only 1 out of 3 UK NICUs, with most commonly sedative drugs being morphine/diamorphine, opiates as fentanyl, benzodiazepines and muscle-relaxants [13].

Drug administration should be chosen based on effectiveness (degree of sedation and/or relaxation and/or sleep), onset of action, duration of effect (time of recovery), safety and side effect, during or after the administration, but also familiarity [10].

Material and methods

Strategy

This study was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines for meta-analysis [14]. Eligible studies reported in PubMed, up to the study data collection time point (February 25, 2022) were selected for inclusion. Only studies published in English language were selected and there was no restriction on publication year, publication type or status.

Search question formation

The search query was formulated according to the PICO framework (P: patient, I: intervention, C: comparison, O: outcomes) [15, 16]. MeSH (Medical Subject Headings) terms were extensively used in order to be compliant as much as possible to the standard practice [17]. However, since there are publications indexed without proper MeSH terms, the search was extended to include also terms in the abstract or paper title.

The query components were created individually for each PICO component within the PubMed database using the advanced search builder, which allows the structured query formation. The individual parts of the query were used for specific searches: the P part was used to search for "infant", "infants", "neonate", "neonates" or "neonatal"; this query component alone identified about 1.5 million publications and, similarly, the other PICO components were also

created. The combination with the AND operator of the above components resulted in the final query.

Selection of publications

Two reviewers (I.C. and G.N.K.) reviewed all search results independently (screening process). The review was based on titles and abstracts, while the relevant studies were included for the subsequent stage of full text review. In case of disagreements, the opinion of a third researcher was requested (G.M.). After the qualitative synthesis of the collected results, a mathematical synthesis of their results was performed.

Study selection criteria/study characteristics

The aim of our study was to assess the effectiveness and safety of premedication in neonates prior to endotracheal intubation.

Premedications were categorized in 3 categories: (1) analgesics (fentanyl, remifentanil, morphine), (2) hypnotics/sedatives (midazolame, thiopental, propofol, lidocaine), (3) muscle relaxants (pancuronium, vecuronium, rocuronium, succinylcholine), while number 0 was assigned to controls (no medication or placebo).

Types of outcome measures

Randomized controlled trial (RCTs) or prospective observational and case-control studies were considered for a possible subsequent analysis.

Statistical analysis

The meta-analysis was performed in the R programming software language (version 4.0.4) [18] within the Microsoft® Windows® environment, utilizing the R package meta (version 4.18-0) [19, 20]. For each parameter under investigation, a forest plot along with the results is presented. A funnel plot was also used to estimate the publication bias. The mean value and the standard deviation are required to perform the meta-analysis when numeric data are used; however, this was not always reported. In these cases, they were estimated, through median and the values of the 1st and 3rd quartiles according to Hozo et al. [21]. Additionally, in cases that minimum and maximum values were reported, it was applied an improved estimation, as proposed by Bland [22]. Finally, if the 1st and 3rd quartiles were not reported, the range rule was used to estimate standard deviation.

We used forest plots to present the meta-analysis results using both the fixed and the random effects model. Notably, the fixed effect model assumes that there is a single phenomenon, and the involved studies are estimating this. The random effects model considers numerous similar phenomena and estimates their mean value. In this study, it is not known if there is a single phenomenon or if it is affected by factors varying across studies (for example age), therefore both models are presented.

Results

The flow diagram of PRISMA results is presented in **Fig. 1**.

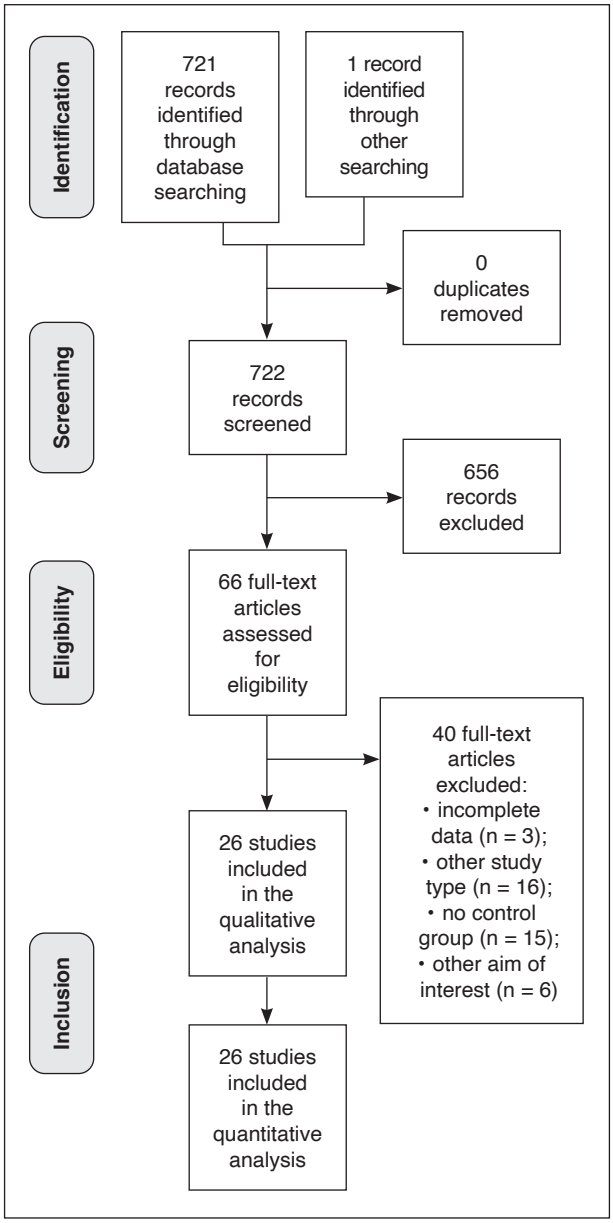

Figure 1. Flow diagram of PRISMA results.

Our search procedure yielded 721 potentially eligible studies. One additional publication [11], not possible to obtain through the systematic search, was also included. As there were no duplicates, 722 studies were screened by title and abstract and after excluding 656, 66 studies were reviewed by full text for eligibility. Finally, 26 studies [8, 11, 23-46] were included in our systematic review.

The outcomes after data extraction process are depicted in **Tab. 1**. Specifically, the first author of each study, along with the year of publication, is reported. In addition, the study type (RCT, prospective observational or case-control), the premedication drugs, the dosage used, premedication and relevant dosage in the control group (if applicable) are also reported. It is of note

Table 1. Characteristics of included studies (continues on the next page).

First author and reference number	Year	Country	Study type	Intervention group		Control group	
				Premedication	Dosage	Premedication	Dosage
Analgesics							
Badiee Z. [46]	2013	Iran	RCT	Remifentanil (+ atropine)	2 µg/kg	(Atropine)	-
Caldwell C.D. [27]	2015	Mexico	Prospective observational	Morphine	0.05-0.1 mg/kg	None	-
				Fentanyl	1-2 µg/kg	None	-
Lemyre B. [36]	2004	Canada	RCT	Morphine	0.2 mg/kg	Placebo	-
Hypnotics/sedatives							
Barois J. [24]	2013	France	Prospective observational	Ketamine (+ atropine)	1 mg/kg	None	-
Bhutada A. [25]	2000	USA	RCT	Thiopental	6 mg/kg	Placebo	-
Caldwell C.D. [27]	2015	Mexico	Prospective observational	Midazolam	0.05-0.2 mg/kg	None	-
Dekker J. [32]	2016	The Netherlands	RCT	Propofol	1 mg/kg	None	-
Dekker J. [33]	2019	The Netherlands	RCT	Propofol	1 mg/kg	None	-
Krick J. [35]	2018	USA	Prospective observational	Sedative	-	None	-
Mussavi M. [38]	2014	Iran	RCT	Lidocaine spray	-	None	-
Milési C. [37]	2018	France	RCT	Midazolam	0.2 mg/kg	Nasal ketamine	2 mg/kg
Van der Lee R. [43]	2016	The Netherlands	RCT	Propofol	2 mg/kg	Vecuronium + morphine	0.1 mg/kg
Muscle relaxants							
Barrington K. [26]	1989	UK	RCT	Succinylcholine (+ atropine)	2 mg/kg	(Atropine)	-
Kelly M.A. [34]	1984	Canada	Case-control	Pancuronium (+ atropine)	0.1 mg/kg	None	-
Analgesics + hypnotics/sedatives							
Caldwell C.D. [27]	2015	Mexico	Prospective observational	Morphine + midazolam	0.05-0.1 mg/kg + 0.05-0.2 mg/kg	None	-
				Fentanyl + midazolam	1-2 µg/kg + 0.05-0.2 mg/kg	None	-
Norman E. [40]	2012	Sweden	RCT	Thiopental + remifentanil	2-3 mg/kg + 1 µg/kg	Morphine	0.3 mg/kg
Avino D. [23]	2014	Belgium	RCT	Morphine + midazolam + atropine	100 µg/kg + 50 µg/kg + 20 µg/kg	Remifentanil + atropine	1 µg/kg + 20 µg/kg
Silva Y.P. [42]	2007	Brazil	RCT	Remifentanil + midazolam	1 µg/kg + 0.2 mg/kg	Morphine + midazolam	0.15 mg/kg + 0.2 mg/kg

Table 1. Characteristics of included studies (continues from the previous page).

First author and reference number	Year	Country	Study type	Intervention group		Control group	
				Premedication	Dosage	Premedication	Dosage
Analgesivs + hypnotics/sedatives + muscle relaxants							
Norman E. [39]	2011	Sweden	RCT	Thiopental + remifentanil + suxamethonium + glucopyrolate	-	Morphine + atropine + glucopyrolate	-
Analgesics + muscle relaxants							
Oei J. [41]	2002	Australia	RCT	Morphine + suxamethonium (+ atropine)	0.1 mg/kg + 1 mg/kg	None	-
Choong K. [28]	2010	Canada	RCT	Fentanyl + succinylcholine (+ atropine)	2 µg/kg + 2 mg/kg	Remifentanil (+ atropine) + placebo	-
Feltman D. [30]	2011	USA	RCT	Rocuronium + fentanyl (+ atropine)	0.5 mg/kg + 2 µg/kg	Fentanyl (+ atropine)	2 µg/kg
Roberts K.D. [44]	2006	USA	RCT	Mivacarium + fentanyl (+ atropine)	0.2 mg/kg + 2 µg/kg	Fentanyl (+ atropine)	2 µg/kg
Durrmeyer X. [29]	2018	France	RCT	Sufentanil + atracurium (+ atropine)	0.1 µg/kg ≤ 1,000 g, 0.2 µg/kg > 1,000 g, + 1st dose 0.3 mg/kg, 2nd dose 0.1 mg/kg	Propofol (+ atropine)	1st dose 2.5 mg/kg > 1,000 g, 1 mg/kg ≤ 1,000 g, 2nd dose 1 mg/kg
Ghanta S. [31]	2007	USA	RCT	Morphine + suxamethonium (+ atropine)	100 µg/kg + 2 mg/kg	Propofol	2.5 mg/kg
Vedrenne-Cloquet M. [11]	2019	France	RCT	Sufentanil + atracurium (+ atropine)	-	Propofol (+ atropine)	-
Pokela M.L. [8]	1994	Finland	RCT	Alfentanil + suxamethonium + glucopyrolate	20 µg/kg + 1.5 mg/kg	Pethidine + suxamethonium + glucopyrolate	1 mg/kg + 1.5 mg/kg
Hypnotics/sedatives + muscle relaxants							
Krick J. [35]	2018	USA	Prospective observational	Sedative with paralytic	-	None	-
				Sedative with paralytic	-	Sedative	-
Millar C. [45]	1994	USA	RCT	Thiopentone + succinylcholine	5 mg/kg + 2 mg/kg	None	-

RCT: randomized controlled trial.
It is of note that some studies are reported multiple times if more than one premedication type was used.

that some studies are reported multiple times if more than one premedication type was used.

Systematic review of the included studies

There were 18 studies in which premedication drugs were compared with controls, thus providing a solid basis for this systematic review and a further step of meta-analysis.

Three studies [27, 36, 46] examined the safety and efficacy of analgesics before intubation in comparison with no premedication. Seven studies [24, 25, 27, 32, 33, 35, 38] examined the safety and efficacy of hypnotics/sedatives in comparison with no premedication, 1 [37] in comparison with nasal hypnotics/sedative and 1 [43] with muscle relaxant plus analgesics. Two studies [26, 34] examined the safety and efficacy of muscle relaxants in comparison

with no premedication. One study examined the safety and efficacy of analgesics plus hypnotics/sedatives in comparison with no premedication [27], 1 [40] in comparison with analgesics alone and 2 [23, 42] in comparison with a different combination of analgesics plus hypnotics/sedatives. One study [39] examined the safety and efficacy of analgesics plus hypnotics/sedatives plus muscle relaxants in comparison with analgesics plus hypnotics/sedatives. One study [41] examined the safety and efficacy of analgesics plus muscle relaxants in comparison with no premedication, 3 studies [28, 30, 44] in comparison with analgesics, 3 studies [11, 29, 31] in comparison with hypnotics/sedatives and 1 [8] in comparison with analgesics plus hypnotics/sedatives. Finally, 2 studies [35, 45] examined the safety of hypnotics/sedatives plus muscle relaxants with no premedication and 1 study [35] with another sedative drug.

Meta-analysis

Initially, in order to ensure that there was no difference in the neonatal population in terms of gestational age (GA) and birth weight (BW), we performed the meta-analysis for these two important parameters; 23 studies with available data for GA and BW were included in this meta-analysis [8, 11, 23-26, 28-34, 36-41, 43-46]. Regarding GA and BW, for GA the I^2 was 86% ($p < 0.01$), while for BW the I^2 was 77% ($p < 0.01$), indicative of the studies heterogeneity between cases and controls. Additionally, the funnel plot is indicative of the publication bias. Nevertheless, the ratio of means (ROM) for GA was 1.0 (95% CI [0.97; 1.02]) and for BW 0.98 (95% CI [0.91; 1.05]), indicating that there is no difference in the studies concerning GA and BW.

As for gender, in most studies males had almost equal percentages between case-control groups. This was evaluated by evaluating the odds ratio (OR) of males versus females in the two groups, which showed no difference (pooled OR = 1.08; 95% CI [0.81; 1.45]) (data not shown).

Safety outcomes

Pain measurement between neonates using premedication and controls was one of the main outcomes of this study. In 12 papers, we analyzed 18 comparisons with and without premedication (n = 996 neonates, intervention cases: ni = 473, control cases: nc = 523) prior to intubation. Studies evaluating pain scores finally were not included in the meta-analysis, since they were based on very different pain scales and measurements, providing inconsistent and heterogenous data. Since data were not available in all studies, we applied the analysis only for studies that had valid data.

In the case of arterial BP (systolic BP [BPS]), the 4 included studies [25, 28, 36, 44] showed that the standardized mean difference (SMD) was negative; thus, BPS during intubation was found lower for neonates that received premedication compared to controls (SMD = -1.27; 95% CI [-2.59; 0.05]; I^2 = 91%; $p < 0.01$) (**Fig. 2**). Noteworthy, BPS at baseline was found without difference between cases and controls (SMD = 0.09; 95% CI [-0.10; 0.28]; I^2 = 0%; p = 0.34), and the studies had excellent homogeneity, indicating that case-control populations were similar.

Heart rate (HR) change during intubation was estimated in 7 studies [8, 25, 28, 29, 32, 35, 44], and was found higher in the control group (SMD = -0.26; 95% CI [-1.07; 0.55]; I^2 = 96%; $p < 0.01$) (**Fig. 3**). Specifically for HR at baseline, meta-analysis of the included studies [8, 11, 26, 28, 33, 36, 38, 41, 45, 46] showed that it was similar between groups (ROM = 1; 95% CI [0.97; 1.04]; I^2 = 76%; $p < 0.01$).

Regarding bradycardia (HR < 100 beats/min) during intubation, intervention groups were found to have higher odds for bradycardia compared to control groups (OR = 1.13; 95% CI [0.79; 1.62]; I^2 = 0%; p = 0.49) (**Fig. 4** and **Fig. 5**). Notably, data related to bradycardia were mainly extracted from Caldwell et al. study [27] (5 different medication schemes were compared with controls) with 6 additional studies included [29, 32, 33, 36, 44, 46].

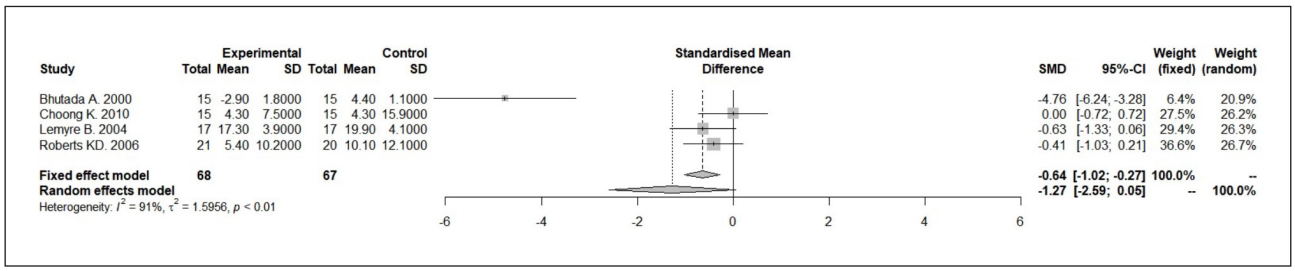

Figure 2. Forest plot regarding the changes in mean systolic blood pressure (BPS) during intubation [25, 28, 36, 44].

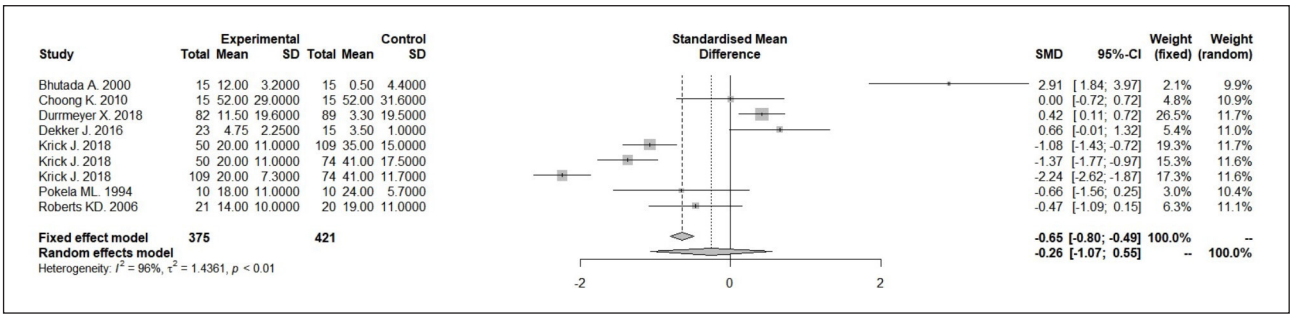

Figure 3. Forest plot regarding the heart rate (HR) changes during intubation [8, 25, 28, 29, 32, 35, 44].

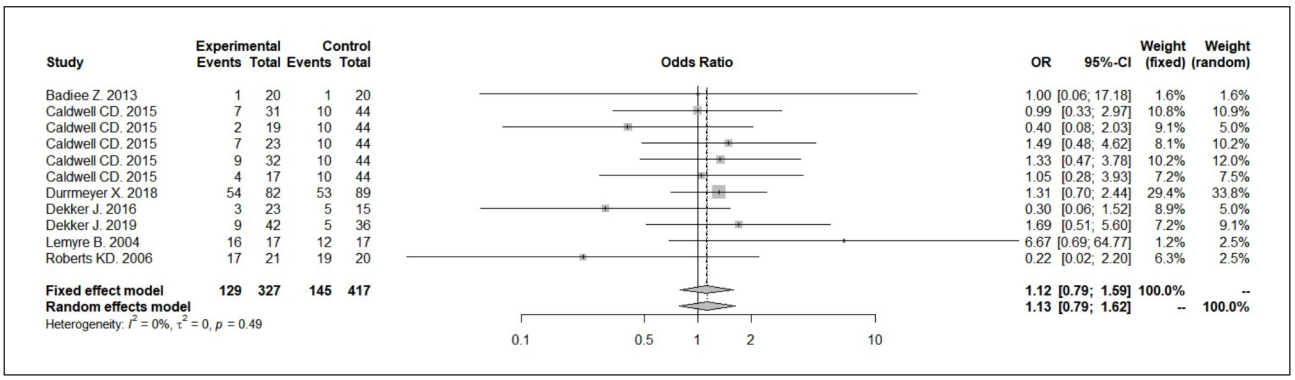

Figure 4. Forest plot regarding bradycardia (heart rate [HR] < 100 beats/min) during intubation [27, 29, 32, 33, 36, 44, 46].

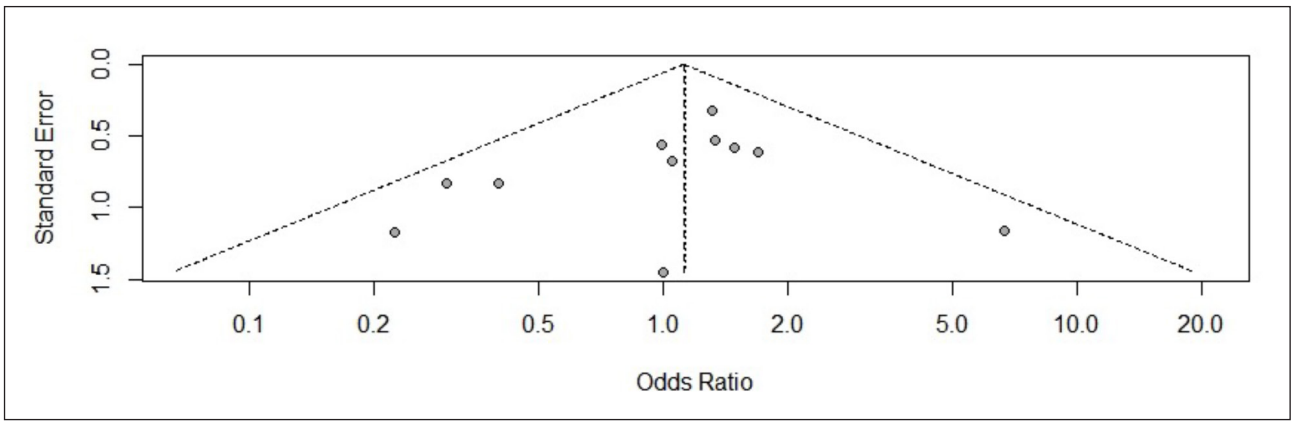

Figure 5. Funnel plot regarding bradycardia (heart rate [HR] < 100 beats/min) during intubation [27, 29, 32, 33, 36, 44, 46].

Finally, with regards to SpO_2 percentage change, meta-analysis [8, 35, 46] showed that there were less odds for desaturation in the intervention groups (OR = 0.69; 95% CI [0.33; 1.45]; I^2 = 63%; p = 0.33).

Adverse events

Adverse events were reported in 13 studies [8, 23, 27-32, 35, 41, 42, 44, 46]. The fixed effect model meta-analysis showed that the odds for adverse events were found 3 times lower in the intervention group, in relation to controls (OR = 0.71; 95% CI [0.55; 0.73]; I^2 = 62%; p = 0.012), indicating that premedication before intubation leads to less adverse events than intubation without medication.

Additionally, intervention group had less odds for intraventricular haemorrhage (OR = 0.72; 95% CI [0.37; 1.42]; I^2 = 0%; p = 0.35) [29, 33, 37, 39, 40, 46], while the odds for mortality were found similar between groups (OR = 1.10; 95% CI [0.43; 2.79]; I^2 = 0%; p = 0.85) [24, 29, 33, 37].

Efficacy outcomes

Intubation time was reported in 15 studies [8, 23-26, 28, 29, 32, 33, 36-39, 41, 46]. SMD was -0.59, indicative that the intubation time for the

intervention groups was lower than controls (SMD = -0.59; 95% CI [-1.06; -0.11]; $I^2 = 89\%$; $p < 0.02$). In a similar manner the number of intubation attempts was found marginally increased in the intervention group (ROM = 1.10; 95% CI [0.79; 1.53]; $I^2 = 96\%$, $p = 0.57$) [24, 28, 33, 36, 37, 39, 41, 43, 44].

Discussion

The present study showed that premedication is beneficial for neonates in terms of efficacy and safety, despite variability of drugs used, dosage and type of studies. In terms of safety, premedication lowers BPS, HR change, SpO_2 percentage change, and has fewer adverse effects. Nevertheless, the use of atropine may have been a confounder in studies that looked at the difference in HR between cases and controls. In terms of efficacy, in neonates, receiving premedication prior to intubation diminishes intubation time. This is in line with recent literature, as intubation is associated with serious non physiologic responses as for oxygenation, circulation and perfusion, leading to increased morbidity [47, 48]. Additionally, it diminishes stress due to better procedural conditions with fewer attempts, time to intubate and airway damage.

Intubation types are elective (non emergent) and emergent (urgent), without premedication (in awake, non-sedated state) or with premedication. Neonates often undergo an elective intubation due to prematurity, initiation of mechanical ventilation for impending cardiorespiratory deficiency, endotracheal tube change, an unstable airway and pre/postoperative ventilation. Existing policy for most NICUs is to use premedication for elective intubations of term neonates because they are easily agitated during the procedure [40, 49]. Additionally, emergent intubation without premedication for neonates during resuscitation or at cardiorespiratory arrest is considered as the acceptable policy in NICUs [12].

HR, BP and ICP changes indicate that neonates are in pain during intubation. Responses caused by pain and accompanying autonomic hyperactivity (stimulation of the vagal activity reflex and peripheral sympathetic nervous system cause sinus bradycardia and BP increase, respectively) finally lead to hypoxia and acidosis [25].

Friesen et al. reported a lesser increase in anterior fontanelle pressure in preterm infants of premedication group compared to non premedication group [50]. Additionally, ICP is elevated by BP increase and reduced venous return from head and neck. Finally, increased ICP, hypoxia and flow deviations can produce reperfusion injury and venous congestion, leading to intraventricular haemorrhage and/or periventricular leukomalacia [36]. Pain experience alters behavior, subsequent neurodevelopmental outcome and diminishes existing threshold. Judicious use of analgesics/anesthetic agents is a logical, more human and scientifically-based strategy [7].

Suppression of reflexes (cough, laryngeal and vomit), movement (voluntary or involuntary), pain with low risk of regurgitation by premedication use seems to offer proper conditions for intubation.

The main findings of our study showed that the use of premedication before intubation is more effective and safer. Regarding safety, premedication lowers BPS and changes in HR/SpO_2 and has fewer adverse events in comparison to intubation without medication. Even though no difference was found with regards to mortality between the two groups, it is important to note that mortality from intubation is extremely rare, especially when done electively by skilled medical providers. As far as the effectiveness is concerned, using premedication leads to shorter intubation time, although with more intubation attempts. The shorter intubation time is in accordance to the fact that sedation of a neonate could lead to fewer intubation attempts. While we would expect fewer attempts in those neonates, our results showed the opposite. This could be due to the fact that the population in the metanalysis regarding the number of intubation attempts included neonates of lower GA and consequently under poorer conditions for intubation.

Study limitations

This systematic review and meta-analysis, despite using structured search strategy and methods, has its limitations concerning the interpretation of its findings. First, non-published studies were not included. Moreover, both prospective and retrospective studies were included. These studies are characterized by different methodological design, with retrospective studies including recall bias. Finally, unmeasured and uncontrolled risk factors have the potential to produce biases. In the present study, we could not compare the different premedication categories with each other.

Conclusion

Most NICUs should consider premedication prior to intubation for vigorously and active term or preterm infants as a safe and efficient procedure that buffers serious physiological responses and assures better procedural conditions.

Supplementary materials

A supplementary file (including Figures and Tables) is available from the corresponding author upon request.

Declaration of interest

All Authors declare that they have no competing interests. There was no funding.

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