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SYSTEMATIC REVIEW

Fetal, Preterm, and Term Neonate Exposure to Remifentanil: A Systematic Review of Efficacy and Safety

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Abstract

Background Owing to its pharmacodynamic properties, especially the rapid onset and short duration of its action, the use of remifentanil in obstetric anesthesia, as well as in neonatology, might be increasingly used.

Objective We conducted a systematic review to assess the efficacy and safety of remifentanil in preterm and term neonates. Outcomes of interest were neonatal adaptation after fetal exposure; neonatal pain, distress, and discomfort control during invasive procedures; and the occurrence of hemodynamic effects or respiratory depression induced by remifentanil infusion.

Methods Given the different contexts of use, we have organized this work into three parts: (A) use of remifentanil for labor or cesarean section, with exposure of the fetus before birth, (B) brief use for neonatal procedural analgesia, and (C) prolonged use for sedation/analgesia of neonates. The bibliographic search was conducted based on keywords using electronic medical databases (DATABASE, Cochrane Library, PubMed, and EMBASE) from 1 January 2000 until 31 December 2022.

Results Twenty-two articles were included (10 in part A, 5 in part B and 7 in part C). Prospective, controlled, randomized, blinded, and intention-to-treat trials were retained. Neonates were well adapted after exposure to remifentanil in the fetal period. Pain, stress, and discomfort were controlled during a brief or prolonged invasive procedure when remifentanil was used for sedation/analgesia. The physiological parameters were stable and the procedures were straightforward. Chest wall rigidity appeared to be a common side effect, but this can be managed by slow and continuous infusion and by using the minimum effective dose.

Conclusions Remifentanil appears to be effective and safe in the short term in preterm and full-term neonates. However, its safety is compromised by the risk of chest wall rigidity. It should be used in appropriate neonatal units and in the presence of physicians able to monitor its side effects. Long-term outcomes have not been evaluated, to our knowledge.

1 Introduction

Remifentanil, a synthetic opioid, is increasingly used in obstetrics for labor analgesia or cesarean section analgesia and anesthesia. There is transplacental passage leading to fetal exposure in utero [1–4]. Literature concerning the impact of fetal exposure to remifentanil on neonatal outcomes and literature concerning the use of remifentanil in neonatal intensive care units (NICU) are poor. Insufficient data are available regarding optimal dosing, effects, and side effects. In fact, its use is not common practice in NICU although the use of opioids

Key Points

Remifentanil appears to be effective in preterm and term neonates. However, concerning its safety, adverse effects (particularly chest wall rigidity) are a potential risk, possibly related to the dose received.

Remifentanil should be used in appropriate care units and in the presence of physicians able to monitor its side effects.

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is widespread, as painful and stressful procedures are performed daily. Both, preterm and full-term newborns with repeated and prolonged exposures to painful procedures end up with long-term effects such as hyperalgesia and psychomotor and cognitive disorders [5]. It has been reported that exposure to anesthetic drugs during the neonatal period can lead to altered brain development [6]. Therefore, the ideal anesthetic agent should have a rapid onset, short duration of action, strong analgesic potency, and no short- or long-term adverse effects. Remifentanil, which is a potent selective μ-opioid receptor agonist, is potentially a good candidate for neonatal analgesia and sedation. It has a rapid onset of action (1–2 min), a short half-life (3–10 min), a brief offset of action, and immediate recovery of the clinical effect after interruption of its administration. It is metabolized by non-specific blood and tissue esterases, irrespective of any renal or hepatic metabolisms [3]. It has a low volume of distribution and its plasma clearance rate is high [2]. Non-specific esterase activity is present in preterm infants, irrespective of the gestational age [7]. In addition, the usually encountered adverse effects are similar to those observed with others opioids, in particular bradycardia, hypotension, chest wall rigidity, nausea, and vomiting [8]. The aim of the present study was to review the efficacy and safety aspects in neonates of remifentanil use in the perinatal period. In order to facilitate the data analysis and to reflect clinical practices, we divided our research into three parts: (A) use of remifentanil for labor or cesarean section, with exposure of the fetus before birth, (B) brief use for neonatal procedural analgesia, and (C) prolonged use for sedation/analgesia of neonates.

2 Methods

2.1 Preliminary Search and Registration

Before drafting the protocol for the systematic review, a preliminary PubMed search was conducted to check for similar systematic reviews and to explore articles of relevance to the review. Our study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) in August 2018 (Use of remifentanil in preterm or term neonates: efficacy and safety [CRD42018099873]). We used the PRISMA checklist to write our manuscript.

2.2 Eligibility Criteria

We selected studies published in English or French. The PICOS framework was set as Table 1. Only prospective, controlled, randomized, blinded trials in intention-to-treat, with high level of evidence were included.

2.3 Search Strategy

The electronic search of the published literature was performed by two pediatricians using DATABASE, the Cochrane Library (Cochrane Central Register of Controlled Trials—CENTRAL), PubMed (Medline), and EMBASE for randomized controlled trials (RCTs). The databases were searched for papers published from January 2000 to October 2022. Part A of the study was in regard to effects of remifentanil, used for delivery analgesia and sedation and before umbilical cord clamping, in full-term neonates during the first 24 hours of life. We used the following search strategy by keywords: remifentanil AND cesarean section AND fetus/fetal effects/neonatal effects, remifentanil AND labor AND fetus/fetal effects/neonatal effects. Part B of the study was in regard to efficacy and safety aspects of remifentanil used in the postnatal period for short-term procedures (e.g., premedication before elective endotracheal intubation or analgesia for insertion of a venous catheter). We used the following search strategy by keywords: remifentanil AND neonate AND intubation, remifentanil AND neonate AND analgesia, remifentanil AND neonate AND sedation. Part C of the study was in regard to efficacy and safety aspects of remifentanil used in the postnatal period for long-term procedures (e.g., sedation for mechanical ventilation or anesthesia for surgery). We used the following search strategy by keywords: remifentanil AND neonate AND mechanical ventilation, remifentanil AND neonate AND anesthesia, remifentanil AND neonate AND surgery.

2.4 Study Selection

Two reviewers independently screened the titles and abstracts and selected articles for full-text review, and potentially eligible articles were retrieved for perusal in full text. Any discrepancies between the assessments were resolved through discussion. Articles were excluded from this review when they did not meet one or more of the eligibility criteria.

2.5 Data Extraction

We extracted data from selected RCTs using the French National Health Authority standardized reading grid for therapeutic articles (items: clearly defined objectives, comparative trial, number of patients needed, adjusted population, adjusted statistical analysis, relevant variable and intention-to-treat analysis) [9]. From each RCT, we extracted (1) the first author and the year of publication, (2) the study design, (3) the study population, (4) the

Table 1 PICOS framework

	Part A: Use of remifentanil for labor or cesarean section, with exposure of the fetus shortly before birth	Part B: Brief use of remifentanil for neonatal procedural analgesia	Part C: Prolonged use of remifentanil for neonatal sedation-analgesia
Participants	Healthy parturients with a non-pathological pregnancy who needed general anesthesia for a cesarean section or intravenous analgesia for labor. The delivery had to be at term	Preterm (< 37 completed weeks of gestation) or full-term neonates (≥ 37 completed weeks of gestation and < 28 days) who were admitted to NICU and needed elective endotracheal intubation or invasive procedures (for example insertion of a venous catheter)	Preterm (< 37 completed weeks of gestation) or full-term neonates (≥ 37 completed weeks of gestation and < 28 days) who were admitted to NICU and needed mechanical ventilation or surgical intervention
Intervention	Use of remifentanil before umbilical cord clamping for cesarean anesthesia or labor analgesia	Brief use of remifentanil for analgesia during a procedure	Use of remifentanil for mechanical ventilation, sedation, or surgery anesthesia
Comparison	Use of other anesthetic agents before cord clamping, without opioids or placebo	Use of other analgesic/anesthetic agents or placebo	Use of other analgesic/anesthetic agents or placebo
Outcomes	1- and 5-minute Apgar scores, 5-minute Apgar score < 7, umbilical arterial and venous blood gases, time to return of spontaneous respiration, resuscitative measures, and admission to NICU	Quality of sedation, time to procedure, number of intubation attempts if applicable, variations of physiological parameters, assessment of pain and stress, and incidence of side effects	Assessment of pain and stress, incidence of side effects, time to extubation, time to recovery, and variations of physiological parameters
Study design	Prospective, controlled, randomized, blinded trials in intention-to-treat	Prospective, controlled, randomized, blinded trials in intention-to-treat	Prospective, controlled, randomized, blinded trials in intention-to-treat

protocol of intervention, (5) the statistical analysis, (6) the outcomes, and (7) the summary estimate of the intervention effects.

2.6 Risk of Bias Assessment

The two reviewers explored the quality of selected RCTs using Cochrane's risk-of-bias tool for randomized controlled trials (RoB2). This tool required evaluation of seven domains: random sequence generation, allocation concealment, blinding of the medical staff and patients, baseline characteristics of similar patients, assessment of incomplete outcome data, and exempt of selective reporting. We rated each domain as containing a low, uncertain, or high risk of bias. We assessed the overall risk for each study and the risk of bias in each domain for all included RCTs.

3 Results

3.1 Study Selection and Characteristics

Our literature search strategy identified 323 potentially relevant studies. After screening the titles and abstracts, 55 manuscripts remained for full-text critical review. Ultimately, we selected 22 studies for inclusion based on our predetermined criteria of inclusion (Fig. 1). All studies were randomized, blinded, controlled trials and were published between 2000 and 2019. Ten studies concerned use of remifentanil in the fetal period (part A) [10–19]. Three studies concerned use of remifentanil for premedication before intubation (part B) [20–22]. Two studies concerned use of remifentanil for analgesia for an invasive procedure (part B) [23, 24]. Two studies concerned use of remifentanil for sedation of mechanical ventilation (part C) [25, 26]. Five studies concerned use of remifentanil for anesthesia of surgery (part C) [27–31]. In total, 1014 preterm and full-term neonates were included (Table 2).

3.2 Risk of Bias in the Studies

The results of this analysis are summarized in Table 3. Most RCTs had a low risk of bias. Except for two studies [20, 31], the studies had blinded medical staff and patients, and the baseline patient characteristics were similar. For seven studies, the outcomes were not clearly stated and defined, resulting in a significant risk of bias [10, 11, 15, 16, 18, 27, 28]. One study was at high risk of selective reporting [20], and another had incompletely assessed the outcomes data [10].

3.3 Results of the Main Outcomes

The following sections present narrative summaries for each outcome measure. Table 4 presents details of the 22 included

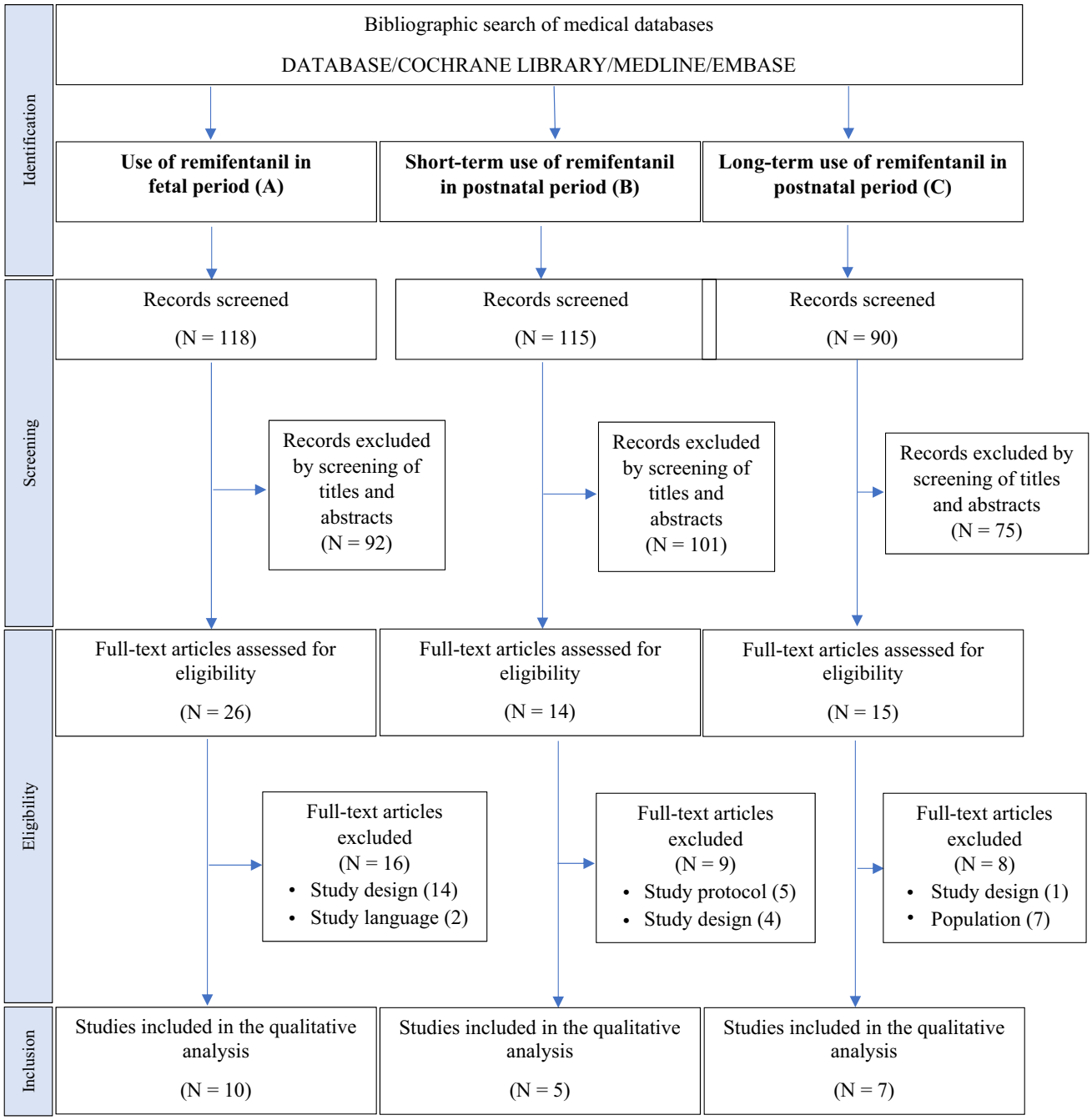

Fig. 1 Flow diagram of the study selection process

studies, and the outcomes measured by the studies are presented in Table 5.

3.3.1 Fetal Exposure to Remifentanil and Neonatal Outcomes

3.3.1.1 Umbilical arterial and venous blood gases Irrespective of the study protocol used in the studies, none of the neonates experienced neonatal hypoxemia.

3.3.1.2 Apgar score and resuscitative measures in the delivery room There is no evidence of effect that remifentanil is associated with an increased risk for newborns with Apgar scores < 7 at 5 min. Moreover, neonatal respiratory depression, if present, usually resolved in a few minutes without a need for prolonged resuscitation measures. Ngan Kee et al. reported similar Apgar scores and neonatal outcomes for the remifentanil and the control group, although two (out of 20) neonates from the remifentanil group needed naloxone

Table 2 Characteristics of the included studies

Characteristics	Studies, $N = 22$	References
Median year of publication (range)	2009 (2000–2019)	
Country of publication, n (%)		
Brazil	2 (9)	[20, 25]
Canada	1 (5)	[21]
China	4 (18)	[11, 14, 17, 18]
Germany	1 (5)	[26]
Iran	3 (12)	[15, 16, 22]
Italy	2 (9)	[13, 24]
South Africa	1 (5)	[28]
South Korea	1 (5)	[23]
Tunisia	2 (9)	[12, 30]
Turkey	2 (9)	[19, 31]
UK	2 (9)	[10, 29]
USA	1 (5)	[27]
Language, n (%)		
English	21 (95)	
French	1 (5)	[12]
Setting, n (%)		
Fetal period (part A)	10 (45)	[10–19]
Premedication before intubation (part B)	3 (14)	[20–22]
Analgesia for invasive procedure (part B)	2 (9)	[23, 24]
Sedation for mechanical ventilation (part C)	2 (9)	[25, 26]
Anesthesia for surgery (part C)	5 (23)	[27–31]
Population (N = 1014), n (%)		
≥ 36 weeks of gestation	776 (77)	[10–19, 26–31]
< 36 weeks of gestation	238 (23)	[20–25]

WG weeks of gestation

[11]. Draisci et al. observed lower Apgar scores or required endotracheal intubation in 14% of neonates in the remifentanil group. This was a significant proportion of newborns, but they were born by emergency cesarean section under general anesthesia, which could have a negative effect on their neonatal adaptation. The resolution of respiratory depression was, however, quick, without a need for naloxone, and the Apgar scores at 5 minutes were 8 or more in most cases [13]. Yu et al. reported that the frequency of 1-min Apgar scores < 7 was significantly higher in the remifentanil group versus dexmedetomidine. Nevertheless, at 5 minutes, there was no difference in the Apgar scores between the groups [17].

3.3.2 Brief and Prolonged Uses of Remifentanil in the Postnatal Period

The results of brief and prolonged uses of remifentanil are combined here to facilitate and synthetize the presentation.

3.3.2.1 Efficacy of remifentanil (control of pain and stress, number of intubation attempts, quality of sedation, time to successful intubation) Primarily, there is evidence of effect that remifentanil provides adequate sedation and analgesia during endotracheal intubation or brief invasive procedures. Silva et al. compared remifentanil versus a combination of morphine and midazolam for endotracheal intubation of preterm neonates. There were no significant differences between the groups in terms of pain, stress, or variations of physiological parameters (heartbeats) [20]. Lago et al. compared remifentanil versus 5% dextrose for percutaneous intravenous central catheter placement [24]. During skin preparation and needle puncture, remifentanil provides adequate analgesia. Secondly, remifentanil appeared to control the surgical stress response and provided adequate analgesia during surgical procedures. Chambers et al. and Weale et al. observed that remifentanil reduced blood endocrine markers of stress during surgical procedures in both neonates and children [28, 29]. In a prospective study, Ben Khalifa et al. showed that there was a greater intraoperative cardiovascular response in full-term neonates receiving isoflu-

Table 3 Risk of bias in the included studies as assessed by the Cochrane risk-of-bias tool

Author	Random sequence generation	Allocation concealment	Blinding of medical staff and patients	Baseline patient characteristics similar	Assessment of incomplete outcomes data	Stated and defined outcomes	Exempt of selective reporting	Other bias
Volikas and Male, 2000, UK [10]	+	+	+	+	−	−	+	−
Ngan Kee et al., 2006, China [11]	+	+	+	+	+	−	+	+
Bouattour et al., 2007, Tunisia [12]	+	+	+	+	+	+	+	+
Draisci et al., 2008, Italy [13]	+	+	+	+	+	+	+	+
Ng et al., 2011, China [14]	+	+	+	+	+	+	+	+
Behdad et al., 2013, Iran [15]	+	+	+	+	+	−	+	+
Varposhti et al., 2013, Iran [16]	+	+	+	+	+	−	+	+
Güneş et al., 2014, Turkey [19]	+	+	+	+	+	+	+	+
Li et al., 2015, China [18]	+	+	+	+	+	−	+	+
Yu et al., 2019, China [17]	+	+	+	+	+	+	+	+
e Silva et al., 2007, Brazil [20]	+	+	+	?	+	+	−	+
Lago et al., 2008, Italy [24]	+	+	+	+	+	+	+	+
Choong et al., 2009, Canada [21]	+	+	+	+	+	+	+	+
Badiee et al., 2013, Iran [22]	+	+	+	+	+	+	+	+
Shin et al., 2014, South Korea [23]	+	+	+	+	+	+	+	+
Davis et al., 2001, USA [27]	+	+	+	+	+	−	+	+
Chambers et al., 2002, South Africa [28]	+	+	+	+	+	−	+	+
Weale et al., 2004, UK [29]	+	+	+	+	+	+	+	+
e Silva et al., 2008, Brazil [25]	+	+	+	+	+	+	+	+

Table 3 (continued)

Author	Random sequence generation	Allocation concealment	Blinding of medical staff and patients	Baseline patient characteristics similar	Assessment of incomplete outcomes data	Stated and defined outcomes	Exempt of selective reporting	Other bias
Ben Khalifa et al., 2009, Tunisia [30]	+	+	+	+	+	+	+	−
Silibuldu et al., 2010, Turkey [31]	+	?	?	+	+	+	+	−
Welzing et al., 2012, Germany [26]	+	+	+	+	+	+	+	+

rane compared with remifentanil [30]. Thirdly, remifentanil appeared to provide efficacy for analgesia and sedation during mechanical ventilation. Silva et al. compared continuous infusion of remifentanil versus continuous infusion of morphine during mechanical ventilation in preterm neonates. The assessments of pain and stress were similar between the groups [25]. In the same way, Welzing et al. compared remifentanil versus fentanyl during mechanical ventilation in full-term neonates, and they found no difference in the pain and stress assessments [26]. Fourth, remifentanil appears to provide good conditions for endotracheal intubation. Silva et al. showed that the endotracheal intubation conditions with remifentanil were better than the conditions with morphine [20]. Choong et al. indicated that doctors rated the intubation conditions for preterm neonates more favorably with fentanyl. Nevertheless, most of the intubation conditions were good with remifentanil [21].

3.3.2.2 Short-term safety of remifentanil (time to return of spontaneous respiration, time to extubation, and time to recovery) Remifentanil presents a major pharmacokinetic advantage. Its short half-life allows a rapid return to spontaneous ventilation. Indeed, after termination of morphine or remifentanil infusion for mechanical ventilation in preterm infants, Silva et al. showed that the time to recovery and the time to extubation were significantly longer in patients receiving morphine [25]. In the same way, concerning mechanical ventilation in full-term neonates, Welzing et al. observed that the median time to tracheal extubation was significantly shorter in the remifentanil group compared with those on fentanyl [26].

3.3.2.3 Incidence of side effects and threats to safety (respiratory depression, hemodynamic effects, chest wall rigidity, and tolerance) Concerning short-term use of remifentanil, infusion of remifentanil appears to increase the risk of chest wall rigidity. Choong et al. compared remifentanil with a combination of fentanyl and succinylcholine. Chest wall rigidity occurred in two neonates in the remifentanil group compared with none in the fentanyl and succinylcholine group [21]. The latter being a curare, its effect can reduce the risk of chest wall rigidity. In the study by Badiee et al., 25% of neonates receiving remifentanil exhibited chest wall rigidity, 45% exhibited laryngospasm, and 25% needed naloxone [22]. Shin et al. found that, in mechanically ventilated preterm infants, a remifentanil infusion of 0.25 µg/kg/min was superior to 0.1 µg/kg/min for providing superior analgesia during insertion of a venous catheter, although there were more apnea and bradycardia events [23]. Concerning prolonged use of remifentanil, none of the studies reported adverse effects attributable to remifentanil. Some complications occurred post-extubation or post-surgery, but these could not be directly related to the drugs used during procedures [25–27, 29].

3.3.2.4 Remifentanil dosing Concerning premedication before intubation or sedation for INSURE (intubation-surfactant-extubation)/LISA (Less Invasive Surfactant Administration) procedures, boluses of 1–3 µg/kg over 1 minute were used [20–22, 26]. Concerning analgesia and sedation for short procedures, continuous infusion of 0.03–0.75 µg/kg/min was used [23, 24]. Concerning analgesia and sedation for mechanical ventilation, continuous infusion of 0.075–0.5 µg/kg/min was used [25, 26]. Concerning surgical anesthesia, continuous infusion of 0.25–0.4 µg/kg/min was used [27–31].

3.3.2.5 Long-term safety of remifentanil No long-term safety data or large trials were found.

4 Discussion/Conclusion

This review describes the safety and efficacy of remifentanil in neonates, including after fetal exposure shortly before birth.

Table 4 General description of the 22 included studies

Author	Setting	Population	Study protocol	Outcomes	Results
Volikas and Male, 2000, UK [10]	Remifentanil use in fetal period	17 parturients	Remifentanil (0.5 µg/kg—bolus) vs pethidine (10 mg)	1- and 5-min Apgar scores 5-min Apgar score < 7 Admission to NICU	*The study was terminated prematurely after 17 subjects included due to concern regarding the poor Apgar scores in the pethidine group* 1- and 5-min Apgar scores were significantly lower in the pethidine group compared with the remifentanil group ($p < 0.05$)
Ngan Kee et al., 2006, China [11]	Remifentanil use in fetal period	40 parturients	Remifentanil (1 µg/kg—bolus) and thiopental (4 mg/kg) and succinylcholine (1.5 mg/kg) vs saline and thiopental (4 mg/kg) and succinylcholine (1.5 mg/kg)	1- and 5-min Apgar scores 5-min Apgar score < 7 Time to return of spontaneous respiration Resuscitative measures Admission to NICU Umbilical arterial and venous blood gases	1- and 5-min Apgar scores were similar between groups and > 8 The median time to sustained respiration was 75 s in the remifentanil group, compared with 25 s in the control group ($p = 0.28$) No neonates required tracheal intubation Two neonates in the remifentanil group required a single dose of naloxone because they had poor respiratory effort at birth, compared with none in the saline group ($p = 0.49$). Both neonates who were given naloxone were admitted to the NICU for observation, but there were no sequelae No neonates experienced neonatal hypoxemia
Bouattour et al., 2007, Tunisia [12]	Remifentanil use in fetal period	40 parturients	Remifentanil (0.5 µg/kg—bolus and 0.2 µg/kg/min) and propofol (2 mg/kg) and suxamethonium (1 mg/kg) vs saline and propofol (2 mg/kg) and suxamethonium (1 mg/kg)	1- and 5-min Apgar scores 5-min Apgar score < 7 Time to return of spontaneous respiration Resuscitative measures Admission to NICU Umbilical arterial and venous blood gases	1- and 5-min Apgar scores were similar between groups and > 7 Three neonates in the remifentanil group and four neonates in the saline group presented apnea No neonates required tracheal intubation or naloxone infusion One neonate in the remifentanil group was admitted to the NICU for PAH, compared with none in the saline group No neonates experienced neonatal hypoxemia
Draisci et al., 2008, Italy [13]	Remifentanil use in fetal period	42 parturients	Remifentanil (0.5 µg/kg—bolus and 0.15 µg/kg/min) and thiopental (4 mg/kg) and suxamethonium (1 mg/kg) vs saline and thiopental (4 mg/kg) and suxamethonium (1 mg/kg)	1- and 5-min Apgar scores Resuscitative measures Umbilical arterial and venous blood gases	1- and 5-min Apgar scores were significantly lower in the remifentanil group compared with the saline group ($p < 0.05$). Nevertheless, at 5 min, Apgar scores were ≥ 8 in all neonates Three neonates in the remifentanil group required tracheal intubation without naloxone infusion, because they had poor respiratory effort at birth, compared with none in the saline group Umbilical blood gas analysis was in the normal range in both groups although umbilical vein pH was significantly lower in the remifentanil group compared with the saline group ($p < 0.01$). Nevertheless, umbilical vein pH was 7.32 or more in all neonates

Table 4 (continued)

Author	Setting	Population	Study protocol	Outcomes	Results
Ng et al., 2011, China [14]	Remifentanil use in fetal period	68 parturients	Remifentanil (< 60 kg: 25 μg and ≥ 60 kg: 30 μg—bolus) vs pethidine (< 60 kg: 50 mg and ≥ 60 kg: 75 mg)	1- and 5-min Apgar scores	1- and 5-min Apgar scores were similar between groups and > 8
Behdad et al., 2013, Iran [15]	Remifentanil use in fetal period	80 parturients	Remifentanil (0.5 μg/kg—bolus) and thiopental (5 mg/kg) and succinylcholine (1.5 mg/kg) vs saline and thiopental (5 mg/kg) and succinylcholine (1.5 mg/kg)	1- and 5-min Apgar scores Umbilical arterial blood gas	1- and 5-min Apgar scores were similar between groups and > 8 No neonates experienced neonatal hypoxemia
Varposhti et al., 2013, Iran [16]	Remifentanil use in fetal period	30 parturients	Remifentanil (0.25 μg/kg—bolus and 0.025 μg/kg/min) and entonox vs saline and entonox	1- and 5-min Apgar scores	1- and 5-min Apgar scores were similar between groups and > 8
Güneş et al., 2014, Turkey [19]	Remifentanil use in fetal period	90 parturients	Remifentanil (0.5 μg/kg—bolus) vs remifentanil (0.5 μg/kg—bolus and 0.025 μg/kg/h) vs meperidine (1 mg/kg)	1- and 5-min Apgar scores Resuscitative measures	1- and 5-min Apgar scores were similar between groups No neonates required tracheal intubation or naloxone infusion
Li et al., 2015, China [18]	Remifentanil use in fetal period	44 parturients	Remifentanil (2 μg/kg—bolus and 2 μg/kg/h) and propofol (2 mg/kg) and cisatracurium (0.2 mg/kg) vs dexmedetomidine (0.4 μg/kg and 0.4 μg/kg/h) and propofol (2 mg/kg) and cisatracurium (0.2 mg/kg)	1- and 5-min Apgar scores 5-min Apgar score < 7 Resuscitative measures Admission to NICU Umbilical arterial and venous blood gases	1- and 5-min Apgar scores were similar between groups and > 7 No neonates required tracheal intubation or naloxone infusion All neonates who were admitted to the NICU were admitted because of maternal medical condition No neonates experienced neonatal hypoxemia
Yu et al., 2019, China [17]	Remifentanil use in fetal period	120 parturients	Dexmedetomidine (0.5 μg/kg—bolus and 0.5 μg/kg/h) and propofol (2 mg/kg) and cisatracurium (0.2 mg/kg) vs remifentanil (0.5 μg/kg—bolus and 2 μg/kg/h) and propofol (2 mg/kg) and cisatracurium (0.2 mg/kg) vs saline and propofol (2 mg/kg) and cisatracurium (0.2 mg/kg)	1-min Apgar score < 7 5-min Apgar score < 7 Umbilical arterial and venous blood gases	Neonates presenting 1-min Apgar score < 7 were significantly higher in the remifentanil group compared with the dexmedetomidine or saline groups ($p < 0.05$) Nevertheless, at 5 min, there was no difference between the three groups One neonate in the remifentanil group and one neonate in the dexmedetomidine group required tracheal intubation for respiratory distress syndrome, compared with none in the saline group No neonates experienced neonatal hypoxemia

Table 4 (continued)

Author	Setting	Population	Study protocol	Outcomes	Results
e Silva et al., 2007, Brazil [20]	Short-term use of remifentanil in postnatal period Premedication before intubation	20 preterm neonates (28–34 WG)	Remifentanil (1 µg/kg—bolus) and midazolam (200 µg/kg) vs morphine (150 µg/kg) and midazolam (200 µg/kg)	Assessment of pain/stress (NIPS, comfort score) Incidence of side effects Number of intubation attempts Quality of sedation Variations of physiological parameters	Excellent intubation conditions were achieved in 6 neonates in the remifentanil group compared with none in the morphine group ($p = 0.0034$) A second attempt to intubate was required for 4 neonates in the morphine group compared with none in the remifentanil group ($p < 0.05$) The assessment of pain/stress and variations of physiological parameters were similar between groups (data not shown) No neonates experienced severe adverse effects
Lago et al., 2008, Italy [24]	Short-term use of remifentanil in postnatal period Analgesia for insertion of venous catheter	54 preterm neonates (26–30 WG)	Remifentanil (0.03 µg/kg/min) vs 5% dextrose	Assessment of pain/stress (NIPS, PIPP) Variations of physiological parameters Incidence of side effects	Pain scores were lower in the remifentanil group than in the control group during skin preparation and needle puncture ($p < 0.05$) No neonates experienced severe adverse effects
Choong et al., 2009, Canada [21]	Short-term use of remifentanil in postnatal period Premedication before intubation	30 preterm neonates (25–30 WG)	Remifentanil (3 µg/kg—bolus) vs fentanyl (2 µg/kg) and succinylcholine (2 mg/kg)	Incidence of side effects Number of intubation attempts Quality of sedation Time to return of spontaneous respiration Time to successful intubation Variations of physiological parameters	The median time to successful intubation ($p = 0.87$), the median time to return of spontaneous respiration ($p = 0.35$), and the variations of physiological parameters were similar between groups Nine patients were intubated on the first attempt in the remifentanil group compared with 6 in the fentanyl group ($p = 0.47$) Excellent intubation conditions were achieved in 8 neonates in the fentanyl group compared with 1 in the remifentanil group ($p = 0.009$) Chest wall rigidity occurred in 2 neonates in the remifentanil group compared with none in the fentanyl group ($p = 0.48$). Four patients in the remifentanil group received additional open-label succinylcholine for intubation (one for chest wall rigidity and desaturation, another for persistent spontaneous respirations despite premedication, and two for repeated intubation attempts) compared with none in the fentanyl group
Badiee et al., 2013, Iran [22]	Short-term use of remifentanil in postnatal period Premedication before intubation/INSURE	40 preterm neonates (25–37 WG)	Remifentanil (2 µg/kg—bolus) vs saline	Assessment of pain/stress (PIPP) Incidence of side effects Number of intubation attempts Time to return of spontaneous respiration Time to successful intubation Variations of physiological parameters	No neonates experienced severe pain in the remifentanil group compared with 19 in the saline group ($p < 0.001$) The median time to successful intubation ($p = 0.33$), the number of intubation attempts ($p = 0.66$), and the variations of physiological parameters ($p = 1$) were similar between groups Chest wall rigidity occurred in 4 neonates and laryngospasm in 9 neonates in the remifentanil group (2 neonates required a single dose of naloxone)

Table 4 (continued)

Author	Setting	Population	Study protocol	Outcomes	Results
Shin et al., 2014, South Korea [23]	Short-term use of remifentanil in postnatal period Analgesia for insertion of venous catheter	12 preterm neonates (24–32 WG)	Remifentanil low dose (0.1 μg/kg/min) vs remifentanil high-dose (0.25 μg/kg/min)	Assessment of pain/stress (PIPP) Variations of physiological parameters	Neonates experienced moderate pain in the low-dose group whereas they experienced minimal or no pain in the high-dose group. The mean PIPP gradually decreased to <6 during the procedure and in the recovery time in the high-dose group. In contrast, the mean PIPP increased during the procedure to > 7 in the low-dose group Apnea and bradycardia occurred in 4 neonates in the high-dose group compared with none in the low-dose group ($p = 0.36$)
Davis et al., 2001, USA [27]	Long-term use of remifentanil in postnatal period Anesthesia before pyloromyotomy	60 full-term neonates and infants (≤8 weeks old)	Remifentanil (0.4 μg/kg/min) and propofol (2.0 mg/kg) and succinylcholine (2 mg/kg vs halothane (0.4%) and propofol (2.0 mg/kg) and succinylcholine (2 mg/kg)	Incidence of side effects Time to extubation Time to recovery Variations of physiological parameters	Three patients required treatment for hypotension in the remifentanil group compared with 9 patients in the halothane group ($p = 0.08$) Five patients experienced surgical complications in the remifentanil group compared with none in the halothane group (bowel perforation, serosal tear, peritonitis and peritoneal leak, exploration for postoperative bleeding, and postoperative drainage from the surgical wound site)
Chambers et al., 2002, South Africa [28]	Long-term use of remifentanil in postnatal period Anesthesia before tunnelling phase of ventriculoperitoneal shunt insertion	62 children (13 full-term neonates, 24 infants, and 25 children aged >1 year)	Remifentanil (1 μg/kg—bolus) and bupivacaine (3 mg/kg) vs saline and bupivacaine (3 mg/kg)	Assessment of pain/stress (by endocrine markers of stress) Incidence of side effects Time to extubation Time to recovery Variations of physiological parameters	There was a greater cardiovascular and norepinephrine response to tunnelling (tachycardia, hypertension) in the saline group compared with the remifentanil group ($p < 0.01$) The time to recovery and the time to extubation were similar between groups. The time to recovery was 5 min in the two groups ($p > 0.9$). The time to extubation was 3 min in the remifentanil group and 2 min in the saline group ($p = 0.44$) No neonates experienced severe adverse effects
Weale et al., 2004, UK [29]	Long-term use of remifentanil in postnatal period Anesthesia before pre-bypass phase of cardiac surgery	49 infants and children over 5 years of age	Remifentanil (0.25 vs 1.0 vs 2.5 vs 5.0 μg/kg/min) and pancuronium (0.1 mg/kg) and isoflurane (0.2%)	Assessment of pain/stress (by endocrine markers of stress: glucose, cortisol, NPY) Incidence of side effects Variations of physiological parameters	There was a greater cardiovascular, glucose, and cortisol response to pre-bypass (tachycardia) in the 0.25 μg/kg/min remifentanil group compared with the other groups ($p < 0.0001$) Nine patients required treatment for hypotension following remifentanil infusion, but 4 of these were neonates with complex cardiac anatomy requiring urgent surgery

Table 4 (continued)

Author	Setting	Population	Study protocol	Outcomes	Results
e Silva et al., 2008, Brazil [25]	Long-term use of remifentanil in postnatal period Sedation for mechanical ventilation	20 preterm neonates (28–34 WG)	Remifentanil (1 µg/kg—bolus and 0.5 µg/kg/min) and midazolam (200 µg/kg) vs morphine (150 µg/kg—bolus and 10 µg/kg/h) and midazolam (200 µg/kg)	Assessment of pain/stress (NIPS, comfort score) Incidence of side effects Time to extubation Time to recovery Variations of physiological parameters	The time to recovery and the time to extubation after interruption of the opioid infusion were significantly shorter in the remifentanil group compared with morphine group ($p < 0.05$). The mean time to awaken was 1173 min in the morphine group versus 62 min in the remifentanil group. The mean time to extubation was 1320 min in the morphine group versus 106 min in the remifentanil group Three patients required treatment for hypotension following remifentanil infusion compared with six patients following morphine infusion The assessments of pain/stress were similar between groups (data not shown) No neonates experienced severe adverse effects
Ben Khalifa et al., 2009, Tunisia [30]	Long-term use of remifentanil in postnatal period Anesthesia before pyloromyotomy	30 full-term neonates	Remifentanil (0.4 µg/kg/min) vs isoflurane (0.75%)	Assessment of pain/stress Time to extubation	The time to extubation was similar between groups There was a greater cardiovascular response to pyloromyotomy (tachycardia) in the isoflurane group compared with the remifentanil group ($p < 0.05$)
Silibuldu et al., 2010, Turkey [31]	Long-term use of remifentanil in postnatal period Anesthesia before thoracotomy or laparotomy	43 full-term neonates	Remifentanil (0.25 µg/kg/min) and ketamine (1 mg/kg) vs morphine (30 µg/kg) and ketamine (1 mg/kg)	Time to extubation Variations of physiological parameters	All outcomes were similar between groups
Welzing et al., 2012, Germany [26]	Long-term use of remifentanil in postnatal period Sedation for mechanical ventilation	23 full-term neonates (at least 36 WG with a postnatal age no greater than 60 days)	Remifentanil (9 µg/kg/h) and midazolam (50 µg/kg/h) vs fentanyl (3 µg/kg/h) and midazolam (50 µg/kg/h)	Assessment of pain/stress (Hartwig score) Incidence of side effects Time to extubation Variations of physiological parameters	The time to extubation was significantly shorter in the remifentanil group compared with the fentanyl group ($p = 0.004$). Median extubation time was 80 min in the remifentanil group and 782 min in the fentanyl group The assessments of pain/stress were similar between groups Heart rates were significantly higher within the first 24 hours of remifentanil infusion compared with fentanyl infusion ($p = 0.002$) Five patients required treatment for hypotension following remifentanil infusion compared with six patients following morphine infusion One patient in the remifentanil group and two patients in the fentanyl group received naloxone because of apnea. One patient in each group had pneumothorax

INSURE method of intubation-surfactant-extubation, *NICU* neonatal intensive care units, *NIPS* Neonatal Infant Pain Scale, *NPY* neuropeptid Y, *PAH* pulmonary arterial hypertension, *PIPP* premature infant pain profile, *WG* weeks of gestation

Table 5 Prespecified outcomes measured by the included studies

Author	1- and 5-min Apgar score	1 min Apgar score < 7	5 min Apgar score < 7	Time to return of spontaneous respiration	Resuscitative measures	Admission to NICU	Umbilical arterial and venous blood gas	Assessment of pain/stress	Incidence of side effects	Number of intubation attempts	Quality of sedation	Time to successful intubation	Time to extubation	Time to recovery	Variations of physiological parameters
Volikas and Male, 2000, UK [10]	X		X			X									
Ngan Kee et al., 2006, China [11]	X		X	X	X	X	X								
Bouattour et al., 2007, Tunisia [12]	X		X	X	X	X	X								
Draisci et al., 2008, Italy [13]	X				X		X								
Ng et al., 2011, China [14]	X														
Behdad et al., 2013, Iran [15]	X						X								
Varposhti et al., 2013, Iran [16]	X														
Güneş et al., 2014, Turkey [19]	X				X										

Table 5 (continued)

Author	1- and 5-min Apgar score	1 min Apgar score < 7	5 min Apgar score < 7	Time to return of spontaneous respiration	Resuscitative measures	Admission to NICU	Umbilical arterial and venous blood gas	Assessment of pain/stress	Incidence of side effects	Number of intubation attempts	Quality of sedation	Time to successful intubation	Time to extubation	Time to recovery	Variations of physiological parameters
Li et al., 2015, China [18]	X		X		X	X	X								
Yu et al., 2019, China [17]		X	X		X		X								
e Silva et al., 2007, Brazil [20]								X	X	X	X				X
Lago et al., 2008, Italy [24]								X	X						X
Choong et al., 2009, Canada [21]				X					X	X	X	X			X
Badiee et al., 2013, Iran [22]				X				X	X	X		X			X
Shin et al., 2014, South Korea [23]								X							X
Davis et al., 2001, USA [27]									X				X	X	X

Table 5 (continued)

Author	1- and 5-min Apgar score	1 min Apgar score < 7	5 min Apgar score < 7	Time to return of spontaneous respiration	Resuscitative measures	Admission to NICU	Umbilical arterial and venous blood gas	Assessment of pain/stress	Incidence of side effects	Number of intubation attempts	Quality of sedation	Time to successful intubation	Time to extubation	Time to recovery	Variations of physiological parameters
Chambers et al., 2002, South Africa [28]								X	X				X	X	X
Weale et al., 2004, UK [29]								X	X						X
e Silva et al., 2008, Brazil [25]								X	X				X	X	X
Ben Khalifa et al., 2009, Tunisia [30]								X					X		
Silibuldu et al., 2010, Turkey [31]													X		X
Welzing et al., 2012, Germany [26]								X	X				X		X

4.1 Chest Wall Rigidity

The use of remifentanil in the fetal period has been recommended and is considered one of the most suitable opioids for obstetric anesthesia and analgesia. Remifentanil used for general anesthesia during cesarean section or for analgesia during labor before umbilical cord clamping crosses the placental barrier, thus resulting in fetal drug exposure. At birth, neonates exposed in utero exhibited good adaptation to extra-uterine life, without signs of perinatal asphyxia. They exhibited opioid side effects, such as chest wall rigidity requiring mask ventilation or tactile stimulation, without a need for intubation. Concerning naloxone, its use is not recommended in the delivery room in neonates presenting with respiratory depression secondary to administration of opioids to the mother. Ventilator support must be the first line of treatment [32].

According to the studies reported in our review, there was frequently a risk of chest wall rigidity when remifentanil was used in the postnatal period for short procedures. This appears to be the main factor limiting the use of remifentanil in neonates. Fentanyl-induced rigid chest syndrome is quite well described, even in neonatology [33–35]. Muscle rigidity appears to be more frequent with high doses for anesthetic induction. In fact, the total received dose of remifentanil could be one of the factors that determine the occurrence of chest wall rigidity. These side effects are reversed by naloxone and/or a neuromuscular blocking agent [36]. Remifentanil or alternative analgesic has been maintained until the effect of the neuromuscular blocking agent has worn off. In addition, the risk of remifentanil-induced chest wall rigidity appears to be related to rapid administration. The development of chest wall rigidity can be minimized by use of a slow, continuous infusion of remifentanil instead of boluses, and by aiming for a minimum effective dose. In a prospective study concerning sedation for the INSURE procedure, de Kort et al. described chest well rigidity in six patients (43%), and they discontinued the study prematurely due to side effects and the lack of efficacy [37]. However, as discussed in a letter to the editor by Chollat et al., an accumulative dose of >3 μg/kg may partly promote chest wall rigidity [38]. Otherwise, the diagnosis of chest wall rigidity is clinical, but the studies cited in our systematic review do not use an objective definition. To our knowledge, there is no objective scale to assess the presence or degree of chest wall rigidity, which may partly explain the variability of its occurrence from one study to another, as its evaluation was subjective and operator-dependent. This may lead to over-diagnosis of thoracic rigidity, especially in preterm neonates, who may have low lung compliance.

For the most part, with continuous infusion and low doses, remifentanil provided safe and effective analgesia and sedation during invasive procedures. The use of excessively high doses raises the question of the intended purpose of the use of this opioid. Its use alone may lead to increased doses to achieve adequate analgesia or even sedation. Its association with a hypnotic agent seems preferable for long and/or very painful procedures.

Some questions remain about the optimal administration of remifentanil. There are no guidelines available on the dosages of remifentanil to be used in preterm and full-term neonates. Analgesia is usually obtained by titration (boluses) then maintained by continuous infusion if necessary. Dosages used are variable depending on indication and ventilatory support.

4.2 Efficacy of Remifentanil

The studies with high levels of evidence presented here showed that remifentanil has an effective analgesic effect in neonates. Remifentanil provides adequate sedation and/or analgesia during endotracheal intubation or brief invasive procedures. Among the brief invasive procedures, remifentanil could allow analgesia during laser treatment of retinopathy of prematurity, especially in hospitals without readily available pediatric anesthetists. In a pilot study, Demirel et al. described no major adverse effects except in two neonates (3%) with bradycardia and hypotension during infusion of remifentanil for laser treatment of retinopathy [39]. Remifentanil controls the surgical stress response and provides adequate analgesia during surgical procedures. Moreover, it provides effective analgesia and sedation during mechanical ventilation.

4.3 Neuroprotection

Other drugs have been proposed for sedation and analgesia in neonates, but their use is still controversial. Propofol has been associated with bradycardia, desaturation, and prolonged hypotension in newborns, and it is not an analgesic agent [40–42]. Further research is needed to establish the safety profiles for the use of ketamine in neonates due to concerns regarding possible neurotoxicity in animal studies [43]. Regarding remifentanil, studies performed in mice have shown that it has an antiapoptotic impact and that it exerts beneficial effects against excitotoxicity on the developing mouse brain that are associated with a reduction in the brain lesion size as well as prevention of a number of behavioral deficits in young mice [44, 45]. It should be noted that the neurotoxicity of some anesthetic agents has mainly been demonstrated in animals, and most of the time in the absence of painful procedures. The potential neurotoxicity of the anesthetic could be therefore counterbalanced by the beneficial effect of pain reduction. In humans, a recent randomized trial (GAS Trial) did not reveal neurodevelopmental

disorders at 5 years of age after exposure to < 1 h of general anesthesia before 3 months of life [46].

Morphine exposure in very preterm neonates is independently associated with impaired cerebellar growth in the neonatal period and poorer neurodevelopmental outcomes in early childhood [47].

Fentanyl exposure demonstrated that cerebellar growth decreases as cumulative fentanyl exposure increases on term equivalent magnetic resonance imaging. Higher cumulative fentanyl dose in preterm infants correlated with a higher incidence of cerebellar injury and lower cerebellar diameter at term-equivalent age [48].

Midazolam has been associated with a high risk of transient hypotension and decreased mean cerebral blood flow velocity [49]. The trial NOPAIN demonstrated the risk of severe intraventricular hemorrhage, periventricular leukomalacia, or death in preterm neonates who received midazolam infusion during mechanical ventilation [50]. Clinical cohort studies demonstrated that midazolam exposure was associated with macro- and microstructural alterations in hippocampal development and poorer outcomes consistent with hippocampal dysmaturation [51].

Dexmedetomidine presented a novel option for the management of pain and sedation in preterm neonates without higher incidence of adverse neurologic effects [52]. Dexmedetomidine was neuroprotective in both in vitro and in vivo models of hypoxic-ischemic injury and this action is mediated via the α_{2A}-adrenoceptor subtype [53, 54].

Isoflurane induced widespread cerebral neuroapoptosis in neonatal rat pups with subsequent long-term neurocognitive impairment of the animals. As the injury occurred in the neonatal period and animal training and testing followed this injury, this indicates impairment in learning and memory consistent with a significant hippocampal lesion [55].

4.4 Limitations

The number of studies included in the systematic review is relatively low, in connection with a rigorous selection of articles. Moreover, the use and indication of remifentanil differ between studies. Therefore, it is difficult to assess remifentanil in a specific indication.

Also, the studies included in the systematic review are small, and thus there is limited power to ascertain the incidence of adverse events, particularly those that are uncommon but potentially severe. Furthermore, enrollment in small RCTs is plagued by population selection bias.

Finally, although remifentanil seems to have potential neuroprotection effects, nevertheless, the lack of studies on long-term outcomes is an additional limitation.

4.5 Perspectives

Remifentanil is potentially a good candidate for premedication before neonatal intubation. Nevertheless, given the risk of chest wall rigidity, its use is controversial. The routine addition of a neuromuscular blocking agent and/or a hypnotic agent may be a promising way to use remifentanil before intubation. If a neuromuscular blocker is administered, the infusion of remifentanil must be adjusted to cover the duration of muscle blockade. Questions remain regarding the optimal mode of administration of remifentanil. No guidelines are available for the dosages of remifentanil to be used in preterm and full-term neonates. Insufficient data are available regarding optimal dosing, effects, and side effects. Research on the clinical applicability of remifentanil in preterm and term neonates should continue, in particular pharmacokinetic and pharmacodynamic studies. To our knowledge, there are no data on the economic impact of remifentanil. Further economic research may be considered.

Declarations

Conflict of interest A.M., C.C., and M.S.A. have no conflicts of interest to declare.

Statement of ethics The authors have no ethical conflicts to disclose.

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Author contributions A.M. drafted the protocol and manuscript; acquired, analyzed, and interpreted the data; and provided final approval for publication. C.C. helped analyze and interpret the data, revised the manuscript for important intellectual content, provided final approval for publication, and agreed to be accountable for all aspects of the work. M.S.A. contributed to the conception and design of the work, revised the manuscript for important intellectual content, helped analyze and interpret the data, and provided final approval for publication.

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