Effect of fentanyl for preterm infants on mechanical ventilation: a systematic review and meta-analysis

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Short Title: Effect of fentanyl for preterm infants on mechanical ventilation

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Abstract

Introduction: Because excessive physical stress is harmful, reducing pain and discomfort in premature neonates during mechanical ventilation is a major challenge for physicians. There is no consensus and systematic review on the use of fentanyl, the most commonly used pain reliever in preterm neonates during mechanical ventilation. We aim to compare the benefits and harms of fentanyl versus placebo or no drug for preterm neonates receiving mechanical ventilation. ***Methods:*** A systematic review of randomized controlled trials (RCTs) was conducted according to the Cochrane Handbook for Systematic Reviews of Intervention. The systematic review was reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Scientific databases such as MEDLINE, EMBASE, CENTRAL, and CINAHL were searched. All preterm infants on mechanical ventilation and enrolled in an RCT of fentanyl versus control were included. ***Results:*** Of 256 reports initially retrieved, 4 reports met the eligibility criteria. Fentanyl was not associated with mortality risk compared to the control (risk ratio: 0.72, 95% confidence intervals (CIs): 0.36–1.44). No increase in ventilation duration (mean difference (MD): 0.04, 95% CIs: -0.63–0.71) and no effect on hospital stay length (MD: 4.00, 95% CIs: -7.12–15.12) was found. Fentanyl intervention does not affect any other morbidities, including bronchopulmonary dysplasia, periventricular leukomalacia, patent ductus arteriosus, intraventricular hemorrhage (IVH), severe IVH, sepsis, and necrotizing enterocolitis. ***Conclusion:*** The present systematic review and meta-analysis failed to demonstrate the benefit of administering fentanyl to preterm infants on mechanical ventilation in mortality and morbidities. Follow-up studies are required to investigate the long-term neurodevelopment of the children.

Introduction

Excessive physical stress is harmful to preterm neonates in both the acute and chronic phases [1]. Because their cerebral circulation is passive to systemic blood pressure, even minor changes in hemodynamics caused by painful stimuli can result in severe destructive brain damage, such as intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL), in the acute postnatal period [2]. Painful stimuli impair neural network maturation and development besides causing destructive brain damage [1, 3]. A growing body of literature has shown a link between painful exposure in early life and altered brain morphology [4-7], abnormal neurosensory responses [8-11], and neurodevelopmental delay [1, 3, 12, 13].

Reducing pain and discomfort in premature neonates during mechanical ventilation is a major challenge for physicians. There is no consensus on the use of pain relievers in preterm neonates during mechanical ventilation [1]. The American Academy of Pediatrics and the Canadian Pediatric Society do not recommend the routine use of sedative and analgesic drugs due to a lack of strong evidence [1]. Nevertheless, a retrospective cohort study of neonatal intensive care units in the United States found that the use of opioids and benzodiazepines for preterm infants increased from 1997 to 2012 [14]. Among the sedative and analgesic pharmacological agents, fentanyl was the most commonly administered drug in that study [14]. Fentanyl is a short-acting synthetic opioid with 100 times the potency of morphine and has fewer side effects such as hypotension and gastrointestinal hypomotility [15, 16]. However, to date, no systematic review of the relationship between fentanyl administration and preterm neonatal clinical outcomes has been conducted. This study aims to compare the benefits and harms of fentanyl for preterm neonates receiving mechanical ventilation versus placebo or no drug.

Methods

A systematic review of randomized controlled trials (RCTs) was conducted according to the Cochrane Handbook for Systematic Reviews of Intervention [17]. The protocol was registered on PROSPERO, the international prospective registry of systematic reviews (registration number: CRD42019132488). The systematic review was reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [18].

Search strategy

The search strategy for this systematic review was described in Supplementary file 1. On October 5, 2022, scientific databases such as MEDLINE, EMBASE, CENTRAL, CINAHL, and any other accessible relevant databases were searched with no restrictions on date/time, language, document type, or publication status. The keywords were collected through expert opinion, literature reviews, controlled vocabulary (Medical Subject Headings, Excerpta Medica Tree, and CINAHL headings), and a review of primary search results. The searches were conducted by an information specialist, and the reviewers conducted supplemental searches manually. There were no language restrictions, and in the case of unpublished or ongoing trials, the authors were contacted for further information.

Eligibility criteria

The following criteria were considered eligible in published studies: (i) individual and cluster RCTs compare fentanyl to control, and (ii) the patients were preterm infants on mechanical ventilation. Studies on the neonatal perioperative period and those involving term infants were excluded.

Study identification

All studies identified in the search for further review were independently assessed by four authors (YS, GK, DK, and JS). Disagreements were resolved through discussion among the four authors or consultation with a third assessor (NY, EO, and FN). The reviewers collected basic study information and details on participants, control interventions, treatments, and outcomes using piloted data extraction forms.

Data analysis

Data were analyzed using the Review Manager 5.4 software (https://training.cochrane.org/system/files/uploads/protected_file/RevMan5.4_user_guide.pdf). The primary outcome was mortality and the secondary outcomes were blood pressure, duration of ventilation, length of hospital or neonatal intensive care unit stay, morbidity including bronchopulmonary dysplasia (BPD), PVL, patent ductus arteriosus (PDA), any IVH, severe IVH, sepsis, necrotizing enterocolitis (NEC), retinopathy of prematurity, and premature infant pain profile (PIPP). For dichotomous data, risk ratios (RRs) were used, whereas for continuous data, the weighted or standardized mean difference (MD) was used. The random effect analysis was used because we assumed differences in the method of intervention, the ages, and the countries where the research was conducted, leading to varied results among studies. The results are presented as average intervention effects with 95% confidence intervals (CIs). The statistical heterogeneity was estimated using the I2 test. An I2 >75% indicates substantial heterogeneity, whereas a value of 30% to 60% indicates moderate heterogeneity (https://training.cochrane.org/handbook/current/chapter-10#section-10-10).

Bias risk assessment in the included studies

The bias risk for each included study was independently assessed by four review authors (YS, GK, DK, and JS) using the Cochrane Handbook for Systematic Reviews of Interventions criteria. Disagreements were resolved through discussion among the authors or consultation with a third assessor (NY, EO, and FN).

Assessment of evidence certainty

To rate the certainty of the evidence, the summary of findings template in the Guideline Development Tool developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group (http://www.gradeworkinggroup.org) was used. The studies were evaluated according to GRADE (https://training.cochrane.org/grade-approach), and the evidence was rated using GRADE's five downgraded criteria: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Each of the following outcomes was assigned a certainty rating: in-hospital mortality; duration of ventilation; length of hospital stay; and the morbidities of BPD, PVL, PDA, and IVH. These ratings were assigned to one of the four GRADE certainty levels: high, moderate, low, or very low.

Results

Search results

Initially, 293 reports were retrieved, with 219 being excluded because they did not meet eligibility criteria or were not RCTs. After reviewing the titles and abstracts, 11 reports were included. Four of them met the eligibility criteria after reading their full texts and excluding 7 reports due to not obtain from data from authors (1 report), irrelevant outcomes (3 reports), and part of the included study (3 reports) (shown in Fig. 1) [19-22].

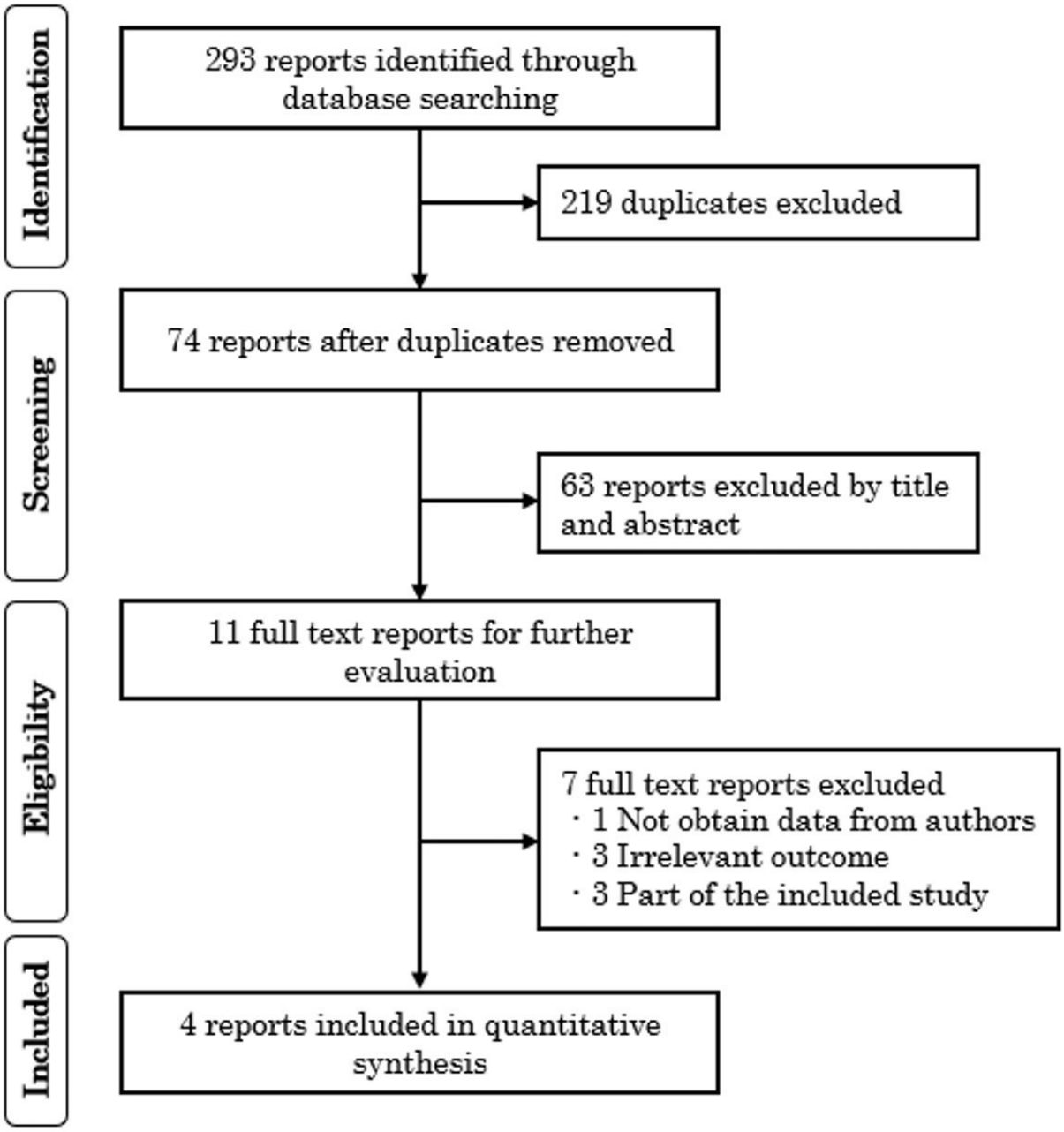

Fig. 1. Flow diagram illustrating search results and study selection.

Characteristics of the included studies

Four studies were included in this review, which compared the outcomes of fentanyl administration versus control in preterm infants on mechanical ventilation. However, they differed in terms of setting, intervention, and participants. In three trials, fentanyl was administered as a continuous infusion, whereas in the fourth; it was administered as a single dose. Two studies [20, 22] included only very preterm infants (<32 weeks), whereas the remaining studies [19, 21] included

both very preterm and preterm infants (33 and 34 weeks). Two of the studies were conducted in Italy, and the other two were in Brazil and China (Table 1).

Table 1. Characteristics of included studies

Study ID	Country	Study design	Fentanyl (n)	Control (n)	GA	Interventions
Ancora 2013	Italy	multicenter RCT	64	67	< 33wks	fentanyl (loading dose of 1 μg/kg, followed by continuous infusion of 1 μg/kg/hr) vs. placebo
Guinsburg 1998	Brazil	single-center RCT	11	11	< 32wks	fentanyl (single dose of 3 μg/kg,) vs. normal saline
Lago 1998	Italy	single-center RCT	27	28	26 to 34wks	fentanyl (continuous infusion of 0.5-2 μg/kg and infusion rate adjustment according to sedation score) vs. no intervention
Qiu 2019	China	single-center RCT	30	30	< 32wks	fentanyl (loading dose of 1 μg/kg, followed by continuous infusion of 1 μg/kg/hr) vs. 5% glucose

GA, gestational age; RCT, randomized controlled trial

Bias risk assessment

The bias risk in all four studies was assessed. Two studies [19, 22] used random number tables for randomization, whereas the other two [20, 21] lacked detailed records, resulting in an unclear risk. The allocation method in the studies by Guinsburg et al. and Qiu et al. was not specified in detail. Blinding was judged to be legitimate or incomplete but unlikely to affect the outcome. In this review, there was no obvious high risk of bias because no previous incomplete data for preterm infant outcomes was established (shown in Fig. 2).

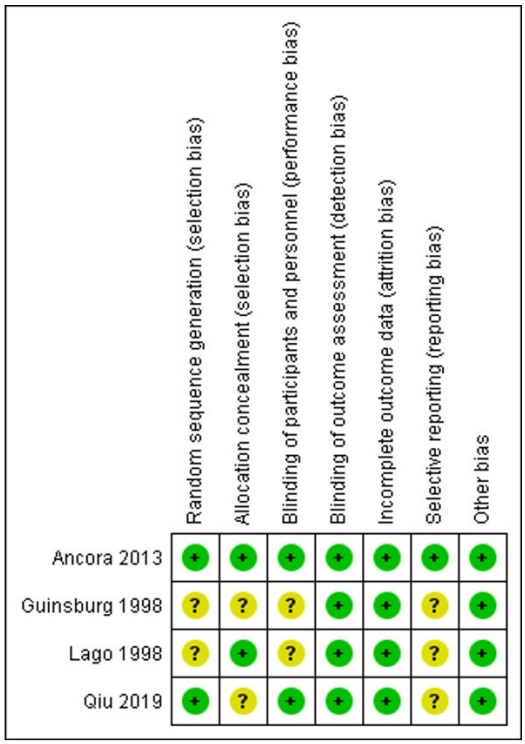

Fig. 2. Bias risk summary. The review authors' judgments of each risk of bias item for each included study.

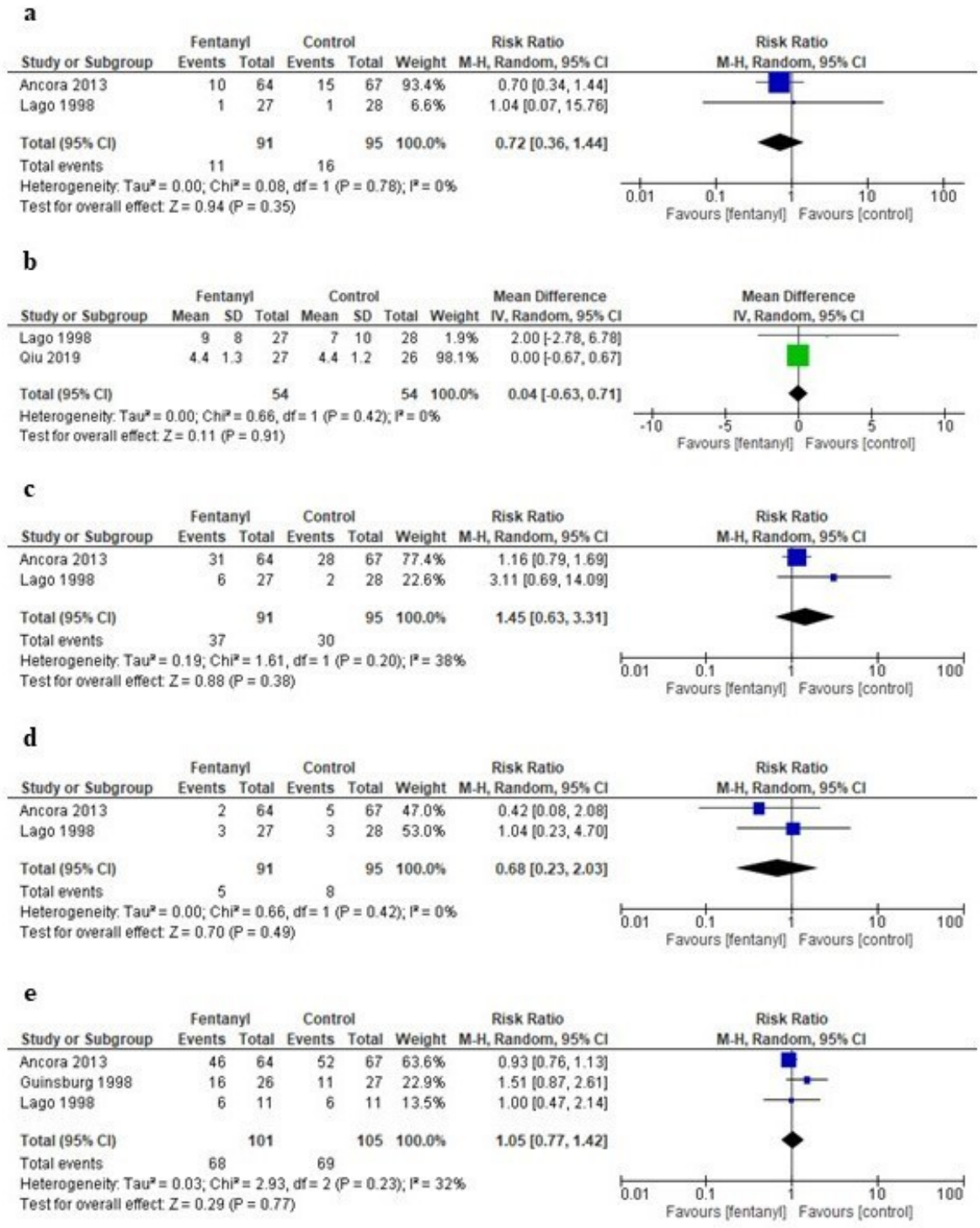

Fig. 3. Meta-analysis forest plots. M-H, Mantel–Haenszel; IV, inverse variance; CI, confidence interval. a, Mortality; b, Duration of ventilation; c, Bronchopulmonary dysplasia; d, Periventricular leukomalacia; e, Patent ductus arteriosus.

Table 2. Summary of findings table

Fentanyl compared to placebo for preterm infants

Patient or population: preterm infants on mechanical ventilation
Setting: Italy, China, and Brazil
Intervention: fentanyl infusions
Comparison: placebo or no fentanyl infusions

	Anticipated absolute effects* (95% CI)				
	Risk with placebo	**Risk with Fentanyl**			
Mortality	168 per 1,000	**121 per 1,000** (61 to 243)	**RR 0.72** (0.36 to 1.44)	186 (2 RCTs)	⊕⊕◯◯ Low[a]
Duration of ventilation	The mean duration of ventilation was **0**	MD **0.04 higher** (0.63 lower to 0.71 higher)	-	108 (2 RCTs)	⊕◯◯◯ Very Low[a,b]
Length of stay in hospital	The mean length of stay in the hospital was **0**	MD **4 higher** (7.12 lower to 15.12 higher)	-	55 (1 RCT)	⊕◯◯◯ Very Low[a,b]
BPD	316 per 1,000	**458 per 1,000** (199 to 1,000)	**RR 1.45** (0.63 to 3.31)	186 (2 RCTs)	⊕⊕◯◯ Low[b]
PVL	84 per 1,000	**57 per 1,000** (19 to 171)	**RR 0.68** (0.23 to 2.03)	186 (2 RCTs)	⊕◯◯◯ Very Low[a,b]
PDA	657 per 1,000	**690 per 1,000** (506 to 933)	**RR 1.05** (0.77 to 1.42)	206 (3 RCTs)	⊕⊕◯◯ Low[b]
Any IVH	358 per 1,000	**312 per 1,000** (193 to 509)	**RR 0.87** (0.54 to 1.42)	131 (1 RCT)	⊕⊕◯◯ Low[b]

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **BPD:** bronchopulmonary dysplasia; **PVL:** periventricular leukomalacia; **PDA:** patent ductus arteriosus; **IVH:** intraventricular hemorrhage

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Wide CI crossing line of no effect; estimate based on small sample size (-2).
b. Selection bias was unclear more than 40% weight in the meta-analysis (-1).

Analysis outcomes

The meta-analysis findings are shown in Figure 3 and summarized in Table 2. In terms of mortality, data from two trials were available, and although there was little difference in mortality between the two groups (fentanyl vs. control; 11/91 (12.0%) vs. 16/95 (16.8%)), fentanyl was not associated with

mortality risk compared to the control group (RR: 0.72, 95% CI: 0.36–1.44; two studies on 186 infants with low evidence certainty), with no statistical heterogeneity. In terms of ventilation duration, data from two trials were available, and no significant increase in ventilation duration (MD: 0.04, 95% CI: −0.63–0.71; two studies on 108 infants with very low evidence certainty) was found with no statistical heterogeneity. In terms of hospital stay length, data from one trial were available, and no statistically significant effect (MD: 4.00, 95% CI: −7.12–15.12; one study on 55 infants with very low evidence certainty) was detected. The trial by Ancora et al. could not be combined with a meta-analysis because the outcome of hospital stay length was described in terms of median and range and original data were not available from their corresponding author. Other morbidities in preterm infants were studied, and the results for each outcome were as follows: BPD (RR: 1.45, 95% CI: 0.63–3.31; two studies on 186 infants with low evidence certainty), PVL (RR: 0.68, 95% CI: 0.23–2.03; two studies on 186 infants with very low evidence certainty), PDA (RR: 1.05, 95% CI: 0.77–1.42; three studies on 206 infants with low evidence certainty), any IVH (RR: 0.87, 95% CI: 0.54–1.42; one study on 131 infants with low evidence certainty), severe IVH (RR: 0.82, 95% CI: 0.35–1.93; two studies on 186 infants), sepsis (RR: 1.00, 95% CI: 0.47–2.14; one study on 22 infants), and NEC (RR: 0.96, 95% CI: 0.40–2.32; two studies on 186 infants). Fentanyl intervention does not affect any of these morbidities. Guinsburg et al. reported on the outcome of blood pressure variability after fentanyl administration. However, due to the limited time available for evaluating circulatory dynamics, we were unable to determine the benefits and harms of fentanyl administration.

The effects of fentanyl infusion on PIPP were compared in two studies. Ancora et al. found that the fentanyl group had significantly lower mean PIPP scores at 1–3 days of age, and Qiu et al. found that the fentanyl group had significantly lower mean PIPP scores 2–48 h after the start of infusion. However, due to the different timing of each evaluation, we were not able to conduct a meta-analysis.

Discussion

This systematic review identified four RCTs of 268 preterm neonates (<35 weeks of gestation) and demonstrated that fentanyl administration was not associated with mortality or ventilation duration. Additionally, there were no significant benefits in terms of BPD, PVL, PDA, IVH, NEC, or sepsis. Two RCTs from the late 1990s were included in this meta-analysis. Over the last two decades, significant advances in technology, medicine, and nursing have improved the treatment and clinical outcomes of preterm infants [23]. Furthermore, due to the small sample sizes in these four RCTs, the evidence, as measured by the GRADE framework, was of low to very low certainty of evidence. Given the

scarcity of studies comparing fentanyl infusions for infants on mechanical ventilation, there is insufficient evidence to indicate whether fentanyl infusion is superior to placebo or no fentanyl infusions. Conversely, fentanyl administration was reported to significantly lower PIPP scores. However, due to the different timing of the respective evaluations, a meta-analysis analysis was not possible [19, 22].

In all studies included in our meta-analysis, fentanyl was given intravenously. Fentanyl infusion was given at a loading dose of 1 µg/kg, followed by continuous infusion of 1 µg/kg/h in two studies [19, 22], continuous infusion of 0.5–2 µg/kg/h with adjustment based on sedation score in one study [21], and a single dose of 3 µg/kg in another study [20]. The fentanyl doses used in these studies varied, but all of them were appropriate according to the consensus statement for the prevention and management of pain in newborns [24].

Another important endpoint, long-term neurodevelopment, was not investigated in this review. Data on this topic are needed, especially for preterm infants, given the hypothesis that fentanyl infusions may improve outcomes by reducing pain and stress or worsen outcomes by interfering with neurotransmitters. These data may become available in a few years as a result of the follow-up of recent RCTs.

Although our meta-analysis found no benefit or harm in terms of mortality and morbidities from fentanyl administration in preterm infants, the findings should be interpreted with caution because of the study's limitations. First, only four studies were included, so clinical trials with larger sample sizes are needed to confirm our findings, and generalizations of our findings should be done with caution. Second, our results are relatively weak due to trial heterogeneity caused by different dosing protocols. Third, even when the same protocols are followed, recent advances in the management of preterm infants, such as a lower proportion of extramural births, an increase in antenatal steroids, delivery by C-section, and use of CPAP during resuscitation, may result in different outcomes.

Conclusion

In conclusion, although the benefits of administering fentanyl to preterm infants have been investigated using an appropriate approach, the present systematic review and meta-analysis failed to demonstrate the benefits on mortality and morbidities. Since the present study did not investigate the long-term neurodevelopment of the children; therefore, follow-up studies are required to clarify the present study's findings.

Acknowledgments

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Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest relating to this manuscript.

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There was no funding relating to this review.

Author Contributions

Protocol development: all authors; literature search and assessment for eligibility: Y.S., J.S.N, D.K., G. K., F.S., and F.N.; data extraction: Y.S., J.S.N, D.K., and M.H.; analysis: Y.S., N.Y., E.O., and F.N.; critical review and approval of the manuscript: all authors.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Supplementary file 1. Search strategy

CENTRAL

([mh "Infant, Premature"] OR [mh "Obstetric Labor, Premature"] OR [mh "Premature Birth"] OR (Prematur* OR Pre-Mature OR Pre-Maturity OR Preterm OR Pre-Term):ti,ab) AND ([mh "Respiration, Artificial"] OR [mh "Ventilators, Mechanical"] OR (Artificial Respiration* OR Controlled Respiration* OR Mechanical Respiration* OR Respirator OR Respirators OR Ventilat*):ti,ab) AND ([mh Fentanyl] OR (Actiq OR Duragesic OR Durogesic OR Fentanest OR Fentanil OR Fentanyl OR Fentora OR Phentanyl OR "R 4263" OR "R4263" OR "R-4263" OR Sublimaze):ti,ab)

CINAHL

S5 S1 AND S2 AND S3 AND S4

S4 ((MH "Randomized Controlled Trials") OR (MH "Crossover Design") OR (MH "Random Assignment") OR (MH "Triple-Blind Studies") OR (MH "Double-Blind Studies") OR (MH "Single-Blind Studies")) OR TI (Random* OR Crossover* OR "Cross Over" OR ((Double OR Single OR Triple OR Treble) N1 (Mask* OR Blind*)) OR Trial*) OR AB (Random* OR Crossover OR "Cross Over" OR Factorial* OR Placebo* OR Assign* OR Allocat* OR Volunteer* OR Groups OR ((Double OR Single OR Triple OR Treble) N1 (Mask* OR Blind*)) OR Trial*))

S3 (MH "Fentanyl") OR TI (Actiq OR Duragesic OR Durogesic OR Fentanest OR Fentanil OR Fentanyl OR Fentora OR Phentanyl OR "R 4263" OR "R4263" OR "R-4263" OR Sublimaze) OR AB (Actiq OR Duragesic OR Durogesic OR Fentanest OR Fentanil OR Fentanyl OR Fentora OR Phentanyl OR "R 4263" OR "R4263" OR "R-4263" OR Sublimaze)

S2 ((MH "Mechanical Ventilation (Iowa NIC)") OR (MH "Respiration, Artificial+") OR (MH "Ventilators, Mechanical")) OR TI (Artificial Respiration* OR Controlled Respiration* OR Mechanical Respiration* OR Respirator OR Respirators OR Ventilat*) OR AB (Artificial Respiration* OR Controlled Respiration* OR Mechanical Respiration* OR Respirator OR Respirators OR Ventilat*)

S1 ((MH "Childbirth, Premature") OR (MH "Infant, Premature") OR (MH "Labor, Premature")) OR TI (Prematur* OR Pre-Mature OR Pre-Maturity OR Preterm OR Pre-Term) OR AB (Prematur* OR Pre-Mature OR Pre-Maturity OR Preterm OR Pre-Term)

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1. Premature Labor/ OR Prematurity/ OR (Prematur* OR Pre-Mature OR Pre-Maturity OR Preterm OR Pre-Term).ti,ab.
2. Exp Artificial Ventilation/ OR Mechanical Ventilator/ OR Ventilator/ OR (Artificial Respiration* OR Controlled Respiration* OR Mechanical Respiration* OR Respirator OR Respirators OR Ventilat*).ti,ab.
3. Fentanyl/ OR (Actiq OR Duragesic OR Durogesic OR Fentanest OR Fentanil OR Fentanyl OR Fentora OR Phentanyl OR "R 4263" OR "R4263" OR "R-4263" OR Sublimaze).ti,ab.
4. Randomization/ OR Crossover-Procedure/ OR Double-Blind Procedure/ OR Randomized Controlled Trial/ OR Single-Blind Procedure/ OR (Random* OR Factorial* OR Crossover* OR Cross Over* OR Placebo* OR ((Singl* OR Doubl* OR Trebl* or Tripl*) adj (Mask* OR Blind*)) OR Assign* OR Allocat* OR Volunteer* OR Groups OR Trial*).ti,ab.
5. 1 AND 2 AND 3 AND 4
6. Exp Animals/ OR Exp Invertebrate/ OR Animal Experiment/ OR Animal Model/ OR Animal Tissue/ OR Animal Cell/ OR Nonhuman/
7. Human/ OR Normal Human/ OR Human Cell/
8. 6 AND 7
9. 6 NOT 8
10. 5 NOT 9

MEDLINE 1946 to May 31, 2019

1. Exp Infant, Premature/ OR Exp Obstetric Labor, Premature/ OR Premature Birth/ OR (Prematur* OR Pre-Mature OR Pre-Maturity OR Preterm OR Pre-Term).ti,ab.
2. Exp Respiration, Artificial/ OR Exp Ventilators, Mechanical/ OR (Artificial Respiration* OR Controlled Respiration* OR Mechanical Respiration* OR Respirator OR Respirators OR Ventilat*).ti,ab.
3. Exp Fentanyl/ OR (Actiq OR Duragesic OR Durogesic OR Fentanest OR Fentanil OR Fentanyl OR Fentora OR Phentanyl OR "R 4263" OR "R4263" OR "R-4263" OR Sublimaze).ti,ab.
4. Randomized Controlled Trial.pt. OR Controlled Clinical Trial.pt. OR (Randomi?ed OR Placebo OR Randomly OR Trial OR Groups).ti,ab. OR Drug Therapy.fs.
5. 1 AND 2 AND 3 AND 4
6. Exp Animals/ NOT Humans.sh.

7. 5 NOT 6