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ORIGINAL ARTICLE

Induction opioids for caesarean section under general anaesthesia: a systematic review and meta-analysis of randomised controlled trials

L.D. White,[a,b] A. Hodsdon,[c,d] G.H. An,[b] C. Thang,[a,b] T.M. Melhuish,[e,f] R. Vlok[g,h]
[a]*School of Medicine, University of Queensland, QLD, Australia*
[b]*Department of Anaesthesia, Sunshine Coast University Hospital, QLD, Australia*
[c]*School of Medicine, University of Wollongong, NSW, Australia*
[d]*Wollongong Hospital, NSW, Australia*
[e]*School of Medicine, University of New South Wales, NSW, Australia*
[f]*Intensive Care Service, Royal Prince Alfred Hospital, NSW, Australia*
[g]*School of Medicine Sydney, University of Notre Dame Australia, NSW, Australia*
[h]*Intensive Care Service, Royal North Shore Hospital, NSW, Australia*

ABSTRACT

Introduction: The adverse effects of induction opioids on the neonate are poorly characterised. The study aim was to investigate whether induction opioids can be used in caesarean section without adversely affecting the neonate.

Methods: Six databases were systematically searched from inception until January 2019. Included studies compared induction opioids and placebo in caesarean section. Results were presented as odds ratios (95% confidence intervals) for dichotomous outcomes and weighted mean difference for continuous outcomes. An I^2 statistic of >50% was significant for heterogeneity. The primary outcome was Apgar score (1 and 5 min). Secondary outcomes included neonatal adverse events, cord blood gas analyses, maternal haemodynamic parameters (systolic blood pressure (SBP), mean arterial pressure (MAP), heart rate (HR) and catecholamine concentrations.

Results: Seventeen studies (n=987) were included in the meta-analysis. Remifentanil 0.5–1 μg/kg or 2–3 μg/kg/h, alfentanil 7.5–10 μg/kg and fentanyl 0.5–1 μg/kg were compared to placebo. There was no significant difference in Apgar scores at 1 min (P=0.25, 0.58 and 0.89 respectively) for all three opioids or at 5 min for remifentanil and alfentanil (P=0.08 and 0.21 respectively). Fentanyl significantly reduced 5 min Apgar scores (P=0.002). There was no difference in neonatal airway interventions with remifentanil or alfentanil (P <0.05). All three induction opioids caused a significant reduction in maximum SBP (P <0.0001), MAP (P <0.00001) and HR (P <0.00001).

Conclusion: Induction opioids are effective sympatholytic agents. Remifentanil and alfentanil appear to be safe, with no significant effect on Apgar scores or neonatal airway intervention, but a well-powered trial is required to confirm these findings.

Keywords: Opioids; Caesarean section; Anaesthesia, general; Randomised trials

Introduction

Caesarean section (CS) under general anaesthesia (GA) is commonly performed due to surgical urgency, inadequate previous block, maternal refusal or contraindication to neuraxial anaesthesia.[1] The induction of general anaesthesia and initial surgical incisions cause significant sympathetic drive which may result in adverse effects, for example intracranial haemorrhage in the context of comorbidities such as pre-eclampsia.[2–5] For this reason sympatholysis is often required on induction of GA and initiation of CS. Opioids are highly effective sympatholytic agents used at induction of GA but are often avoided due to their potential adverse effects on the neonate.[6–10] Recommendations to omit opioids from the induction of anaesthesia are based on evidence from the use of older, longer-lasting opioids.[1] The newer, shorter-acting opioids (e.g. remifentanil, alfentanil and fentanyl) have been proposed as 'safe' options for the induction of GA for CS. There has been one small meta-analysis investigating the effect of remifentanil.[11] This study showed a high

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Correspondence to: Dr L. White, Department of Anaesthesia, Sunshine Coast University Hospital, QLD, Australia.
E-mail address: lw844@uowmail.edu.au

degree of efficacy and no statistically significant adverse effects, however the authors also recommended further studies to clarify these findings. Since that meta-analysis, there have been a number of randomised controlled trials (RCTs) performed to investigate the use of remifentanil and other agents.

The primary aim of this review was to determine the effect of induction opioids on Apgar scores. The secondary aim was to assess the effect on other neonatal outcomes, as well as the efficacy of induction opioids for sympatholysis.

Methods

Search strategy

Two independent reviewers (AH and GA) searched the Cochrane trials registry, SCOPUS, Medline, CINAHL, PubMed and Web of Science from inception until January 2019. This search was conducted using the terms (1) 'opioid' AND 'Caesarean section' OR 'Cesarean section'; (2) 'opioid' AND 'intubation' AND 'Caesarean section' OR 'Cesarean section'; (3) 'opioid' AND 'general anaesthesia' AND 'Caesarean section'. A manual reference check and citation check of included papers was performed to identify any additional studies.

Study eligibility

To be eligible for inclusion the authors were required to report on the use of induction opioids for CS. Only RCTs with a placebo control group were eligible and there were no language criteria for exclusion. Two reviewers (LW and AH) independently assessed and agreed upon each study for inclusion in this systematic review. Studies comparing induction opioids to alternative agents, studies using opioids only after cord clamping and studies of obstetric patients having operations other than CS were excluded.

Data extraction

LW and AH extracted data from each article that met the inclusion criteria independently. The extracted data included the study design, patient characteristics and clinical outcome results. The data collected by each reviewer was then compared for homogeneity.

Clinical outcome measures

Our a priori primary outcomes were Apgar scores at one and five minutes post delivery. Secondary outcomes included neonatal adverse outcomes such as bag-mask-ventilation (BVM), intubation and neonatal intensive care unit (NICU) admission, neonatal cord blood results (pH and base excess (BE)), highest maternal systolic blood pressure (SBP), mean arterial pressure (MAP) and heart rate (HR), as well as maternal epinephrine and norepinephrine concentrations.

Level of evidence, risk of bias and outcome level of evidence ranking

Each article was evaluated using the Centre for Evidence Based Medicine (CEBM) Levels of Evidence Introduction Document.[12] These studies were then assessed for risk of bias and methodological quality using the Cochrane Collaboration's tool for assessing the risk of bias.[13] A study was deemed to be of low risk if it scored four or more low-risk criteria on the risk of bias tool. Studies were rated high risk if they scored three or less low-risk criteria.

Statistical analyses

The combined data were analysed using RevMan 5.3 software (The Nordic Cochrane Centre, Copenhagen, Denmark), using the risk ratio (RR) with 95% confidence interval (CI) for dichotomous outcomes and the weighted mean difference (WMD) with 95% CI for continuous outcomes. The Mantel-Haenszel (M-H) random effects model was used. Heterogeneity was assessed using the I^2 statistic, with an I^2 >50% indicating significant heterogeneity. A P-value <0.05 provided evidence of significant RR and WMD. A P-value of <0.10 was used to demonstrate heterogeneity of intervention effects.

Reporting

This study was reported in line with PRISMA guidelines.[14]

Results

Literature search results

The initial systematic search yielded 2138 citations and a further six citations were identified through a manual citation and reference search of relevant articles (Fig. 1). Following the removal of duplicates, 1196 citations remained. Of these, 63 abstracts were screened and 29 full texts were retrieved for review. Seventeen articles met the inclusion criteria (Fig. 1). These studies included 987 patients. All studies investigated the use of either remifentanil, alfentanil or fentanyl versus placebo for the induction of anaesthesia for CS (Table 1). The doses used in these studies included remifentanil 0.5–1 μg/kg bolus or 2–3 μg/kg/h infusion, alfentanil 7.5–10 μg/kg bolus and fentanyl 0.5–1 μg/kg bolus. The study by Deogaonkar et al. included intervention groups 0.5 μg/kg and 1 μg/kg fentanyl.[17] These groups have been analysed separately. The risk of bias in the studies is shown in Fig. 2. Thirteen studies met the criteria for high-quality RCTs, leaving four low-quality RCTs.

Primary outcomes

Overall, 12 studies measured Apgar score at one minute post delivery and showed no significant difference (WMD −0.05; 95%CI −0.23 to 0.13; I^2=65%; P=0.60;

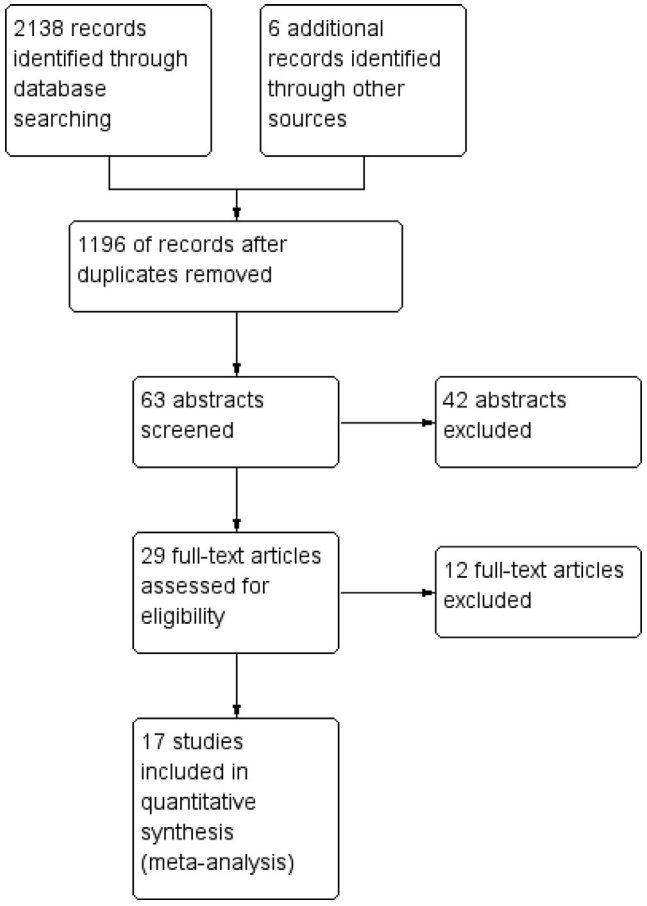

Fig. 1 The PRISMA diagram of trial selection

Fig. 3).[7,9,15–24] Of these 12 studies, six investigated the effect of remifentanil,[16,18,20,22–24] three alfentanil[9,15,21] and three fentanyl.[7,17,19] When divided into the individual agents there was no significant difference after remifentanil (WMD −0.27; 95%CI −0.74 to 0.19; I^2=78%; P=0.25), alfentanil (WMD 0.05; 95%CI −0.12 to 0.21; I^2=0%; P=0.58) or fentanyl (WMD −0.02; 95%CI −0.30 to 0.26; I^2=72%; P=0.89).

The same 12 studies investigated Apgar scores at five minutes post delivery, again showing no significant effect overall (WMD −0.11; 95%CI −0.22 to 0.01; I^2=81%; P=0.07; Fig. 4).[7,9,15–24] Fentanyl was the only opioid to show a significant reduction in Apgar scores (WMD −0.20; 95%C −0.33 to −0.08; I^2=0%; P=0.002). There was no difference with remifentanil (WMD −0.19; 95%CI −0.40 to 0.02; I^2=82%; P=0.08) or alfentanil (WMD 0.14; 95%CI −0.08 to 0.36; I^2=73%; P=0.21).

Secondary outcomes

Six remifentanil studies investigated the requirement for post-delivery BVM and showed no difference (RR 1.45; 95%CI 0.88 to 2.39; I^2=0%; P=0.71).[10,16,20,22,25,26] Similarly there was no significant difference in neonatal intubation rate with remifentanil (RR 1.34; 95%CI 0.67 to 2.68; I^2=0%; P=0.97)[10,16,18,20,22,25,26] or alfentanil (RR 1.65; 95%CI 0.60 to 4.56; I^2=0%; P=0.69).[9,15] There was no increase in NICU admission with remifentanil (RR 0.95; 95%CI 0.77 to 1.19; I^2=0%; P=0.67).[10,22,25] Only one study mentioned NICU admission following alfentanil use and showed no difference (P=0.72).[9]

Ten studies investigated umbilical artery pH[7,8,10,15–18,20,22,25] and six studies investigated umbilical artery BE.[7,10,18,20,22,25] There was no significant difference in umbilical artery pH with remifentanil (WMD 0.01; 95%CI −0.00 to 0.02; I^2=33%; P=0.14), alfentanil (WMD 0.02; −0.04 to 0.08; I^2=0%; P=0.55) or fentanyl (WMD 0.00; 95%CI −0.01 to 0.01; I^2=22%; P=0.90). Similarly, there was no significant difference in BE with remifentanil (P=0.16) or fentanyl (P=0.58).

Overall, there was a significant reduction in maximum SBP (WMD −22.29 mmHg; 95%CI −27.96 to 16.61 mmHg; I^2=73%; P <0.0001)[8–10,16–18,20,22–24,26], MAP (WMD −13.68 mmHg; 95%CI −19.00 to 8.36 mmHg; I^2=69%; P <0.00001)[8,10,17,27] and HR (WMD −13.81 bpm; −16.92 to −10.70 bpm; I^2=14%; P <0.00001) with opioids.[8–10,17,19,20,23,27] All three agents had a similar magnitude of effect on SBP, MAP and HR (P <0.001). Intra-operative maternal epinephrine concentrations were significantly reduced by remifentanil (WMD −122.56 pg/mL; 95%CI −206.20 to −38.93 pg/mL; I^2=0%; P=0.0004)[18,22] but not alfentanil (WMD −29.11 pg/mL; 95%CI −127 to −69.43 pg/mL; I^2=0%; P=0.56).[8,15] There was no difference in intra-operative norepinephrine concentrations with remifentanil (WMD 88.27 pg/mL; −46.76 to 223.31 pg/mL; I^2=0%; P=0.20)[18,22] or alfentanil (WMD 14.78 pg/mL; −80.71 to 110.28 pg/mL; I^2=0%; P=0.76).[8,15]

Discussion

The use of induction opioids for CS remains a controversial topic with many theorised risks and benefits. To date, only one small meta-analysis of five RCTs had investigated the use of remifentanil.[11] This review has expanded the topic to include studies using alfentanil and fentanyl as well as remifentanil. Our search yielded 17 studies for inclusion.[7–10,15–27] Of these, there were 10 remifentanil, four alfentanil and three fentanyl studies. Overall, opioids appeared not to affect neonatal outcomes, with the exception of fentanyl which caused a significant reduction in five-minute Apgar scores. As expected, all three opioids were associated with a significant reduction in maternal haemodynamic parameters. This is in keeping with a previous small study by Rout and Rocke[28]. This was the only study found in our search that compared two different opioids for

Table 1 Study characteristics

Author	Blinding	Patient	Induction agents	Opioid dose	Sample size opioid:control	Primary outcome
Alfentanil						
Ashton et al.[15]	Double blinded	● Pre-eclampsia ● Elective or emergency CS ● Diastolic BP >90 mmHg ● Two or more proteinuria	Suxamethonium 4–8 mg/min infusion and magnesium sulphate 30–40 mg/kg	Alfentanil 7.5 g/kg	19:19	1. Apgar scores 2. Neonatal intubation 3. Cord pH 4. Maternal epinephrine and norepinephrine concentration
Dann et al.[9]	Double blinded	● Uncomplicated pregnancy ● No medications except iron and folate supplement ● No hypertension ● No medical conditions	Thiopentone 3.5 mg/kg and suxamethonium 1 mg/kg	Alfentanil 10 μg/kg	21:16	1. Apgar scores 2. Neonatal intubation 3. NICU admission 4. Highest SBP 5. Highest HR
Gin et al.[8]	Double blinded	● Uncomplicated singleton pregnancy ● Elective CS	Thiopentone 4 mg/kg and suxamethonium 1.5 mg/kg	Alfentanil 10 μg/kg	18:22	1. Cord pH 2. Highest SBP 3. Highest MAP 4. Highest HR 5. Maternal epinephrine and norepinephrine concentration
Valami et al.[21]	Double blinded	● Uncomplicated pregnancy ● Age 18–40 years ● Gravida 1 or 2 ● Elective CS	Thiopentone 5 mg/kg and suxamethonium 1.5 mg/kg	Alfentanil 10 μg/kg	25:25	1. Apgar
Remifentanil						
Behdad et al.[16]	Double blinded	● Uncomplicated singleton ● Term pregnancy	Thiopentone 5 mg/kg and suxamethonium 1.5 mg/kg	Remifentanil 0.5 μg/kg bolus	40:40	1. Apgar scores 2. Neonatal BVM 3. Neonatal intubation 4. Highest SBP 5. Cord pH
Bouattour et al.[25]	Double blinded	● Uncomplicated pregnancy ● Term pregnancy ● Elective CS	Propofol 2 mg/kg and Suxamethonium 1 mg/kg	Remifentanil 0.5 μg/kg bolus	20:20	1. Neonatal BVM 2. Neonatal intubation 3. NICU admission 4. Cord pH and BE

(*continued on next page*)

Table 1 (*continued*)

Author	Blinding	Patient	Induction agents	Opioid dose	Sample size opioid:control	Primary outcome
Draisci et al.[18]	Double blinded	● Uncomplicated pregnancy ● Term pregnancy ● Elective CS	Thiopentone 4 mg/kg and suxamethonium 1 mg/kg	Remifentanil 0.5 μg/kg before induction, followed by an infusion at 0.15 μg/kg/min until peritoneal incision.	21:21	1. Apgar scores 2. Neonatal intubation 3. Highest SBP 4. Cord pH and BE 5. Maternal epinephrine and norepinephrine
Hasannasab et al.[24]	Double blinded	● Uncomplicated pregnancy ● Term pregnancy ● Elective CS	Unclear	Remifentanil infusion 2 μg/kg/min	50:50	1. Apgar scores 2. Highest SBP
Kart and Hanci[27]	Double blinded	● Uncomplicated pregnancy ● Term pregnancy ● Elective CS	Propofol 2 mg/kg and rocuronium 0.6 mg/kg	Remifentanil 1 μg/kg bolus	30:30:30	1. Highest SBP 2. Highest HR
Lee et al.[23]	Double blinded	● Uncomplicated pregnancy ● Term pregnancy ● Elective CS	Thiopentone 4 mg/kg and suxamethonium 1.5 mg/kg	Remifentanil infusion effect site 3 μg /mL	10:10	1. Apgar scores 2. Highest SBP 3. Highest HR
Ngan Kee et al.[10]	Double blinded	● Uncomplicated pregnancy ● Term pregnancy ● Elective CS	Thiopentone 4 mg/kg and suxamethonium 1.5 mg/kg	Remifentanil 1 μg/kg bolus	20:20	1. Apgar scores 2. Neonatal BVM 3. Neonatal intubation 4. NICU admission 5. Highest SBP 6. Highest MAP 7. Highest HR 8. Cord pH and BE
Noskova et al.[20]	Double blinded	● Uncomplicated pregnancy ● Term pregnancy ● Elective CS ● Multiple pregnancy	Thiopentone 5 mg/kg and suxamethonium 1.25 mg/kg	Remifentanil 1 μg/kg bolus	76:75	1. Apgar scores 2. Neonatal BVM 3. Neonatal intubation 4. Highest SBP 5. Cord pH and BE
Orhan Sungur et al.[26]	Double blinded	Unavailable	Thiopentone and suxamethonium Doses unclear	Remifentanil 1 μg/kg bolus	11:11	1. Neonatal BVM 2. Neonatal intubation 3. Highest SBP

Yoo et al.[22]	Double blinded	● Severe pre-eclamptic women ● Elective/emergency CS	Thiopentone 4 mg/kg and suxamethonium 1.5 mg/kg	Remifentanil 1 μg/kg bolus	21:21	1. Apgar scores 2. Neonatal BVM 3. Neonatal intubation 4. NICU admission 5. Highest SBP 6. Cord pH and BE 7. Maternal epinephrine and norepinephrine
Fentanyl						
Deogaonkar et al.[17]	Double blinded	● Uncomplicated pregnancy ● Term pregnancy ● Elective or Emergency CS ● Multiple pregnancy	Thiopentone 5 mg/kg and suxamethonium 1.5 mg/kg	Fentanyl 0.5 μg/kg or 1 μg/kg bolus	15:15:15	1. Apgar scores 2. Highest SBP 3. Highest MAP 4. Highest HR 5. Cord pH
Karbasy and Derakhshan[19]	Double blinded	● Uncomplicated pregnancy ● Term pregnancy ● Elective CS	Thiopentone 4 mg/kg and suxamethonium 1.5 mg/kg	Fentanyl 1 μg/kg bolus	45:45	1. Apgar scores 2. Highest MAP 3. Highest HR 4. Cord pH
Maghsoudloo et al.[7]	Double blinded	● Uncomplicated pregnancy ● Term pregnancy ● Elective CS	Thiopentone 5 mg/kg and suxamethonium 1 mg/kg	Fentanyl 1 μg/kg bolus	30:30	1. Apgar scores 2. Cord pH and BE

CS: caesarean section; BP: blood pressure; SBP: systolic blood pressure; NICU: neonatal intensive care unit; BVM: bag-mask ventilation; BE: base excess; HR: heart rate; MAP: mean arterial pressure.

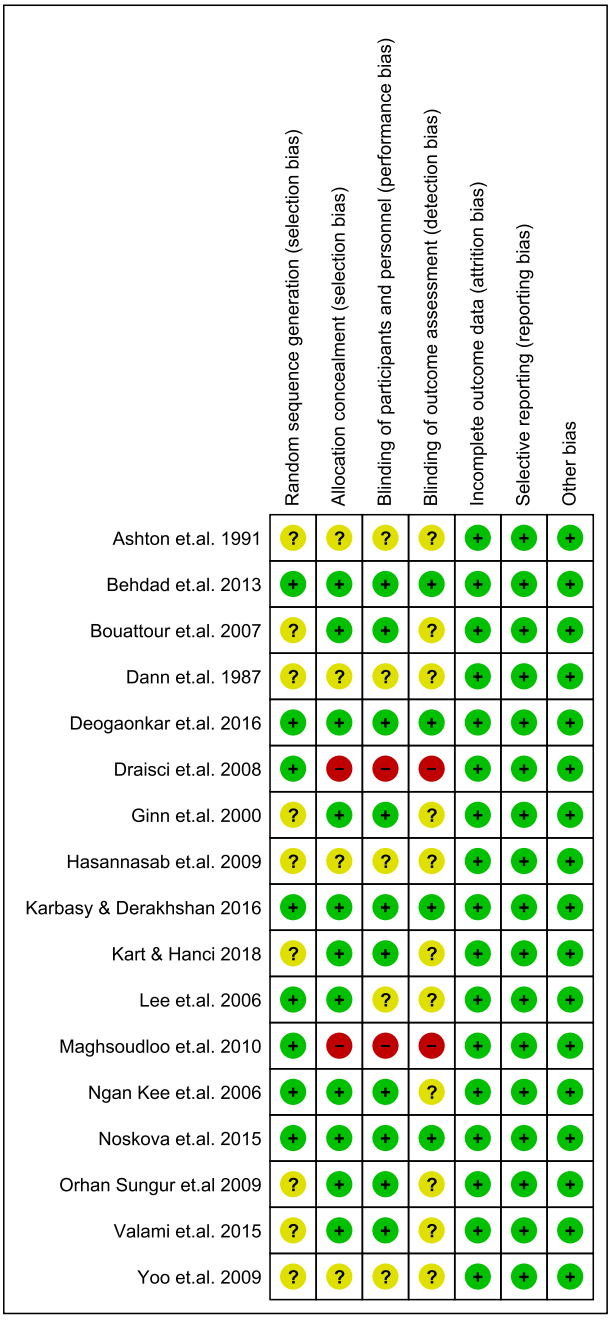

Fig. 2 The risk of bias summary for included studies

induction of CS. Their study found no statistically significant difference between alfentanil and fentanyl for any outcome among patients with severe pregnancy-induced hypertension.[28]

The sympatholytic properties of opioids are well demonstrated in the literature and the hesitance to use them for CS relates to the risk to the neonate.[6–10] For this reason, the primary outcome of interest was related to neonatal adverse effects. The results of this review showed no significant effect on Apgar scores associated with remifentanil or alfentanil. There was, however, a significant reduction in five-minute Apgar score with the use of fentanyl, which is likely related to the significantly shorter duration of action of remifentanil and alfentanil compared to fentanyl. According to a power analysis performed by Karbasy and Derakhshan, 43 patients are needed in each group to detect a significant difference in Apgar scores.[19] Unfortunately, the majority of studies included in this review were not adequately powered. Of the studies that were, three investigated remifentanil,[16,20,24] and one fentanyl.[19] For remifentanil there was conflicting evidence regarding Apgar scores at one minute. One study showed a significant reduction[20] but the other two showed no difference.[16,24] All three showed no difference at five minutes. In contrast to the overall results, Karbasy and Derakhshan showed no significant difference in one- or five-minute Apgar score from the use of fentanyl.[19] The heterogeneity in these findings still leads to the possibility that the overall lack of significance we found could be due to chance.

Apgar scores are commonly used as surrogate measures to predict subsequent adverse neonatal outcomes. Similar to the Apgar scores, there was no significant difference in neonatal airway intervention or NICU admission with remifentanil or alfentanil. These outcomes were not measured in the fentanyl studies. While this appears reassuring for those advocating the routine use of opioids, these results should be interpreted with caution. Previous studies have performed power analyses and determined that in order to detect a significant increase in airway events, 500 patients would be required in each group.[11,29,30] Therefore, all studies included in this review are significantly underpowered.

The studies included in this review generally included a sufficient number of patients to be adequately powered to detect significant differences in haemodynamic parameters and plasma catecholamine levels.[16,18,22] Four studies investigated plasma catecholamine levels associated with remifentanil and alfentanil administration. There was a significant reduction in plasma epinephrine, but not norepinephrine, for remifentanil but not alfentanil. These findings support the theory that the predominant source of norepinephrine is from sympathetic nerves and this is not significantly affected by the presence of opioids.[31,32] In contrast, epinephrine is released from the adrenal medulla and this may be modulated by systemic opioids.[31,32] Although there was no attenuation of epinephrine release with alfentanil, all three agents demonstrated significantly reduced haemodynamic responses. This suggests alternative mechanisms of cardiovascular stabilisation. All three opioids resulted in a reduced response to laryngoscopy and surgical stimulation with respect to maternal maximum HR, MAP and SBP. More importantly, this sympatholytic effect was demonstrated in the two studies investigating patients

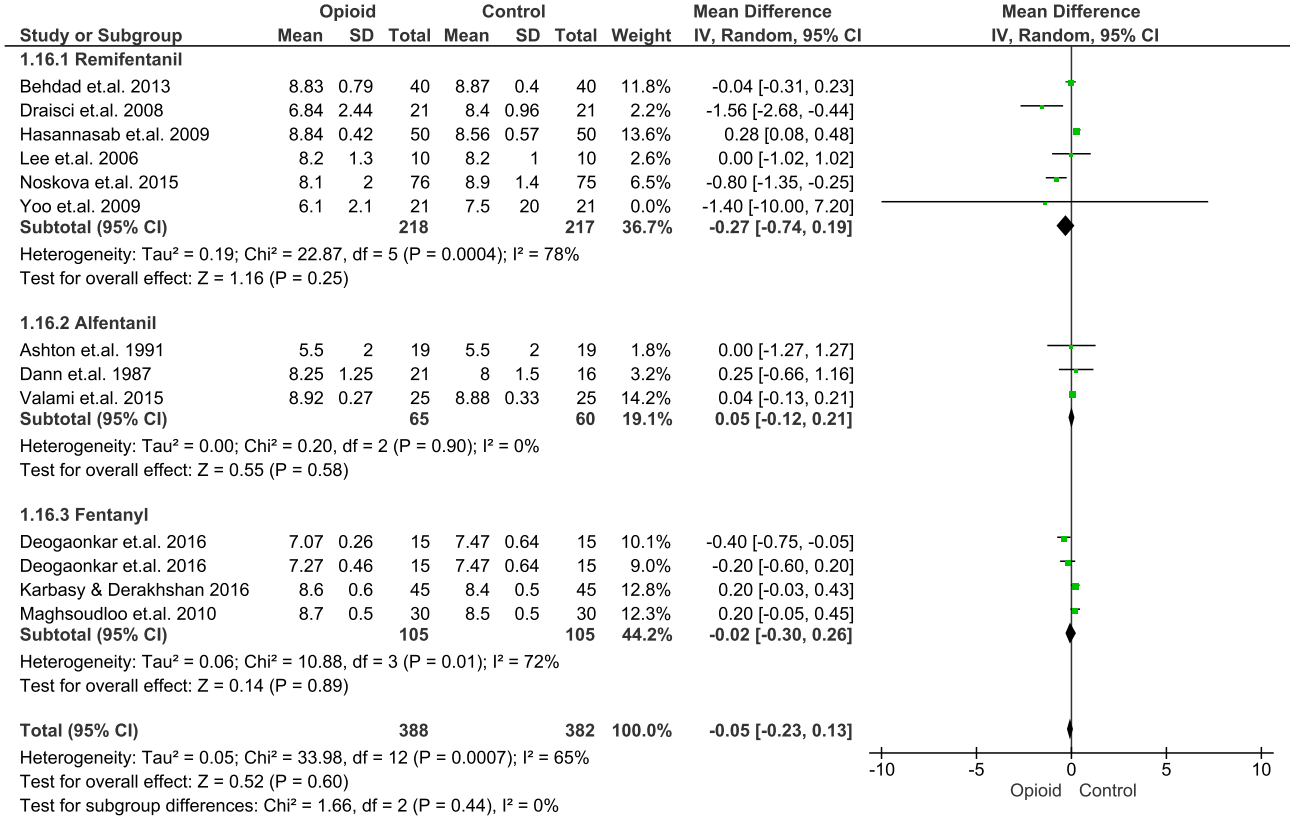

Fig. 3 Forest plot of comparison Apgar scores at one minute

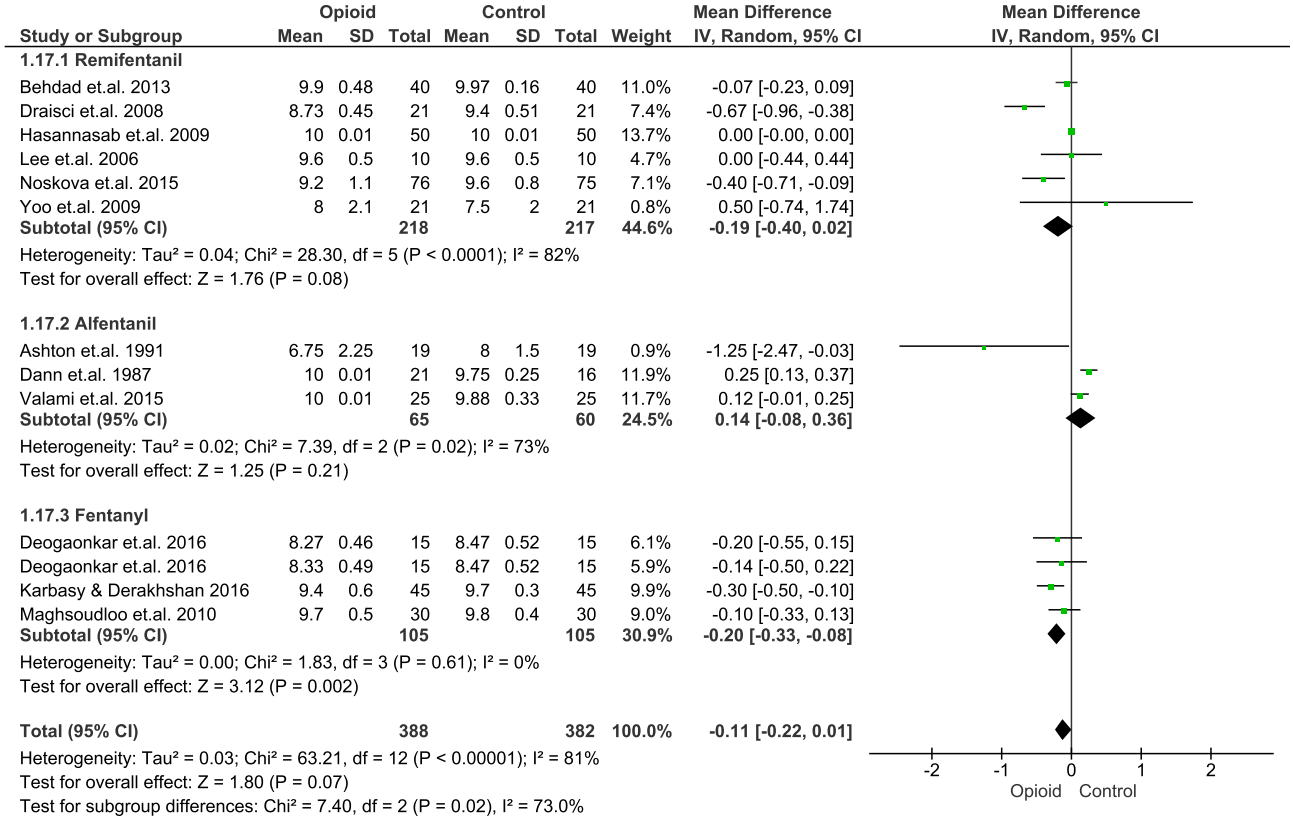

Fig. 4 Forest plot of comparison Apgar scores at five minutes

with pre-eclampsia.[15,22] Both remifentanil and alfentanil significantly reduced maximum HR and blood pressure compared to the control groups.

There are several limitations to this review. The most significant is the lack of power to investigate neonatal 'hard endpoints' such as intubation and NICU admission in the studies included. Furthermore, only two studies included at-risk pre-eclamptic patients and no studies investigated high-risk parturients such as those with significant cardiac defects. Therefore, the results of the review cannot be applied to at-risk patient populations.

In conclusion, induction opioids are effective sympatholytic agents. Remifentanil and alfentanil appear to be safe and without a significant effect on Apgar scores. There was no effect of remifentanil and alfentanil detected in regard to neonatal airway intervention, however a large well-powered trial is still required to assess this.

Disclosure of interests

All authors have no conflicting or competing interests to declare.

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