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Current Women's Health Reviews, 2019, *15*, 000-000

SYSTEMATIC REVIEW ARTICLE

Maternal and Neonatal Effect of Fentanyl as A Premedication before Induction of General Anesthesia in Cesarean Surgery: A Systematic Review and Meta-analysis of Randomized Clinical Trials

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Abstract: ***Background*:** Although, some clinical trials investigated the maternal and neonatal effect of fentanyl as a premedication before induction of general anesthesia in cesarean section, to the best of our knowledge, there is no systematic review to summarize these results.

***Objectives*:** The present systematic review and meta-analysis evaluated the maternal and neonatal effect of intravenous fentanyl as a premedication before induction of general anesthesia in cesarean section.

***Methods*:** The databases of Pubmed, Embase, Scopus and Cochrane library were searched till July 2017 to identify randomized clinical trials which evaluated the effects of intravenous fentanyl as a premedication before induction of general anesthesia compared with placebo on neonate first and fifth minute Apgar score and maternal heart rate and mean arterial pressure (MAP) in cesarean section. Standard Mean difference (SMD) was calculated and I-square statistic test was used for heterogeneity analysis.

***Results*:** The present systematic review and meta-analysis consisted of three clinical trials including 180 women in labor. Considering the results of meta-analysis, there is no significant differences between fentanyl and placebo in the case of Apgar score at 1 minute; however, the Apgar score of 5 minutes was significantly lower in fentanyl group compared with placebo (SMD -0.68, 95%CI: -0.98, -0.38, p<0.001). In the term of maternal hemodynamics, the heart rate (SMD -0.43, 95%CI: -0.72, -0.13, p=0.004) and MAP (SMD -0.78, 95% CI: -1.09, -0.48, p<0.001) in fentanyl group were significantly lower compared with placebo group.

***Conclusion*:** The present meta-analysis showed that using intravenous fentanyl as a premedication before induction of general anesthesia had adverse effects on neonate Apgar score. However, it had positive effects on preventing adverse consequences of intubation on maternal hemodynamics.

ARTICLE HISTORY

Received: March 25, 2018
Revised: September 26, 2018
Accepted: December 04, 2018

DOI:
10.2174/1573404815666190111151651

Keywords: Fentanyl, cesarean section, Apgar score, mean arterial pressure, heart rate, maternal hemodynamics.

1. INTRODUCTION

Reducing pain during delivery is the main determinant of maternal satisfaction with birth experience and due to short-term and long-term adverse effects of stress response, reducing stress response is the main objective in cesarean section [1, 2]. In this regard, depending on fetal and maternal conditions of pregnant women, and anesthesiologists' preferences, local or general anesthetic methods can be administered. Although, at present, local blocks are considered as a gold standard for labor analgesia, in emergency situations, or when neuraxial anesthesia techniques have failed or are contraindicated, general anesthesia is preferred method [3]. In general anesthesia for cesarean section, the anesthetists for satisfying the different requirements of the mother and her newborn, face a challenge and different methods including neuromuscular blocking agents and opioids are used.

Although opioids are considered as a gold standard for reaching analgesia during general anesthesia [4], because of their suppressive effects on newborns' central nerves system, there is concern about their applications in cesarean delivery. However, the results of the studies about the adverse effects of opioids are controversial [5-7].

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1573-4048/19 $58.00+.00

Table 1. Search terms (PICO strategy) used for search strategy.

PICO Criteria	Description and Search Strategy
Patients	women expecting cesarean delivery: (cesarean OR c-section) AND (labor women)
Intervention	Fentanyl: Phentanyl OR Fentanest OR Fentanyl Citrate OR Fentora
Comparison	Placebo: Placebo OR "normal saline"
Outcome	Neonatal outcomes: "Apgar score" Maternal outcomes: "heart rate" OR "Pulse rate" OR "Mean arterial pressure" OR "MAP"

A synthetic opioid, Fentanyl, is the rapid onset and short duration action anesthetic agent. Different studies investigated the effect of Fentanyl alone or in combination with epidural analgesics (such as Bupivacaine and Ropivacaine) on maternal and neonatal outcomes in cesarean delivery [8-11]. Although, some clinical trials investigated the maternal and neonatal effect of fentanyl in cesarean section, to the best of our knowledge there is no systematic review to summarize these results. In the present systematic review and meta-analysis, we aimed at comparing the neonatal and maternal effect of intravenous fentanyl as a premedication before induction of general anesthesia in comparison with placebo in cesarean delivery.

2. METHOD

This systematic review and meta-analysis were performed according to Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA). The ethics committee of Tabriz University of medical sciences approves the study.

2.1. Criteria for Including Studies in this Systematic Review and Meta-analysis

Types of participants (P): We included studies that assessed the use of fentanyl as a premedication before induction of general anesthesia compared with placebo in women undergoing cesarean.

Types of interventions (I/C): 1 (μg/kg) intravenous fentanyl as a premedication before induction of general anesthesia compared with placebo

Types of outcome measures (O):

Neonatal outcomes including the first and fifth minute Apgar score.

Maternal hemodynamics including heart rate and mean arterial pressure (MAP).

Types of studies: clinical trials of any duration irrespective of their publication status were included in this study.

Editorials, review articles and articles published in other languages rather than English or Persian were excluded.

2.2. Citations Capture

We searched databases of Pubmed, Embased, Cochrane library and Scopus till June 2017. Keywords were selected based on Mesh terms and are presented in Table **1**. Briefly, the keywords included: "Fentanyl", "phentanyl", "fentanest", "fentora", cesarean, Apgar, mean arterial pressure, and heart rate. Besides, the references of recent reviews and other eligible articles were manually searched for additional trials not identified by the electronic search. We also searched clinicaltrials.gov for finding ongoing studies.

2.3. Data Extraction

The following information was extracted by two authors (ZN and LN) using an extraction table: the surname of the first author and publication date, age of participants, sample size in each group, dose of interventions and outcomes. Any discrepancies were resolved through discussion and by consulting a third reviewer.

2.4. Risk of Bias Assessment

Two investigators independently rated the methodological quality of selected studies using Cochrane collaboration`s tool for assessing the risk of bias. The following domains were assessed: Randomization sequence generation, blinding of participants and study personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other biases.

2.5. Statistical Analysis

The Comprehensive Meta-Analysis version 2.0 was used for analyses of data. The pooled results were expressed as the mean difference or standardized mean difference with 95% CI and the effect size was calculated. In one publication, only the *P* value for the difference in MAP values between arms was reported as a measure of deviation. The *P* value and the sample sizes of the arms were used to calculate the SD of the difference in MAP between two arms values. The chi-square test and associated p-value and also I^2 test were used for heterogeneity analysis. I^2>50% were considered as clinically important heterogeneity. The random effects or fixed effects models were performed for meta-analysis based on the inverse variance (IV) statistical approach. To assess the potential for publication bias, we used funnel plots and Egger's regression. Four separate main meta-analyses were conducted (first and fifth minute Apgar score, mean arterial pressure and heart rate).

3. RESULTS

The search strategy resulted in 429 titles, reduced to 266 following deletion of duplicates using the Endnote 7.2.1 lit-

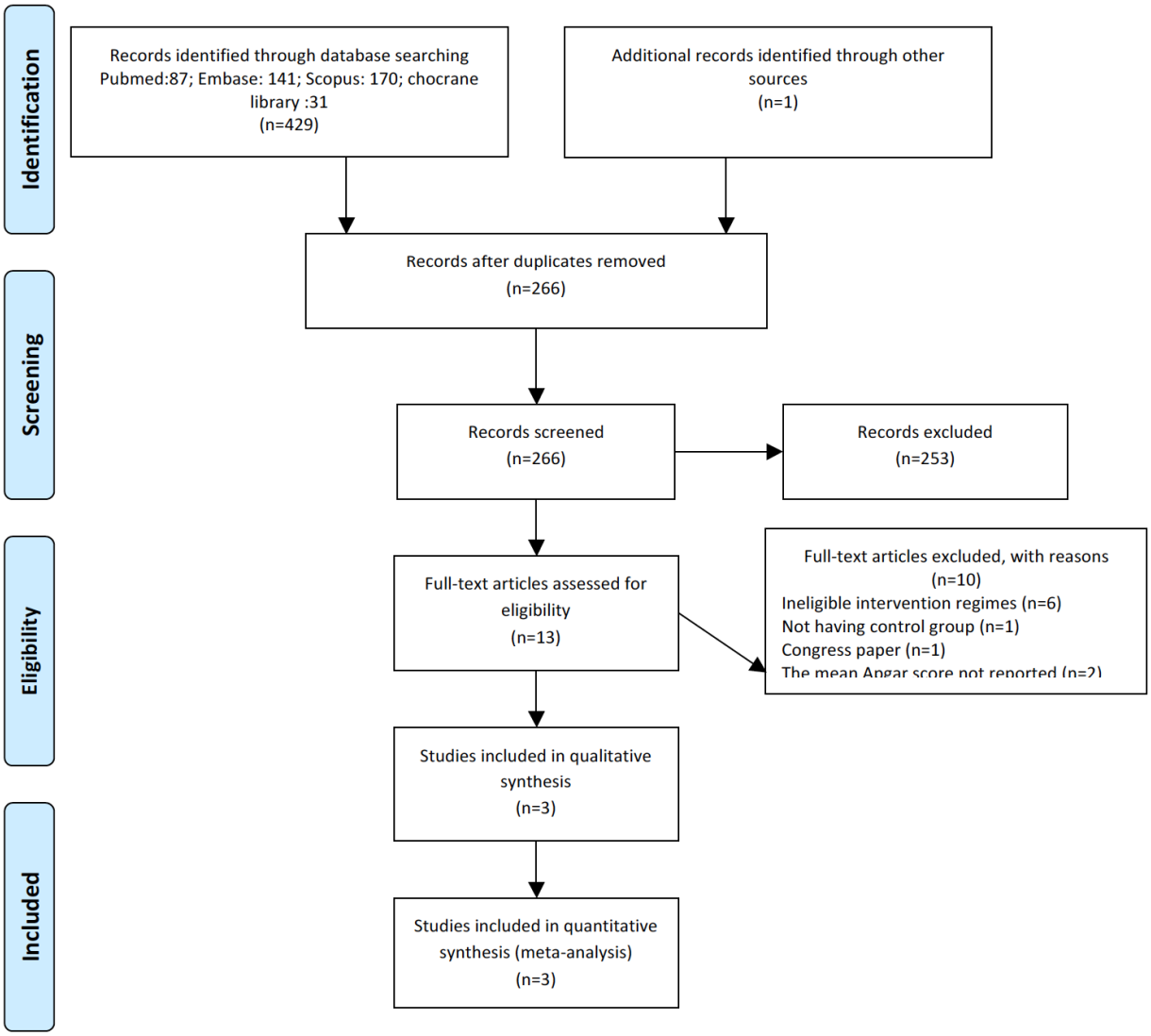

Fig. (1). Flow diagram of studies for inclusion in the systematic review and meta-analysis.

erature manager software. Initial assessment of the titles reduced the number of papers to 13 and further reduced to three on closer assessment of the abstract and full text (Fig. **1**). The reasons for exclusion of 10 studies are as follows: six were performed based on ineligible intervention regimes which included using fentanyl concomitantly with tramadol or bupivacaine or midazolam, the design of one study was before-after and did not include a control group, one study published as an abstract and one study reported the results just as a text, of which, the exact number could not be estimated and finally one study reported the result not as mean. A flow chart of literature retrieval is shown in Fig. (**1**).

3.1. Study Characteristics and Assessing Risk of Bias

We identified 3 eligible trials which included 180 women in labor [8, 10, 11]. The mean age of participants ranged between 22.80±1.86 and 30.1±5.9 years. All studies used the 1 µg/ml dose of fentanyl in the intervention group and an equivalent volume of normal saline as a placebo. Basic characteristics and summary of findings of the included studies are presented in Table **1**.

The quality assessment of included papers is shown in Table **2**. All of three studies stated the randomization method. None of the included studies appropriately reported the allocation concealment, all studies reported the drop-out and expected outcome measures of interest; and no other biased sources were detected (Table **3**).

3.2. Publication Bias

Fig. (**2**) shows a symmetric Begg's funnel plot, indicating that there was no publication bias in 1 minute Apgar score (P = 0.12) and 5 minute Apgar score (p=0.77).

3.3. Meta-analysis of Apgar Score

Three studies reported the data of Apgar score at 1 minute and 5 minute and effect size was shown as mean difference with 95% CI. Given that we did not identify statistical heterogeneity for Apgar score at 5 minute (Q=1.70, df=2, P=0.42 and I2=0.00%), the fixed effect model was used. The results showed that there was no significant difference between fentanyl and placebo in the case of Apgar score

Table 2. Basic characteristics and summary of findings of included studies.

Author	Date	Dose (μg/kg)	N (Fentanyl)	N (Placebo)	Age (Fentanyl)	Age (Placebo)	Apgar 1 Minute (Fentanyl)	Apgar 1 Minute (Placebo)	Apgar 5 Minute (Fentanyl)	Apgar 1 Minute (Placebo)	HR (Fentanyl)	HR (Placebo)	MAP (Fentanyl)	MAP (Fentanyl)
Magsoodloo	2011	1	30	30	28±5	27.9±4.8	8.7±0.5	8.5±0.5	9.7±0.5	9.8±0.4	98 (p=0.001)	119 (p=0.001)	68.25 (P=0.001)	77.25 (p=0.001)
Deogaonkar	2016	1	15	15	22.87±1.88	22.80±1.86	7.07±0.26	7.47±0.64	8.33±0.49	8.47±0.52	101.6±12.66	117.33±14.31	103.33±8.57	112.73±6.42
Karbasy	2016	1	45	45	28.6±5	30.1±5.9	8.6±0.6	8.4±0.5	9.4±0.6	9.7±0.3	109.2±16.9	115.9-±15.5	108±21	120±20

HR: Hear Rate; MAP: Mean Arterial Pressure.

Table 3. Assessment of risk of bias.

Study	Other Bias	Selective Reporting	Incomplete Outcome Data	Blinding of the Outcome Assessment	Blinding of the Participants/Personnel	Allocation Concealment
Magsoudloo	L	L	L	L	L	UC
Deogaonkar	L	L	L	L	L	UC
Karbasy	L	L	L	L	L	UC

L: Low; UC: Un Clear.

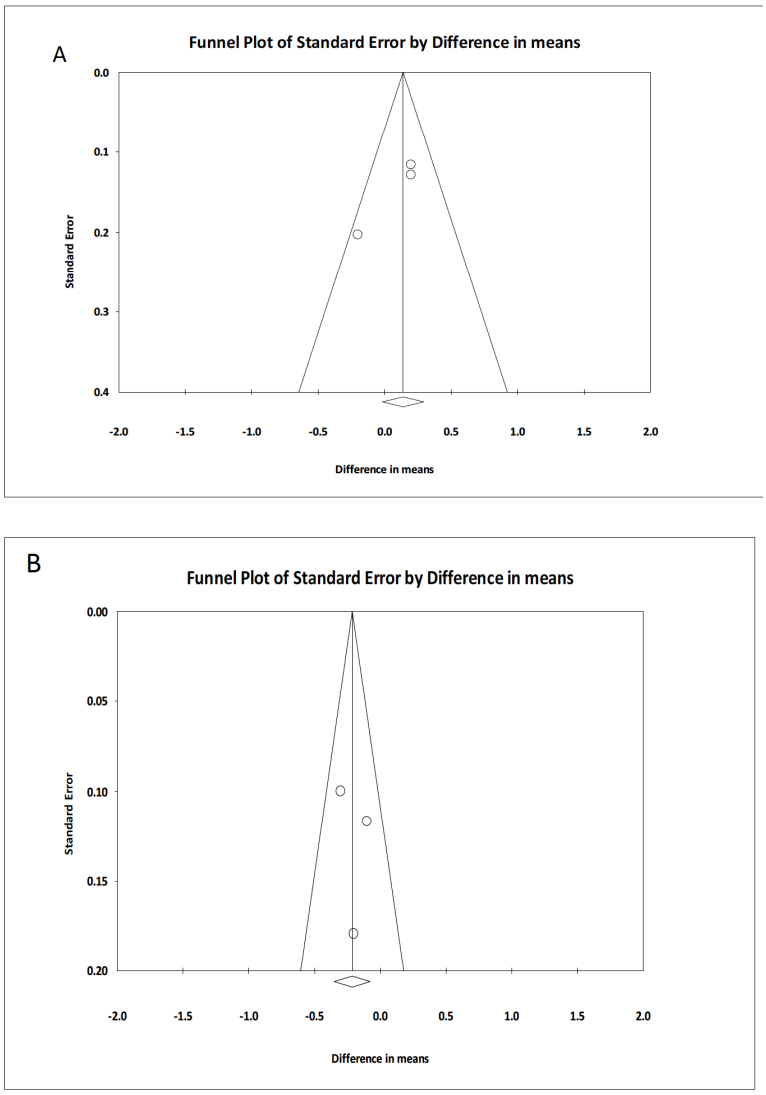

Fig. (2). Begg's Funnel Plot of (**A**): fentanyl use and 1 minute Apgar score (**B**): fentanyl use and 5 minute Apgar score.

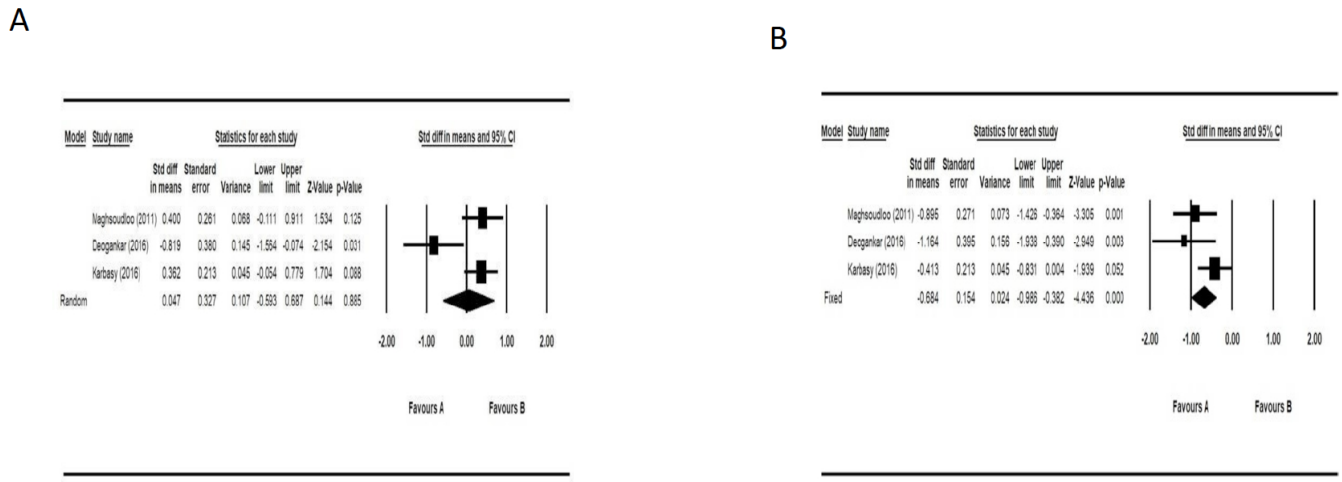

Fig. (3). Meta-analysis on neonatal outcomes: (**A**): Pooled analysis of 1 minute Apgar score: Random effect model (**B**): Pooled analysis of 5 minute Apgar score: Fixed effect model.

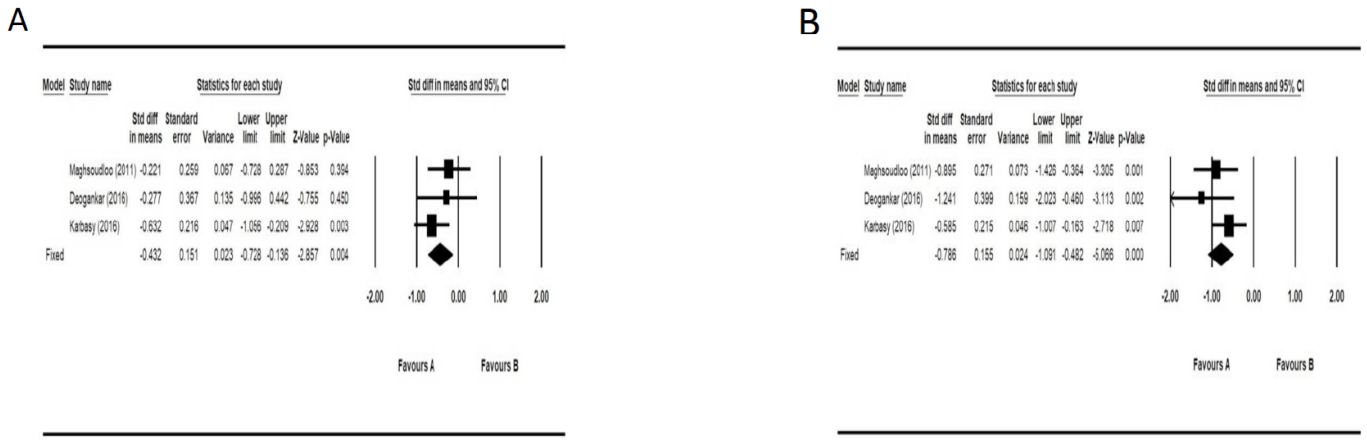

Fig. (4). Meta-analysis on maternal outcomes: (**A**): pooled analysis of Heart rate: Random effect model (**B**): pooled analysis of Mean arterial pressure (MAP): Fixed effect model.

at 1 minute (SMD 0.04, 95%CI: -0.59, 0.68, p=0.88) (Fig. **3A**). However, the Apgar score of 5 minutes was significantly lower in fentanyl group compared with placebo group (SMD -0.68, 95%CI: -0.98, -0.38, p<0.001) (Fig. **3B**).

3.4. Meta-analysis of Maternal Hemodynamics

Two indices of maternal effect including mean arterial pressure and heart rate were included in the meta-analysis. In the case of heart rate, we did not identify statistical heterogeneity (Q-value=4.22, p=0.12, I2=52.61%), so, the fixed effect model was used. The results indicated that the heart rate in fentanyl group was significantly lower compared with placebo group (SMD -0.43, 95%CI: -0.72, -0.13, p=0.004) (Fig. **4A**).

In case of mean arterial pressure, considering the identification of no statistical heterogeneity between studies, fixed effect model was used. The results showed that, compared with the placebo group, the mean arterial pressure in fentanyl group was significantly lower (SMD -0.78, 95% CI: -1.09, -0.48, p<0.001) (Fig. **4B**).

4. DISCUSSION

To the best of our knowledge, this is the first systematic review and meta-analysis aimed to compare the maternal and neonatal effect of 1 (µg/kg) intravenous fentanyl as a premedication before induction of general anesthesia in cesarean section and the results showed that using fentanyl in cesarean section had no adverse effect on 1 minute Apgar score. However, 5 minute Apgar score was significantly lower in fentanyl group compared with placebo group. All included studies in the present meta-analysis showed that the 5-minutes Apgar score in fentanyl group was lower compared to placebo. Other studies conducted by other opioids such as Nalbuphine [5] and remifentanyle [12] also showed the adverse effects of opioids on Apgar score of neonates. Fentanyl is a lipid soluble opioid and it rapidly crosses the placenta [13]. Fentanyl is detectable in neonate blood as early as 1 minute after maternal injection [14]. So, these results suggest that fentanyl may have a significant adverse effect on neonate 5-minute Apgar score.

The results of the present meta-analysis also showed that 1-minute heart rate and also MAP in fentanyl group was significantly lower compared with placebo in cesarean section. Flacke *et al*. demonstrated that fentanyl alone could induce hypotension by reducing sympathetic outflow and that its effects are mediated by the ANS [15]. Sympathomimetic effects of intubation in cesarean delivery may result in increasing in mean arterial pressure and heart rate [11]. Fentanyl has a potent sympatholytic effect even at low doses and reduces the autonomic nervous system activity, and through this mechanism, it confronts with sympathomimetic effects of intubation [16].

Similar to any other systematic reviews, the low risk of subjective data selection is one of the most important advantages of our systematic review. Nevertheless, our analysis has some limitations. First, the publication bias could not be fully excluded, *i.e*. negative findings being less likely to be published. Second, any systematic review is only as good as the included studies. Only a few trials were included in our systematic review which were conducted in developing countries (Iran and Sri Lanka). So, the generalizability of results is limited. Other potential limitations included small sample size and unclear allocation concealment.

CONCLUSION

In summary, the present meta-analysis showed that using 1 (μg/kg) intravenous fentanyl as a premedication before induction of general anesthesia in cesarean section has an adverse effect on neonate Apgar score. However, it had a sympatholytic effect, through that, confronting with sympathomimetic effects of intubation

FUNDING

The study was funded by "Research Center for Evidence Based Medicine (RCEBM) (Grant No.:100/12), Tabriz University of Medical Sciences, Tabriz, Iran.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors wish to thank the Research Center for evidence-based medicine (RCEBM), Tabriz University of Medical Sciences, Iran for financial and scientific support.

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