Review Article

The Effects of Epinephrine, as a Supplement for Epidural and Spinal Anesthesia, on the Duration of Analgesia during Childbirth and Apgar Score: A Systematic Review and Meta-Analysis

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Abstract

Background: Labor pain is one of the most severe pains that woman may experience during their lifetime. **Objectives:** This study aimed to systematically review and meta-analyze studies into the effects of epinephrine on the duration of analgesia during childbirth and Apgar score. **Methods:** This systematic review was conducted in 2018. Data were collected through searching online databases, namely the PubMed, Scopus, Google scholar, SID, Medlib, Magiran, and Iranmedex. Inclusion criteria were an interventional design, comparison of the effects of epinephrine with other modalities on the duration of analgesia and Apgar score, and publication from January 1990 to October 2018 in English or Persian in peer-reviewed journals. Meta-analysis was performed using the fixed and the random effects models with a 95% confidence interval (CI). The *Q* and the I^2 statistics were used to assess heterogeneity, while the funnel plot and the Egger's test were used to evaluate the possibility of publication bias. **Results:** The standardized mean difference between the epinephrine and the comparison groups respecting the duration of analgesia was 0.65 (95% CI: 0.32–0.98). This difference was statistically significant ($P < 0.05$). The between-group standardized mean differences respecting the total, 1 min, and 5-min Apgar scores were −0.33 (95% CI: −0.97–0.30), −0.26 (95% CI: −1–0.47), and −0.54 (95% CI: −1.79–0.70), respectively. None of these differences was statistically significant ($P > 0.05$). **Conclusion:** Epinephrine increases the duration of analgesia without causing serious side effects.

Keywords: *Childbirth, Epinephrine, Labor, Obstetric, Pain, Systematic review*

Introduction

Normal vaginal delivery (NVD) is the best route of childbirth. Yet, its rate has reduced in recent years,

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causing great concerns in maternal healthcare.[1] Labor pain is one of the main reasons behind the reduced rate of NVD.[2] After causalgia and mutilation-related pain, labor pain is considered as the third most severe pain a woman may experience during her life.[3,4] The severity of labor pain has even been reported to be the same as the severity of mutilation-related pain.[5]

Various methods have been developed to reduce labor pain and discomfort,[6] including nitrous oxide, narcotics, anesthetics,[7-11] epidural block, and spinal anesthesia.[8] Spinal anesthesia, epidural anesthesia, or a combination of them produces deeper analgesia[12] and allows the parturient to be conscious and cooperate in delivery. Compared with general anesthesia, spinal and epidural anesthesia need smaller amounts of anesthetics and are associated with lower side effects and complications.[13] For instance, they are less likely to cause aspiration, pneumonia, and depression due to fetal death.[13,14]

Epinephrine, as a supplement for epidural and spinal anesthesia, can cause regional vasoconstriction and thereby prolongs the absorption of anesthetics and generates longer analgesia.[15-17] However, some studies demonstrated that the intrathecal co-administration of epinephrine and sufentanil had no significant effects on the duration of analgesia among parturient women.[18] Moreover, because of their small sample sizes, studies in recent years provided no comprehensive view about the effects of epinephrine as a supplement for epidural and spinal anesthesia. Therefore, a systematic review is needed to provide firmer evidence in this area.

Objectives

The aim of this study was to systematically review and meta-analyze studies into the effects of epinephrine on the duration of analgesia during childbirth and Apgar score.

Methods

This systematic review and meta-analysis were conducted in 2018 based on the preferred reporting items for systematic reviews and meta-analyses statement.[19] As this study was conducted on already published studies, ethical approval was not necessary. The PICOS of the study were as follows: Population: Parturient women; Intervention: Epidural or spinal administration of epinephrine as a supplement for anesthesia; Comparison: Nonintervention or nonepinephrine group; Outcome: Duration of analgesia and Apgar score; Study design: Interventional.

Data collection

Study data were collected through searching the PubMed, Scopus, SID, Medlib, Magiran, and Iranmedex online databases. Search keywords were epinephrine, labor, pain, obstetric, childbirth, analgesia, and Apgar. The Boolean operators AND, OR, and NOT were used to combine or limit search results. The search protocol was limited to January 1990–October 2018. The reference lists of the retrieved studies were also assessed to retrieve relevant studies. Two reviewers independently screened the titles and the abstracts of the retrieved studies for eligibility. The studies were managed using the EndNote X5 (Thomson Reuters, New York, NY, USA), where duplicate records were identified and excluded. Studies were included if they had been conducted using an interventional design, had compared the effects of epinephrine with other modalities on the duration of analgesia and Apgar score, and had been published in English or Persian in peer-reviewed journals.

Quality appraisal and data extraction

The quality of the retrieved studies was independently appraised by two reviewers using the Consolidated Standards of Reporting Trials 2010 checklist. This checklist consists of 37 items to assess the following six main areas as follows: title and abstract, introduction, methods, results, discussion, and other information.[20] Its total score can range from 1 to 37. The 75% cutoff point of compliance has been used as an adequate measure of compliance in the study.

A data extraction table was designed with the following main items as follows: author name, publication year, country, sample size, study design, duration of analgesia (minutes), Apgar score, and author conclusion. Data from the included studies were extracted and are summarized in Table 1.

Data analysis

The Comprehensive Meta-Analysis software (CMA; Englewood, NJ, USA) was employed to estimate the duration of analgesia and Apgar score in the epinephrine and the comparison groups. Meta-analysis was performed with a confidence level of 95% using the fixed and random effects models. The Q and the I^2 statistics were used to assess heterogeneity, where an I^2 statistic of 50% or more was interpreted as heterogeneity. The funnel plot was also used to evaluate the possibility of publication bias. It is a useful tool to visually evaluate potential publication bias.[21] Publication bias was also assessed through the Egger's test.

Results

Among the 245 screened studies, eight were eligible for this study and included in our systematic review and meta-analysis [Figure 1]. These eight studies had been conducted in the United States (three studies), Iran (two studies), Belgium (two studies), and Japan (one

Table 1: The characteristics of the included studies

Authors, years of publication	Country	Sample size and age mean		Study design	Analgesia duration (min)		1- and 5-min Apgar scores		Author conclusion
		Epinephrine	Comparison		Epinephrine	Comparison	Epinephrine	Comparison	
Golfam *et al.*, 2011[15]	Iran	45	45	Quasi-experimental	173	143	M1: 7.8 ± 1.5 M5: 9.3 ± 0.6	M1: 7.4 ± 1.5 M5: 9.1 ± 0.5	Adding epinephrine to sufentanil and bupivacaine seems to increase analgesia duration without sensory alteration
Connelly *et al.*, 2011[22]	USA	30 25 ± 6	30 25 ± 6	Randomized double-blind trial	221 ± 111	159 ± 62			Compared with the administration of 0.625 mg/mL bupivacaine at a rate of 10 mL/h, the administration of 0.625 mg/mL bupivacaine with epinephrine 5 µg/mL at a rate of 10 mL/h provides longer analgesia, alleviates pain, has no significant effects on labor duration, and exerts no serious side effects
Soetens *et al.*, 2006[23]	Belgium	34 28 ± 4	33 29 ± 4	Prospective randomized double-blind trial			M1: 7 (3-9) M5: 8 (6-10)	M1: 8 (6-10) M5: 9 (8-10)	Epinephrine intensifies the effects of epidural levobupivacaine and sufentanil but may cause more motor block
Jabalameli and Zahiri, 2005[12]	Iran	30 25 ± 5	30 22 ± 4	Clinical trial	95.3 ± 18.2	81.2 ± 15.1			Intrathecal administration of low-dose epinephrine with bupivacaine and fentanyl can prolong analgesia duration and relieve pain intensity without any maternal or fetal side effects
Okutomi *et al.*, 2003[24]	Japan	54 31 ± 4	54 31 ± 4	Double-blind randomized clinical trial			M1: (7-10) M5: 9 (8-10)	M1: 9 (8-9) M5: 9 (8-10)	The addition of epinephrine to intrathecal bupivacaine-fentanyl reduces the need for additional epidural analgesia without increasing the rates of hypotension, nausea, or pruritus. Yet, it may increase the incidence of motor block
Vercauteren *et al.*, 2001[16]	Belgium	23 29 ± 7	21 29.5 ± 6	Clinical trial	93.2 ± 24.2	79.3 ± 18.1			Epinephrine in a dose of 2.25 µg significantly prolongs the duration of intrathecal analgesia of bupivacaine-sufentanil by 15 min
Camann *et al.*, 1993[18]	USA	20 29 ± 5	20 28 ± 5	Randomized blind trial	95 ± 45	109 ± 56			Intrathecal sufentanil at a dose of 10 µg, with and without epinephrine, provides rapid-onset short-duration analgesia during labor. Epinephrine does not prolong the duration of intrathecal sufentanil analgesia. Epinephrine addition increases nausea incidence and decreases pruritus incidence and severity
Grice *et al.*, 1990[25]	USA	50 24 ± 1.1	50 23 ± 0.9	Randomized clinical trial	180	138			The addition of epinephrine 3.33 µg/mL significantly increases the duration of analgesia induced by 0.25% bupivacaine with 5 µg/mL fentanyl

study) and had been published between 1990 and 2011 [Table 1].

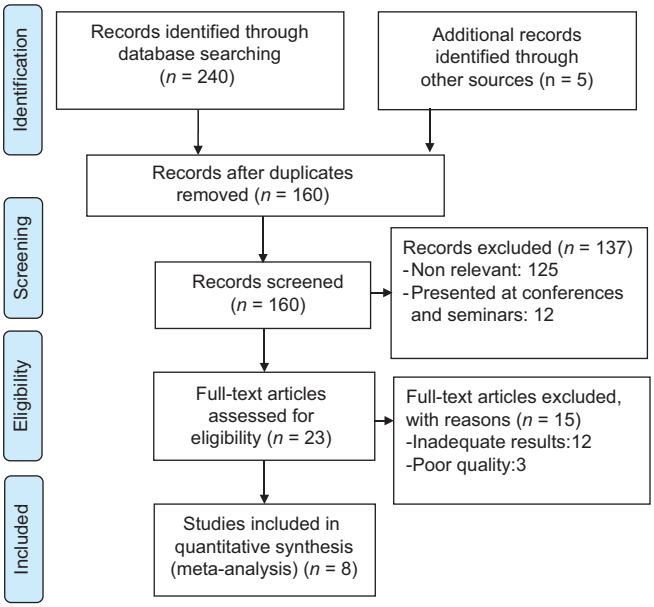


Figure 1: The flow diagram of the study

The standardized mean difference between the epinephrine and the comparison groups respecting the duration of analgesia based on the random-effects model was 0.65 [95% confidence interval [CI]: 0.32–0.98, Q = 12.5, df = 5, P = 0.02, and I^2 = 60; Figures 2 and 3]. This difference was statistically significant (P < 0.05). Because of heterogeneity in the results of the included studies, sensitivity analysis was conducted after excluding the study conducted by Camann *et al*.[18] Results showed that after sensitivity analysis, the standardized mean difference between the epinephrine and the comparison groups respecting the duration of analgesia based on the fixed effects model was 0.82 [95% CI: 0.61–1.04, Q = 1.8, df = 4, P = 0.76, and I^2 = 0.00; Figure 3]. This difference was also statistically significant (P < 0.05).

Respecting total Apgar score, the standardized mean difference between the epinephrine and the comparison groups based on the random-effects model was −0.33 [95% CI: −0.97–0.30, Q = 79.5, df = 5, P < 0.001, and I^2 = 93.7; Figure 4]. This difference was

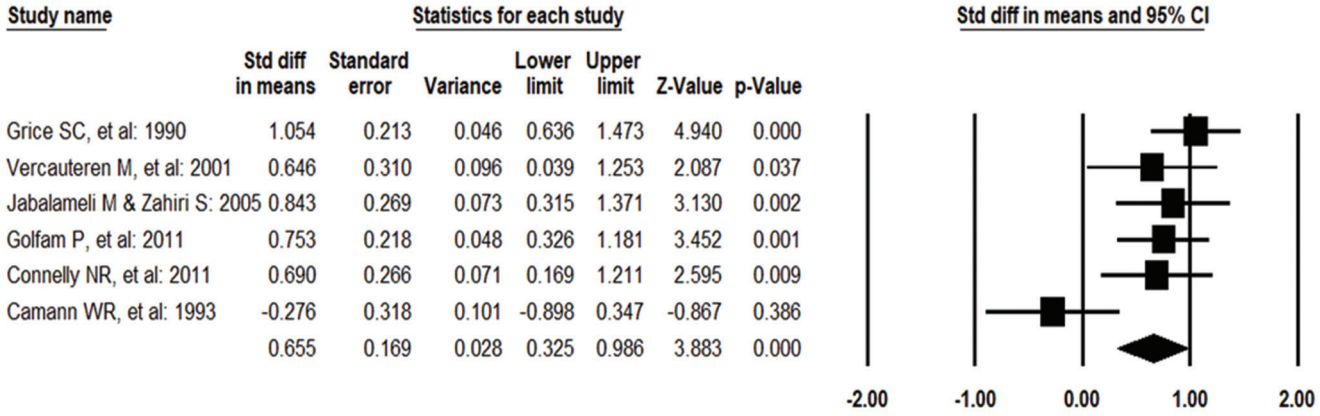


Figure 2: Standardized mean difference between the epinephrine and the comparison groups respecting the duration of analgesia

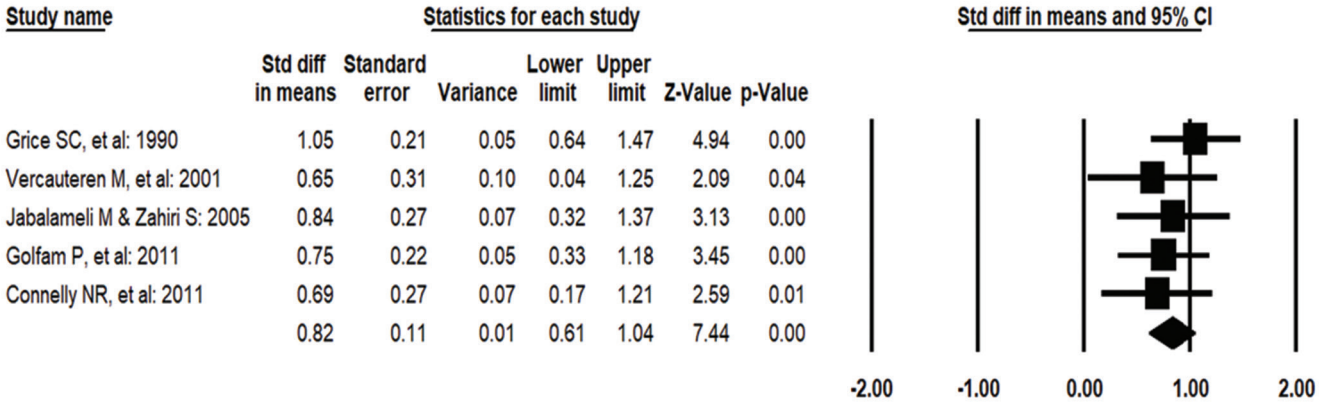
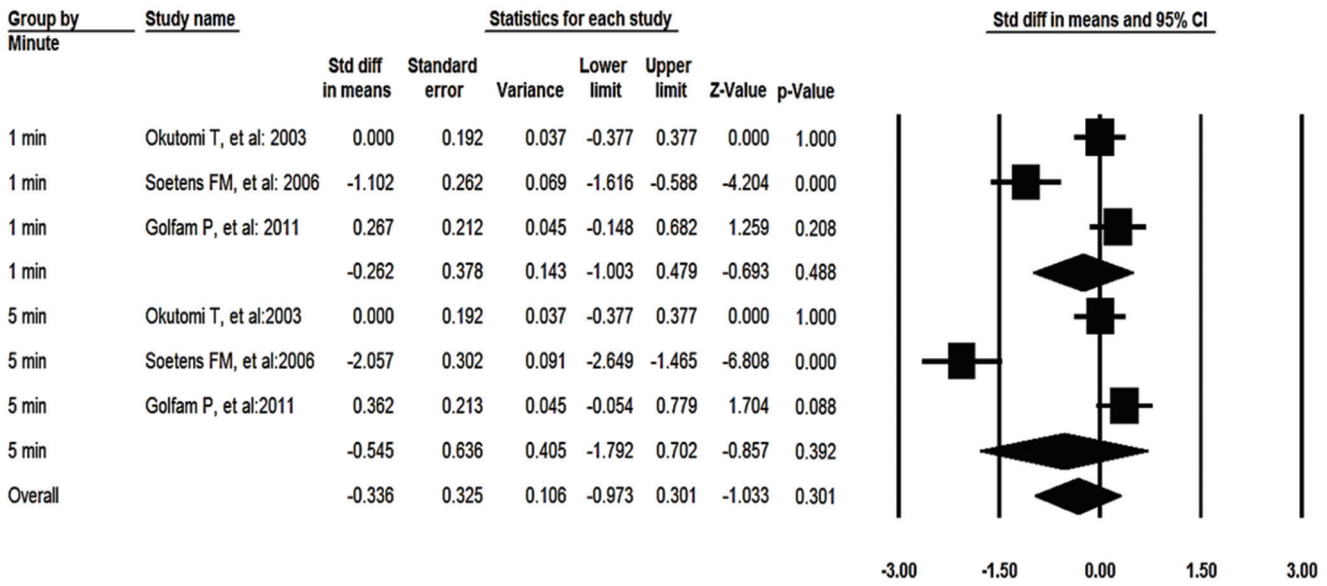


Figure 3: Standardized mean difference between the epinephrine and the comparison groups respecting the duration of analgesia after sensitivity analysis (the study of Camann *et al*. was excluded)



Group by Minute	Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
1 min	Okutomi T, et al: 2003	0.000	0.192	0.037	-0.377	0.377	0.000	1.000
1 min	Soetens FM, et al: 2006	-1.102	0.262	0.069	-1.616	-0.588	-4.204	0.000
1 min	Golfam P, et al: 2011	0.267	0.212	0.045	-0.148	0.682	1.259	0.208
1 min		-0.262	0.378	0.143	-1.003	0.479	-0.693	0.488
5 min	Okutomi T, et al:2003	0.000	0.192	0.037	-0.377	0.377	0.000	1.000
5 min	Soetens FM, et al:2006	-2.057	0.302	0.091	-2.649	-1.465	-6.808	0.000
5 min	Golfam P, et al:2011	0.362	0.213	0.045	-0.054	0.779	1.704	0.088
5 min		-0.545	0.636	0.405	-1.792	0.702	-0.857	0.392
Overall		-0.336	0.325	0.106	-0.973	0.301	-1.033	0.301

Figure 4: Standardized mean difference between the epinephrine and the comparison groups respecting Apgar score

not statistically significant ($P > 0.05$). Moreover, the between-group standardized mean difference respecting the 1-min Apgar score was − 0.26 (95% CI: −1–0.47, $Q = 17.7$, df = 2, $P < 0.001$, $I^2 = 88.6$). This difference was not statistically significant ($P > 0.05$). Finally, the between-group standardized mean difference respecting the 5-min Apgar score was −0.54 (95% CI: −1.79–0.70, $Q = 61.7$, df = 2, $P < 0.001$, and $I^2 = 96.7$). This difference was also statistically insignificant ($P > 0.05$). The funnel plot [Figure 5] and the results of the Egger's test ($P > 0.05$) revealed no evidence of publication bias in the studies.

Discussion

Results showed that epinephrine enhances the effects of local anesthetics and the duration of local analgesia during childbirth. Adding epinephrine to the anesthetics used for local anesthesia during childbirth can produce different effects. Epinephrine prolongs and intensifies the effects of local anesthetics and decreases their systematic absorption[26] through inducing peripheral vasoconstriction.[23] Thereby, it can reduce the use of anesthetics during local anesthesia.[27] Similarly, an earlier study reported that the epidural administration of epinephrine 1:300,000 (66 μg) resulted in a significant 29% reduction in the minimum local analgesic concentration of bupivacaine.[28] Another study also suggested that adding epinephrine to the combination of standard intrathecal doses of bupivacaine and fentanyl in combined spinal–epidural anesthesia for labor significantly prolonged spinal analgesia.[29] Moreover, a study concluded that epinephrine in a small dose of 2.25 μg brought about a 15 min increase in the duration of intrathecal analgesia induced by bupivacaine-sufentanil. That study also noted that diluting the commercially available bupivacaine 0.5% with epinephrine 1:200,000 may eliminate the need for freshly prepared epinephrine solutions.[16] Combination of opioid with a local anesthetic and epinephrine not only helps reduce the doses of each of these medications without any change in analgesia quality or duration, but also reduces their side effects.[30]

Epinephrine may cause side effects such as nausea, vomiting, itching, and fluctuations in heart rate and blood pressure among parturient women and also fluctuations in Apgar score among their infants. However, the results of the present study showed that though the Apgar score in the epinephrine group was slightly less than the comparison group, the difference was not statistically significant. The studies reviewed in the present study also reported that epinephrine had no significant effects on nausea and vomiting,[13] itching, pain intensity,[15] maternal heart rate,[12,23] maternal blood pressure,[12,15,23] and fetal heart rate.[15,23] Yet, a study reported higher nausea and vomiting rate in the epinephrine group.[15] The use of labor pain management techniques which have no serious side effects can increase parturient women's childbirth satisfaction.[31] Given the contradictory results of previous studies about the side effects of epinephrine for local anesthesia during labor, further evidence-based studies are still needed to produce conclusive evidence in this area and to help determine the safest and the most effective local anesthesia protocol for childbirth.[32]

Among the limitations of the present study were the inaccessibility of some databases and the inclusion of

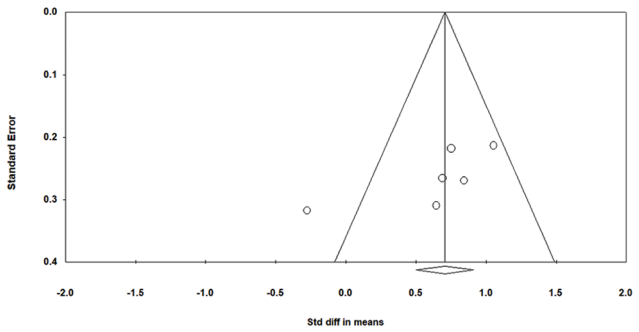


Figure 5: The funnel plot of standard error by standardized mean difference

studies which had been published only in English or Persian. Moreover, subgroup analysis was impossible due to the small number of the reviewed studies.

Conclusion

This systematic review and meta-analysis suggest that without causing serious side effects, epinephrine can significantly increase the duration of local anesthesia. Thereby, it can facilitate labor pain management, enhance women's birth satisfaction, promote their acceptance of NVD, reduce their stress and anxiety, and improve maternal and infantile health-related outcomes. Obstetricians and gynecologists can use the results of the present study to make wiser decisions about the best labor pain management methods.

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Conflicts of interest

There are no conflicts of interest.

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