Is Pethidine Safe during Labor? Systematic Review

A petidina é segura durante o trabalho de parto? Revisão sistemática

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Abstract

Purpose To verify if pethidine is safe for the conceptus when used during labor.
Methods Systematic review in the Capes Periodicals/PubMed and MEDLINE/Virtual Health Library (BVS, in the Portuguese acronym) databases.
Results A total of 17 studies published from January 1st, 2000, to September 2nd, 2016, with a total of 1,688 participants involved were included in the present review. There was no record of conceptus vitality decrease associated with low doses of pethidine being administered to mothers during labor.
Conclusions Intramuscular (IM) or intravenous (IV) pethidine at low doses, of up to 50 mg, is safe to administer during labor.

Keywords
- pethidine
- safety
- labor

Resumo

Objetivo Verificar se a petidina é segura para o concepto quando utilizada durante o trabalho de parto.
Método Revisão sistemática nas bases de dados dos Periódicos Capes/PubMed e MEDLINE/Biblioteca Virtual em Saúde (BVS).
Resultados Um total de 17 estudos, publicados de 1° de janeiro de 2000 a 2 de setembro de 2016, totalizando 1.688 participantes envolvidos, foram incluídos nesta revisão. Não houve registro de depressão na vitalidade dos conceptos com doses baixas de petidina administradas às mães durante o trabalho de parto.
Conclusão Petidina intramuscular (IM) ou intravenosa (IV) em baixas doses, de até 50 mg, é segura durante o trabalho de parto.

Palavras-chave
- petidina
- segurança
- trabalho de parto

Introduction

Strictly speaking, all drugs cause changes of different magnitudes and with variable duration in the maternal and/or fetal organism. In order for a drug to be considered safe to be used during labor, it must be unable to cause deleterious changes that could result in any sequel to the mother or her conceptus.

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Labor pain is described as strong in 40 to 70% of cases.[1,2] Intense suffering is usual in many parturients. Science has been trying to solve this problem for centuries; however, progress has been slow in achieving this goal. Since the 19th Century, medicine has used systemic analgesics during labor[3], but, even after nearly 200 years, medicine has not found any potent, safe, easy to use and affordable drug to be administered during this period.

The side effects of the drugs used during pregnancy have always been a medical concern. A drug that is safe for the mother can be harmful to the conceptus because of its immaturity. Therefore, the use of any drug should take into account maternal and fetal safety.[4]

For the past 50 years, the gold standard in labor analgesia has been continuous epidural anesthesia.[5] When it is not available, contraindicated or refused, opioids are the best option.[6] Pethidine is an opioid derivative first synthesized in 1939 in Germany.[7] Like any drug, it has its potency and its side effects related to the administered dose. During labor, pethidine may be administered intravenously (IV, at doses between 25–50 mg) or intramuscularly (IM, at doses between 50–100 mg).[8] It has been used for 76 years in labor analgesia, with various dosages and routes of administration.[9] It is a low-cost and easy to handle analgesic.[10] However, its use has been widely questioned because of the possible side effects on the conceptus, mainly respiratory depression.[11,12] Traditionally, asphyxia and respiratory depression in newborns are measured by means of clinical and laboratorial analyses of the Apgar score, the pH and the blood gases (hypoxemia and hypercapnia).[13] This drug has not been correlated with significant negative impacts on the maternal organism when administered in moderate doses during labor.[14]

After analyzing conflicting studies about the safety of pethidine for the conceptus, many services are decreasing or abolishing its use during labor.

This systematic review aims to compare the results of 17 studies involving pethidine use during labor. The purpose is to verify if pethidine is safe for the conceptus.

Methods

This systematic review was conducted through a search for publications indexed in the Capes Periodicals/PubMed and MEDLINE/Virtual Health Library (BVS, in the Portuguese acronym) databases and published from January 1st, 2000, to September 2nd, 2016. The following keywords were used alone or combined with each other: *pethidine in labor*. A total of 243 articles were found. The exclusion criteria were: a) repeated articles; b) systematic review articles; c) lack of evaluation of conceptus vitality; d) studies using pethidine associated with promethazine; e) sample size below 25 patients; f) articles whose participants were not given pethidine IV or IM; g) non-randomized articles, h) meta-analysis articles; and i) articles of very restricted access.

Systematic reviews and meta-analyses were excluded to avoid duplication in the data analysis; articles with less than 25 patients were not included because they are more prone to erroneous conclusions; non-randomized studies were left out of the review because they have less reliable results, and studies in which promethazine was administered were excluded because promethazine can cause respiratory depression in the newborn.[15]

After exclusion of 68 duplicated articles, 175 were selected; of these, 11 were excluded because they were systematic reviews; 3 articles did not assess the conceptus vitality; 4 were excluded because they used promethazine; 3 studies were excluded because they had less than 25 participants; 123 articles were excluded for not using pethidine IV or IM in labor analgesia; 6 articles were non-randomized, and 8 were excluded for being of very restricted access. Finally, 17 articles were analyzed for the present review, being 10 free-access articles and 7 restricted-access articles (►**Fig. 1**).

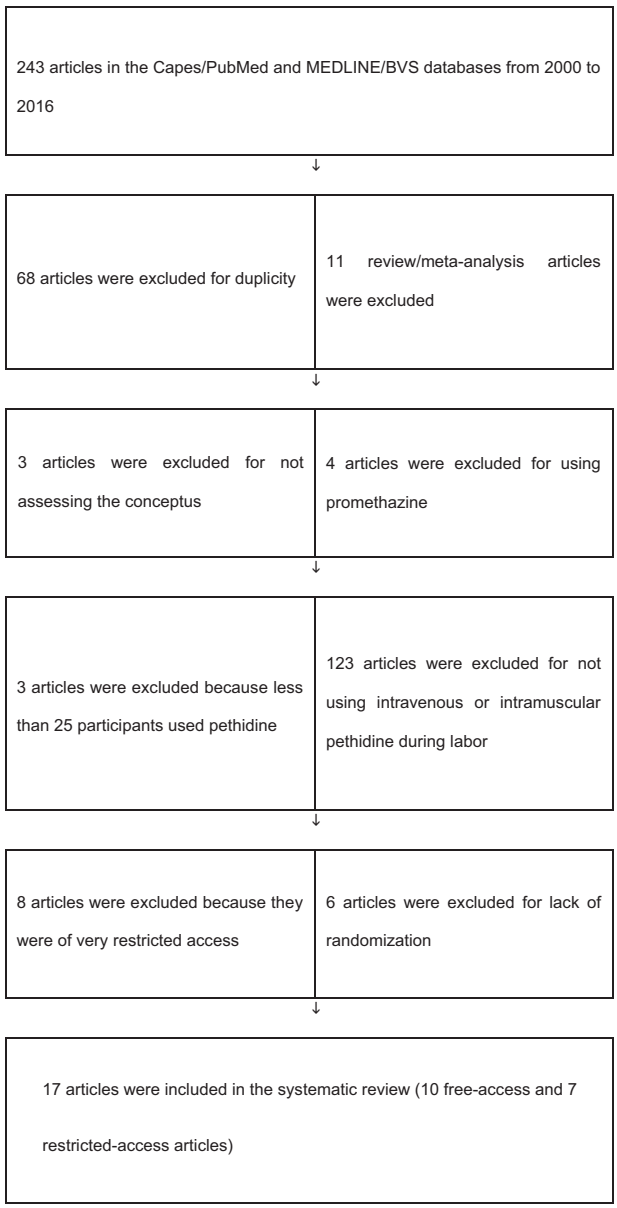

Fig. 1 Flow chart of the excluded and selected articles.

Table 1 Analyzed articles

Author, publishing date	Type of study/country	N	Dose/route of administration	Neonatal outcomes
El-Refaie et al[16] 2012	RCT/ Egypt	120	50 mg/IV	Pethidine x placebo. There were no differences in Apgar scores (7.4 × 7.7), respiratory depression, pH, and arterial blood gases of the NBs.
Khooshideh and Shahriari[17] 2009	RCT/Iran	80	50 mg/IM	Pethidine x tramadol. All Apgar scores at 1 and 5 minutes were > 7. There were 3 cases of fetal distress (2 participants had been given pethidine).
Allameh et al[18] 2015	RCT/ Iran	30	50 mg/IM	Pethidine x acupuncture x placebo. The Apgar scores were 8/9 in the 3 groups. There were no differences in the number of NBs who passed meconium.
Yilmaz et al[19] 2009	RCT/ Turkey	48	50 mg/IV	Pethidine x valethamate x placebo. There were no differences in the number of NBs who passed meconium or the number of Apgar scores at 1 or 5 minutes < 7.
Sekhavat and Behdad[20] 2009	RCT/ Iran	75	50–75 mg/IM	Pethidine x placebo. There was a decrease in the variability of the fetal heart rate. There were no significant adverse effects on the NBs.
Ng et al[21] 2011	RCT/ China	34	50–75 mg/IM	Pethidine x remifentanil. The Apgar scores were 8/9. No complications were reported.
Elbohoty et al[22] 2012	RCT/ Egypt	50	50 mg/IV	Pethidine x paracetamol. The Apgar scores at 1 minute were lower in the group using pethidine (6 × 7). All Apgar scores at 5 minutes were 9. No adverse effects or admissions to the intensive care unit were reported.
Fleet et al[23] 2015	RCT/ Australia	51	100 mg/IM, every 3 hours	Pethidine x fentanyl. Apgar score at 1 and 5 minutes was 9 for both groups. There was a higher number of NBs admissions to the nursery with pethidine.
Loughnan et al[24] 2000	RCT/ England	213	100 mg/IM, every 2 hours	Pethidine x epidural. No differences in the number of Apgar scores < 9 at 5 minutes.
Keskin et al[25] 2003	RCT/ Turkey	29	100 mg/IM	Pethidine x tramadol. The Apgar scores of both groups were > 7/9. There were no differences in Apgar scores number of the respiratory depression. There were 3 cases of respiratory depression in the NBs of the participants who were given pethidine (10.3%).
Wee et al[26] 2014	RCT/ England	240	150 mg/IM	Pethidine x diamorphine. The Apgar at 1 minute was < 7 in 15% of the participants who were given pethidine, and there was need for resuscitation in 19% of the participants.
Sosa et al[27] 2004	RCT/ Uruguay	205	100 mg/IV	Pethidine x placebo. There was respiratory depression and acidosis in the NBs whose mothers were given pethidine.
Sharma et al[28] 2002	RCT/ United States	207	50 mg/IV + 15 mg/IV, every 10 minute, limited to 100 mg every 2 hours	Pethidine x epidural. There were no differences in arterial blood pH between the two groups. In the group that was given pethidine, Apgar scores < 7 at 1 minute were more frequent.
Sosa et al[29] 2006	RCT/ Uruguay	189	100 mg/IV	Pethidine x placebo. There was no association between pethidine and acidosis in the NBs.

Table 1 (*Continuation*)

Author, publishing date	Type of study/country	N	Dose/route of administration	Neonatal outcomes
Tsui et al[30] 2004	RCT/ China	25	100 mg/IM	Pethidine x placebo. There were no differences in the pH of the umbilical vein. The number of Apgar scores < 7 at 1 and 5 minutes was equal.
Douma et al[31] 2010	RCT/ Netherlands	53	49,5 mg/IV + 5 mg/IV, every 5 minutes	Pethidine x fentanyl x remifentanil. The Apgar scores with pethidine were 8.6/9.7. Those using pethidine had umbilical cord IV, blood with pH 5/5 minute 7.21 (0.1)-limitary and NACS 36.8 (2.1)-limitary.
Jain et al[32] 2003	RCT/ India	39	50–75–100 mg/IM	Pethidine x epidural x tramadol. There were no differences in the Apgar scores at 1 and 5 minutes among the three groups. Umbilical cord pH was similar in all groups.

Abbreviations: IM, intramuscular; IV, intravenous; N, size of the sample who was given pethidine; NACS, neurological and adaptive capacity score (normal: > 35); NBs, newborns; RCT, randomized clinical trial.
Note: Normal pH of the umbilical vein: between 7.20 and 7.45.

Results

The 17 remaining articles, which included a total of 1,688 participants to whom pethidine was administered during labor, were analyzed (►**Table 1**). The publications were from countries located in Europe, Asia, South America, North America, Oceania and Africa. They were grouped in order according to the drug dosages administered (from the lowest to the highest dosages) to facilitate the analysis. There was a wide variation in the number of participants in each study, from 25 to 240. Seven articles compared pethidine with placebo (totaling 692 participants), and 10 articles compared pethidine with another analgesic drug (totaling 996 participants). Even when compared with other drugs, it was possible to analyze the safety of pethidine for the conceptus when it was administered during labor.

Discussion

More than 70% of the 17 studies were concentrated in Asia, Africa and Latin America (Iran: 03; Turkey: 02; Egypt: 02; China: 02; India: 01; and Uruguay: 02). Most studies involving pethidine in labor analgesia are conducted in the developed countries of North America or Europe. Emerging countries are more concerned in seeking options for labor analgesia.

A total of 10 articles were published in the past 7 years. The 7 articles in which pethidine was administered at a dose of 50 mg were published in the past 7 years. The articles show that currently there is a tendency to use lower doses of pethidine.

Several articles provided incomplete data for an optimal analysis. Some articles did not publish the Apgar scores; others articles did not report how many newborns required cardiopulmonary resuscitation, admission to the nursery or intensive care unit (ICU). An ideal evaluation of newborn vitality should include at the same time: the Apgar score; the need for ventilator assistance; and an analysis of the umbilical vein blood, to determine the pH and the blood gases. The analysis of some of these parameters alone or partially combined may not show the correct answer to the harm caused by the use of certain medications.

During the evaluation of neonatal outcomes, the following clinical and/or laboratory criteria were used: presence of respiratory depression; need for resuscitation; Apgar score; pH; hypoxemia; and hypercapnia. Only one study used the neurological and adaptive capacity score (NACS), which is inaccurate and unreliable.[33]

More than one variable was used in 88% of the articles to analyze the safety of pethidine, and 82% of them used the Apgar score to assess the newborns. Although the Apgar score may have a minor subjective aspect, it is easy to use, and is widely adopted in the evaluation of newborns.

The Apgar score was devised in 1952 by Virginia Apgar, an American anesthesiologist. It consists of 5 parameters, which can receive scores from 0 to 2: pulse rate; respiratory effort; activity; reflex reaction; and skin color. ►**Table 2** shows the parameters of the Apgar score. It is the most widely used assessment of neonatal vitality, as it is quick and easy to perform. The 1-minute Apgar score is related to birth conditions, and the 5-minute Apgar score regards the prognosis of the newborn. Ideally, both the 1-minute and 5-minute Apgar score must be > 7.[34]

A study in Egypt, in which 50 mg of IV pethidine was administered to 120 pregnant women in labor, showed that there were no changes in the vitality of the newborns compared with placebo. The Apgar scores were similar, and all above 7; the pH and the arterial blood gases of the newborns were equal, and there was no record of respiratory depression. The results of this study lead us to conclude that

Table 2 Apgar score

Vital sign	0	1	2
Pulse rate	Absent	Low (below 100)	More than 100
Respiratory effort	Absent	Slow, irregular	Good, crying
Muscle tone	Flaccid	The presence of any bending of the ends	Active movements
Reflex reaction	No reaction	Grimace	Vigorous cry
Color	Blue, pale	Body pink, blue ends	Completely rosy

Source: Adapted from Apgar.[34]

pethidine is safe at this dose and with the route of administration used.

In 6 studies in which pethidine was administered at a dose of 50 mg IV or IM, there were no significant adverse effects on the newborns, and no Apgar scores < 7 were found.[16–21] Only in a survey using 50 mg of IV pethidine, the Apgar score at 1 minute was 6,[22] but without complications for the newborn or admissions to the ICU. These findings demonstrate that pethidine, IM or IV, is safe during labor at this dose.

In studies that used more than 50 mg of pethidine, IM or IV, there was inconsistency in the results: 3 of them (totaling 117 participants) concluded it was safe;[30–32] and 7 studies (totaling 1,134 participants) found correlations with alterations in the newborn, especially respiratory depression, low Apgar scores, or need for resuscitation.[23–29]

The number of participants who were given 50 mg of pethidine was 437, representing $\sim$ 26% of the total; this reflects the preference for researches employing more than 50 mg of pethidine, especially before 2006. Ideally, we need a study comparing pethidine at 2 doses: 50 mg and $>$ 50 mg, with the same number of participants in each group.

Depending on the habits of the population, such as the frequent use of certain drugs, the metabolism of pethidine can be faster among the inhabitants of some countries. As these were multicenter studies, there may be a variation in the side effects of pethidine associated with the observed pharmacological culture in the region.

As a rule, the risk of a drug depends on the route of administration and dose used. There is no harmless drug. The risk/benefit ratio should always be taken into account before administering pethidine.

Some studies used placebo and found lower Apgar scores than others that used pethidine.[16,31] This is due to the subjectivity in determining the Apgar scores in the different studies, which leads to some difficulty in comparing them.

Drugs such as pethidine should have a table listing increasing doses with the appearance of side effects. Thus, it would be easier to use these drugs, always taking into account their risks and benefits.

Conclusions

The administration during labor of IM or IV pethidine at low doses, of up to 50 mg, is safe for the conceptus. Doses above $>$ 50 mg should be avoided, since they require further studies to obtain definitive evidence.

Note

This study was conducted in partnership with Universidade de of Fortaleza (UNIFOR), through the access granted to the digital library of the institution. The authors are part of the MSc Academic Course in Medical Sciences at UNIFOR.

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