



## Systematic review

# Prolonging the duration of single-shot intrathecal labour analgesia with morphine: A systematic review



Hadeel Al-Kazwini<sup>a</sup>, Irene Sandven<sup>b</sup>, Vegard Dahl<sup>c,d</sup>, Leiv Arne Rosseland<sup>d,e,\*</sup>

<sup>a</sup> Department of Anaesthesia, Skien Hospital, Telemark Hospital Trust, Skien, Norway

<sup>b</sup> Oslo Centre for Biostatistics and Epidemiology, Research Support Services, Oslo University Hospital, Norway

<sup>c</sup> Department of Anaesthesia and Intensive Care Medicine, Akershus University Hospital, Loerensskog, Norway

<sup>d</sup> Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Norway

<sup>e</sup> Department of Research and Development, Division of Emergencies and Critical Care, Oslo University Hospital, Norway

## HIGHLIGHTS

- Meta-analysis of RCTs of duration of analgesia after spinal morphine during labour.
- Adding morphine ( $\leq 250$  mcg) to spinal bupivacaine + fentanyl or sufentanil may prolong pain relief.
- Spinal bupivacaine + morphine may be a cost effective alternative to epidural analgesia for labour-pain.

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## ABSTRACT

**Background and aims:** Single-shot spinal with bupivacaine plus fentanyl or sufentanil is commonly used as analgesia during labour, but the short duration limits the clinical feasibility. Different drugs have been added to prolong the analgesic duration. The additional effect of intra-theal morphine has been studied during labour pain as well as after surgery. We assessed whether adding morphine to intra-theal bupivacaine + fentanyl or sufentanil prolongs pain relief during labour.

**Methods:** Meta-analysis of placebo-controlled randomized clinical trials of analgesia prolongation after single-shot intrathecal morphine  $\leq 250$   $\mu$ g during labour when given in combination with bupivacaine + fentanyl or sufentanil. After identifying 461 references, 24 eligible studies were evaluated after excluding duplicate publications, case reports, studies of analgesia after caesarean delivery, and epidural labour analgesia. Mean duration in minutes was the primary outcome measure and was included in the calculation of the standardized mean difference. Duration was defined as the time between a single shot spinal until patient request of rescue analgesia. All reported side effects were registered. Results of individual trials were combined using a random effect model. Cochrane tool was used to assess risk of bias.

**Results:** Five randomized placebo-controlled clinical trials (286 patients) were included in the meta-analysis. A dose of 50–250  $\mu$ g intrathecal morphine prolonged labour analgesia by a mean of 60.6 min (range 3–155 min). Adding morphine demonstrated a medium beneficial effect as we found a pooled effect of standardized mean difference = 0.57 (95% CI: –0.10 to 1.24) with high heterogeneity ( $I^2 = 88.1\%$ ). However, the beneficial effect was statistically non-significant ( $z = 1.66$ ,  $p = 0.096$ ). The lower-bias trials showed a small statistically non-significant beneficial effect with lower heterogeneity. In influential analysis, that excluded one study at a time from the meta-analysis, the effect size appears unstable and the results indicate no robustness of effect. Omitting the study with highest effects size reduces the pooled effect markedly and that study suffers from inadequate concealment of treatment allocation and blinding. Trial quality was generally low, and there were too few trials to explore sources of heterogeneity in meta-regression and stratified analyses. In general, performing meta-analyses on a small number of trials are possible and may be helpful if one is aware of the limitations. As few as one more placebo-controlled trial would increase the reliability greatly.

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\* Corresponding author at: Department of Research and Development, Division of Emergencies and Critical Care, Oslo University Hospital, Box 4950 Nydalen, 0424 Oslo, Norway. Tel.: +47 92204274.

E-mail addresses: [halkazwini@gmail.com](mailto:halkazwini@gmail.com) (H. Al-Kazwini), [uxair@ous-hf.no](mailto:uxair@ous-hf.no) (I. Sandven), [vegard.dahl@ahus.no](mailto:vegard.dahl@ahus.no) (V. Dahl), [l.a.rosseland@medisin.uio.no](mailto:l.a.rosseland@medisin.uio.no) (L.A. Rosseland).

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**Conclusions:** Evidence from this systematic review suggests a possible beneficial prolonging effect of adding morphine to spinal analgesia with bupivacaine + fentanyl or +sufentanil during labour. The study quality was low and heterogeneity high. No severe side effects were reported. More adequately-powered randomized trials with low bias are needed to determine the benefits and harms of adding morphine to spinal local anaesthetic analgesia during labour.

**Implications:** Epidural analgesia is documented as the most effective method for providing pain relief during labour, but from a global perspective most women in labour have no access to epidural analgesia. Adding morphine to single shot spinal injection of low dose bupivacaine, fentanyl or sufentanil may be efficacious but needs to be investigated.

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Epidural analgesia (EDA) is the most effective method of providing pain relief during labour [1]. From a global perspective, most women in labour have no access to EDA, either because hospitals lack anaesthesiologist or the facilities for EDA in the hospital is limited for economic reasons. Single-dose spinal analgesia, if proven safe and efficient, may be a feasible option under such circumstances. Compared with EDA, this technique is easier to administer and monitor and the costs may be significantly reduced [2]. After introducing thin (25–27G) non-traumatic spinal needles, the risk of post dura puncture headache is minimal. The use of single-shot spinal analgesia during labour has been limited due to its short duration of action.

The local anaesthetic bupivacaine combined with a lipophilic, rapidly absorbed and removed, and therefore short-acting opioid, usually fentanyl or sufentanil, are common drugs used for spinal analgesia during labour. These combinations produce analgesia for up to 3 h [3].

The duration of spinal analgesia can be prolonged by adding the hydrophilic morphine that stays in the CSF longer, increasing the duration of analgesia [4]. Published studies of morphine added to spinal anaesthesia for surgery have documented this effect [5]. Studies on morphine added to spinal analgesia for labour-pain are mostly small-number studies and the results are conflicting.

The aim of this study was to perform a systematic review of randomised controlled trials assessing the prolongation of analgesia after adding morphine to local anaesthetic spinal analgesia during labour.

## 1. Methods

Because the review was based on previously published studies, research ethical board approval of the protocol was not necessary. The protocol for this systematic review was registered on the International Prospective Registry of Systematic Reviews (PROSPERO, CRD42013005402).

### 1.1. Literature search

A qualified medical librarian was consulted at the medical library of Oslo University Hospital. Electronic searches in Ovid Medline, EMBASE, Cochrane Library, PubMed, and Google were performed with reference to the following definitions of participants, interventions, comparators, and outcomes (PICO): labouring women, single-shot spinal analgesia with intrathecal morphine compared to placebo, and with prolongation of analgesia duration as an outcome. We also performed hand searches of the reference lists of the obtained articles. Search terms were as follows: “intrathecal opioid in labour analgesia”, “intrathecal analgesia in labour”, “spinal analgesia in labour”, “labour pain”, “obstetric analgesia”, “labour management” or “vaginal delivery”, and “morphine in labour analgesia”. Authors were contacted for detailed information when needed.

### 1.2. Trial selection

All studies that used intrathecal morphine during labour for analgesia published after 1946 up to 15th March 2016 were assessed. Only placebo-controlled randomised clinical trials evaluating the prolongation of analgesia after adding morphine to spinal analgesia (bupivacaine, fentanyl and/or sufentanil) during labour, and not during caesarean section, were considered eligible for inclusion in the systematic review. Studies of single shot spinal and combined spinal epidural technique were included. After identifying 461 references, 61 were removed due to duplicate publications. Three hundred forty-six references were excluded for the following reasons: case reports, intrathecal analgesia during caesarean delivery, and epidural labour analgesia. Of the 54 studies screened, 30 were excluded because drugs other than intrathecal morphine were studied (Fig. 1), leaving 24 eligible studies.

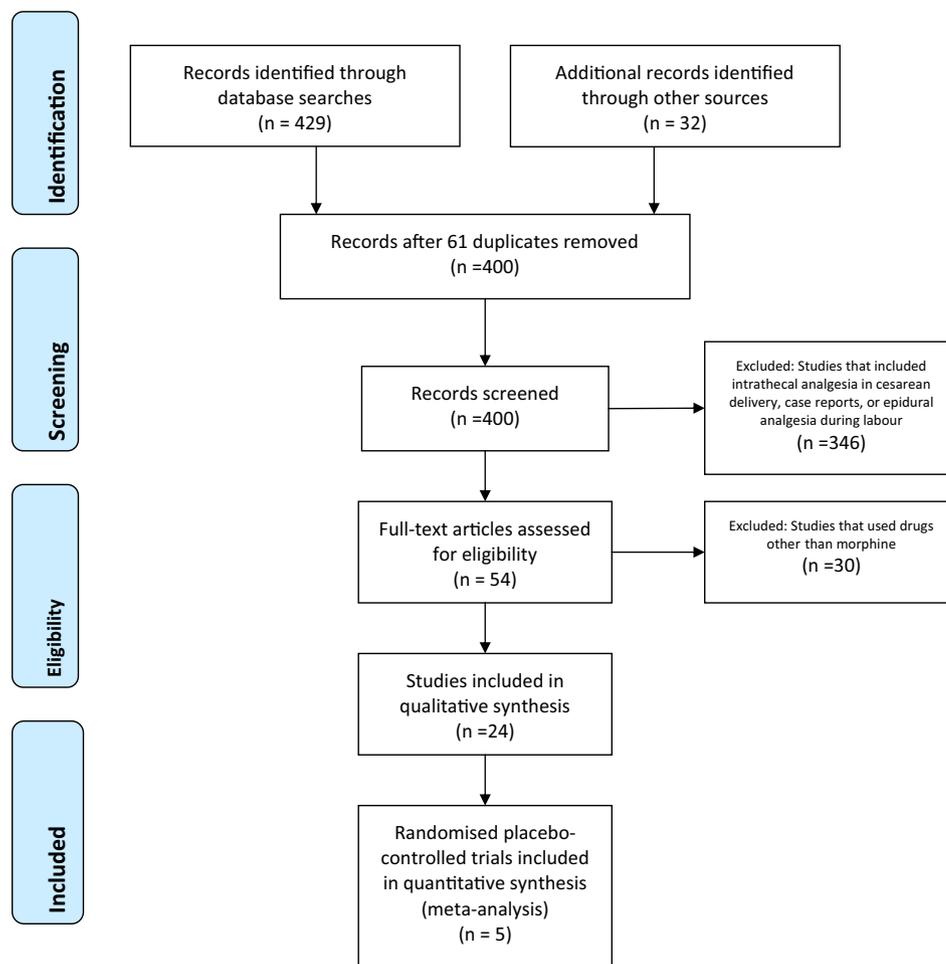


Fig. 1. Flow-chart showing screened literature, number of excluded and included publications.

### 1.3. Data collection

The following information was collected for each study: (1) patient characteristics, such as number of patients included and the patients mean age; (2) information about the study itself, such as its design, variables studied, outcomes, and adverse events; (3) the details of the data analysis, statistical methods, and a priori power analysis; and (4) year and source of publication. Mean duration in minutes (SD) was the primary outcome measure and included in the calculation of the standardized mean difference. Duration was defined as the time between a single shot spinal until patient request of rescue analgesia. All reported side effects were registered.

### 1.4. Quality assessment

Assessment of each included study was conducted using the Cochrane Collaboration's tool focusing on seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting and other bias [6]. Concealment of allocation was considered adequate when everyone involved in the study were blinded for allocation until data collection was complete. Analysis was considered adequate if all recruited patients were analysed in the group in which they were originally allocated, regardless of the treatment received (intention-to-treat principle). All four authors assessed the papers independently. Data regarding publication status, patient- and

study-related characteristics, and results were extracted in duplicate on a standardized form according to an a priori protocol. Disagreements were resolved by discussion between the authors and subsequent consensus. The analyses and report was performed according to guidelines given in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) document [7].

### 1.5. Statistical analyses

In order to calculate the pooled effect of the intervention, the standardized mean difference (SMD) with 95% confidence intervals (CI) was estimated for fixed and random effects models. We used the method suggested by Cohen, dividing the mean difference in each study by the study's standard deviation to create an index (SMD) that would be comparable across studies. If the value of zero is not inside the 95% CI, then the SMD is statistically significant at the 5% level ( $p < 0.05$ ) [8]. Cohen's rule of thumb for interpretation of the SMD statistic is that a value of 0.2 indicates a small effect, a value of 0.5 indicates a medium effect, and a value of 0.8 or more indicates a large effect. Due to heterogeneity among studies, we applied a random effect model according to the Der Simonian and Laird method [9]. Statistical heterogeneity among the studies was assessed using Cochrane's Q test. The magnitude of heterogeneity was evaluated with the  $I^2$  statistic, which describes the proportion of total variation due to heterogeneity rather than chance [10].  $I^2$ -values of 25%, 50%, and 75% indicate low, moderate, and high heterogeneity, respectively. In order to investigate possible sources of heterogeneity, we stratified the data according

**Table 1**  
Characteristics of included trials.

Reference	Country	Para 0 (%)	Mean age (years)	Number of patients analyzed. Morphine/control group	Morphine dose (µg)	Duration of pain relief in minutes. <sup>a</sup> Morphine/control group	Effect size (95% CI)
Grieco	USA	100	27	14/12	250	135(38)/115(40)	0.513 (−0.255 to 1.281)
Yeh	Taiwan	100	27	47/48	150	252(63)/148(44)	1.918 (1.430 to 2.405)
Hess	USA	51	31	24/24	125	101(43)/80(21)	0.617 (0.085 to 1.149)
Vasudevan	USA	42	32	27/28	100	419(298)/264(262)	0.553 (0.014 to 1.092)
Hein <sup>b</sup>	Sweden	100	30	26/26	100	100(38)/113(50)	−0.293 (−0.839 to 0.254)
				26/26	50	116(32)/113(50)	0.071 (−0.472 to 0.615)

<sup>a</sup> Mean (standard deviation).

<sup>b</sup> Study with two IT morphine treatment arms; morphine dose 100 µg and 50 µg.

**Table 2**  
Assessment of risk of bias.

Reference	Concealment of randomization	Blinding of patient to treatment group	Blinding of outcome assessor to treatment group	Intention to treat strategy	A priori power estimation
Grieco [31]	0	0	0	0	0
Yeh [32]	0	1	1	1	0
Hess [33]	1	1	1	1	1
Vasudevan [34]	1	1	1	0	1
Hein [35]	1	1	1	0	1

Notes: 1 = presence of the condition, 0 = absence of the condition or unclear.

to major components of internal validity; randomization and concealment of treatment allocation (selection bias) and blinding of patients and outcome assessors to the treatment group (detection bias). We generated a variable called “lower risk of bias”, which was scored as “yes” if the trial satisfied the above mentioned domains and “no” otherwise. Sources of heterogeneity were not investigated further by meta-regression because the number of trials was fewer than 10 [11]. An additional sensitivity analysis was undertaken to investigating the influence of each study by deleting each in turn from the meta-analysis and assessing the degree to which the size and significance of the treatment effect changes. To gain power, both treatment arms in the study by Hein et al. [12] were included in the meta-analysis at the same time although creating some similarity between the control arms. In order to assess potential publication bias or small-study effects, we used the funnel-plot, which is a good visual evaluation of sampling bias. To avoid evaluating the publication bias only according to visual judgment, a test of asymmetry (Egger’s test of the intercept) was applied on the funnel-plot [13]. However, a test for funnel plot asymmetry should only be conducted if the number of studies is ten or more [14]. All statistical analyses were performed with STATA 13.0 (StataCorp LP, College Station, TX, USA) and R-Package-Meta [15].

**2. Results**

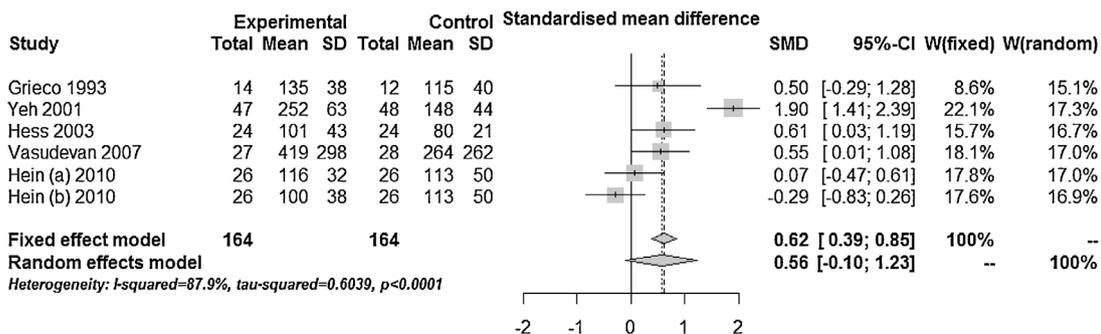
We identified 461 references in our literature search and 24 were considered to be potentially eligible. Twelve were observational studies [16–25], one a review article [4], and six were

randomised clinical trials that were excluded because they did not include a placebo control [26–31]. Finally, five placebo-controlled, randomised clinical trials were included in the meta-analysis, all studies used the combined spinal epidural technique, activating the EDA when the effect of the spinal analgesia decreased or vanished (Fig. 1) [12,32–35]. The studies compared morphine 50–150 mcg with placebo.

Mean duration of spinal analgesia during labour varied between 80 and 264 min in the placebo groups and between 100 and 419 min in the morphine groups (Table 1). Intrathecal morphine prolonged the duration of analgesia during labour by 60.6 min (pooled mean; range, 3–155 min). In the five trials bupivacaine (0 to 2.5 mg) were combined with either sufentanil (5 µg or 10 µg) or fentanyl (12.5 µg or 25 µg), and the doses of morphine, compared with placebo, used in these trials varied between 50 and 250 µg. Four trials found a statistically significantly prolonged duration compared with placebo [32–35].

The risk of bias assessment results is presented in Table 2. Randomization and adequate concealment were described in three trials, blinding of the endpoint assessor to treatment allocation were described in four trials, an intention-to-treat strategy was followed in two, and a priori power estimation was performed in three trials. One trial satisfied all core domains.

The results of the meta-analysis are summarized in Fig. 2. The study by Hein et al. compared two different morphine doses with placebo [12]. The meta-analysis considering both treatment arms, we found a pooled effect of SMD=0.57 (95% CI: −0.10 to 1.24) with high heterogeneity ( $I^2 = 88.1%$ ), indicating a medium beneficial



**Fig. 2.** Forest plot showing the effect of adding morphine to spinal analgesia in labour.

**Table 3**  
Subgroup analyses performed according to study level characteristics.

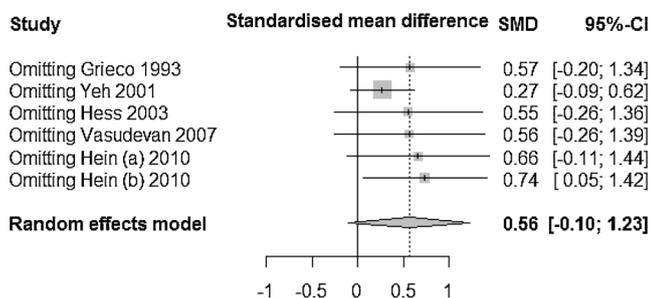
Subdivision	Number of trials	SMD (95% CI)	I <sup>2</sup> (%)
All trials	6 <sup>a</sup>	0.57 (–0.10 to 1.24)	88.1
Study level characteristics			
Low risk of bias	4 <sup>a</sup>	0.23 (–0.19 to 0.65)	56.9
High risk of bias	2	1.25 (–0.12 to 2.62)	88.7

Abbreviations: SMD, standardized mean difference; CI, confidence intervals.

<sup>a</sup> Includes both treatment arms in the trial by Hein et al. [35], comparing two different morphine doses (50 µg and 100 µg) with placebo.

**Table 4**  
Side effects of intrathecal morphine.

	Number of patients		Hypotension		Pruritus		Sedation		Nausea/vomit	
	N		n (%)		n (%)		n (%)		n (%)	
	Morphine	Placebo	Morphine	Placebo	Morphine	Placebo	Morphine	Placebo	Morphine	Placebo
Grieco	14	13								
Yeh	47	48	3(6)	2(4)	36(77)	32(67)			16(34)	13(27)
Hess	29	28			15(52)	16(57)	1(3)	0	4(14)	0
Vasudevan	27	28			1(4)	0	0	0	4(15)	0
Hein	26	26	1(4)	3(12)	17(65)	15(58)				
	26		2(8)		15(58)					



**Fig. 3.** Forest plot showing the result from sensitivity analyses investigating the influence of each study by excluding each study subsequently from the meta-analysis.

effect of adding morphine to spinal analgesia during labour. However, the beneficial effect was statistically non-significant ( $z = 1.66$ ,  $p = 0.096$ ). Results from the stratified analysis are summarized in Table 3. The lower-bias trials showed a small statistically non-significant beneficial effect with lower heterogeneity. In influential analysis, that excluded one study at a time from the meta-analysis, the effect size appears unstable and the results indicate no robustness of effect (Fig. 3). Adverse events reported in the studies are presented in Table 4. The study by Grieco et al. [32] reported adverse events as repeated assessments of degree of hypotension, nausea and pruritus. There was no indication of publication bias as the Egger's test rejected the null-hypothesis of small-study effect ( $p = 0.524$ ). However, we need at least 10 trials to be conclusive as for asymmetry for funnel plots [14].

### 3. Discussion

This systematic review of placebo-controlled trials evaluating the prolongation of analgesia during labour by adding morphine to spinal analgesia revealed a high degree of heterogeneity among the trials. When trials with lower risk of bias were considered separately, heterogeneity was lowered and a small beneficial effect of adding morphine compared to placebo was shown. However, because influential meta-analysis shows there is no robustness of our result we cannot be conclusive. Therefore, additional adequately powered randomised trials with a low risk of bias are needed.

Based on a comprehensive literature search, it seems unlikely that important trials are missing from our search [36]. Each author assessed the trials, and the components used for quality assessment are validated [6]. The major limitations of our study were the quality and small number of trials available, which restricted our ability to explore the influence of study- or patient-level characteristics on the effect size. Only three trials [12,34,35] among a total of five were considered to have a lower risk of bias, and it has been shown that inadequate concealment of treatment allocation and blinding of the outcome assessor is associated with overestimation of treatment effects [37]. This may explain the prominent effect size in the study by Yeh et al. [33]. The differences in methods complicate the interpretation of the analysis. The doses of bupivacaine, sufentanil, and fentanyl varied as did the morphine doses. The combined spinal epidural technique was used but in one study an epidural infusion of bupivacaine, fentanyl and adrenaline was initiated immediately after the spinal injection, making evaluation of duration of spinal analgesia uncertain [34]. The duration of labour and duration of analgesia varies a lot. These factors will all increase the differences between the trials and make direct comparisons difficult.

EDA is documented as the most effective method for providing pain relief during labour. However, from a global perspective most women in labour have no access to EDA. Intrathecal administration of morphine may provide more women with analgesia during labour because a single-shot spinal is a less costly technique. However, one must be familiar with the pharmacology of intrathecally delivered opioids, as well as be able to anticipate and deal with any complications that might arise. This review of placebo-controlled trials indicates that there may well be a beneficial additive effect of intrathecal morphine. The studies used combined spinal epidural technique and centres that use EDA as the standard analgesic treatment for labour pain may consider including intrathecal morphine in future controlled trials.

Due to its hydrophilic properties compared with fentanyl and sufentanil, intrathecal morphine has a slower onset. The gradual cephalic spread within the cerebrospinal fluid to the upper spinal cord and the higher centres may increase the spread of spinal analgesia, but may also increase the risks of adverse events [26]. Prolongation of spinal analgesia by adding morphine is most likely due to the slow absorption of the hydrophilic morphine from the CSF. In our review, no respiratory depression was registered (Table 4). The study by Grieco et al. did not report adverse events. However, they excluded one patient with respiratory depression in the

control group from final analysis [32]. A few local anaesthetic analgesia trials of intrathecal morphine at doses of 500–1000  $\mu\text{g}$  during labour showed significantly prolonged pain relief, but reported a high incidence of pruritus, nausea, vomiting, somnolence, or urinary retention [5].

Life-threatening respiratory depression is associated with intrathecal administration of morphine [38–41]. In a nationwide follow-up survey evaluating the use of intrathecal morphine in the management of postoperative pain, delayed respiratory depression occurred in patients given intrathecal morphine at doses of 300–750  $\mu\text{g}$  [5]. However, it was concluded that respiratory depression was unlikely to occur when the intrathecal morphine dose is less than 250  $\mu\text{g}$ , and a minimum of 12 h observation was recommended. This was reinforced by Abouleish et al. in a prospective observational study of intrathecal morphine 200  $\mu\text{g}$  given to 856 patients undergoing caesarean delivery [42]. Respiratory depression was identified in 8 patients, all of whom were morbidly obese. The fact that most studies were performed in a post caesarean delivery population represents an important limitation. Even if pain after vaginal delivery is higher than previously reported [43], it is less intense than pain after caesarean delivery. It may not be justified to generalize the results from a postoperative population to vaginal delivery. Despite the rarity of respiratory depression, parturient having intra-thecal morphine should be under surveillance for at least 12 h after morphine was injected intrathecally [5,44].

Direct negative effects on the baby are unlikely, but maternal respiratory depression and hypoxia may put the foetus at risk, and clearly the intrathecal morphine dose must be below a safe limit. The literature of respiratory depression in clinical postoperative pain is important, but the validity in labour pain is questionable.

Other side effects could be alleviated by using naloxone without decreasing the analgesia during labour, i.e. the analgesic properties of intrathecal opioids do not seem to be affected by small doses of opioid antagonists given systemically [45]. The reporting of maternal side effects differed a lot between the five trials included in the systematic review, and the number of patients was low. Clearly, we are unable to answer questions about the incidence of even the most common adverse events.

The least effective dose of intrathecal morphine during labour is undetermined, and we were unable to draw conclusions from this systematic review. Each of the trials was underpowered due to small group sizes, and the number of eligible placebo-controlled randomised clinical trials is small. Even when the trials supported the hypothesis of significant prolongation of analgesia during labour after adding intrathecal morphine, the results are conflicting. The study by Hein et al. even indicated that intrathecal morphine 50  $\mu\text{g}$  was efficacious, but intrathecal morphine 100  $\mu\text{g}$  was not. The authors do not discuss the reason for this, and it is not clear why there should be an inverse dose response. The morphine 100  $\mu\text{g}$  group had a shorter mean duration of labour, less motor block, and higher epidural requirements compared with the group receiving intrathecal morphine 50  $\mu\text{g}$  or placebo. In small trials, such group differences may occur by chance and introduce bias.

Performing meta-analyses on a small number of trials is possible and may be helpful if one is aware of the limitations. As few as one more placebo-controlled trial would increase the reliability greatly. The analysis revealed a need for more sufficiently powered randomised clinical trials of rigorous scientific quality. Considering the assessment of risk of bias, the subgroup analysis of the three low-risk trials showed a small but non-significant effect of intrathecal morphine with lower heterogeneity. The effect size in the study by Yeh et al. were more prominent than the other studies [33]. Interestingly, the sensitivity analyses investigating the influence of each study by excluding each study subsequently from the meta-analysis illustrates that by omitting this study the positive trend in the meta-analysis is markedly reduced. Reliable data on

the incidence of rare events like maternal respiratory depression require large prospective cohort registries of adverse outcomes.

Improving maternal health is one of the World Health Organization's key priorities [46]. All women in labour should be offered safe relief from pain. A single-shot spinal with low dose bupivacaine combined with intrathecal morphine (150  $\mu\text{g}$  or less) may represent the best choice and should be included in future trials.

#### 4. Conclusions

Results from this systematic review showed a small but non-significant beneficial effect of adding morphine to spinal analgesia. But there is no robustness of our result, as highlighted by influential meta-analysis, and we cannot be conclusive whether morphine may be associated with prolonged pain relief during labour. Further well-designed and adequately powered randomised trials are needed.

#### Ethical issues

Approval of ethical board not required: See Section 2.

#### Conflicts of interest

The authors declare no conflicts of interest. The project received no funding.

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