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META-ANALYSIS

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Epidural Analgesia with Amide Local Anesthetics, Bupivacaine, and Ropivacaine in Combination with Fentanyl for Labor Pain Relief: A Meta-Analysis

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Background: The study compares the effectiveness of bupivacaine and fentanyl (BUPI-FEN) and ropivacaine and fentanyl (ROPI-EFN) in epidural analgesia for labor pain through a meta-analysis of relevant randomized clinical trials.

Material/Methods: Multiple electronic databases were searched using appropriate MeSH terms and keywords for original English language research papers published between 1990 and March 2014. Meta-analyses results were based on the mean differences between the groups as well as odds ratios where appropriate. Statistical heterogeneity amongst the included studies was tested by I^2 index.

Results: Nine studies that met the inclusion criteria were selected for analysis which consisted of 556 parturient patients. The duration of the second stage of labor was significantly shorter in the BUPI-FEN group by a mean of –6.87 (–10.98, –2.77; $P<0.002$). On the other hand, the ROPI-FEN group had a significantly lower incidence of motor blockade by a mean of 0.31 (0.18, 0.51; $P<0.00001$). A positive relationship between the amide local anesthetic concentration and the number of women having motor blockade was observed, but a negative relationship between fentanyl concentration and the number of women experiencing a motor block. Moreover, a positive correlation was found between the concentration of ropivacaine and the incidence of instrumental delivery and between the concentration of bupivacaine and the incidence of cesarean delivery.

Conclusions: In combination with fentanyl, bupivacaine and ropivacaine exhibit comparable efficacy and safety. However, BUP-FEN analgesia led to a shortened second-stage labor and ROPI-FEN resulted in a significantly lower incidence of motor block.

MeSH Keywords: Anesthesia, Caudal • Anesthesia, Spinal • Injections, Spinal

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Background

Effectiveness of analgesia during labor, along with the avoidance of adverse effects of administration, is vital for obstetric management. Painful labor can negatively impact both maternal and fetal physiology. In neuraxial anesthesia, anesthetics are injected via a catheter, either intrathecally into the cerebrospinal fluid or epidurally into the fatty tissues around the dura. This serves as a nerve block for afferent transmissions of pain [1,2]. Use of these neuraxial analgesic techniques during labor and delivery has been associated with higher maternal satisfaction and lower pain scores without adverse effects on maternal cardiovascular or pulmonary function or fetal physiology [3].

Epidural analgesia has gained great importance due to its safety, and administration of local amide anesthetics in combination with opioids has become commonplace for relief of labor pain [4–6]. Synthetic opioids like sufentanil and fentanyl can increase the potency of local amide anesthetics such as bupivacaine, levobupivacaine, and ropivacaine by modifying their minimum potencies [7,8].

Bupivacaine, a racemic mixture of 2 stereoisomers, is the most widely used long-acting local amide anesthetic, along with ropivacaine, a propyl homologue of bupivacaine (a pure S-enantiomer). Previous studies have suggested that use of single enantiomers is more desirable than racemic agents [9]. Ropivacaine is a levorotatory (left-isomer) and although it possesses a relatively low potency, it has been found to be less toxic to the nervous system and heart when compared with bupivacaine [5,10,11]. Fentanyl, a synthetic opioid, has been used for decades in labor analgesia and is characterized by low molecular weight, high potency, and lipid solubility, which make it a suitable analgesic for transdermal infusions [12,13].

A number of studies, including a randomized controlled trial (RCT) that utilized fentanyl with bupivacaine and ropivacaine, have evaluated the safety and efficacy of administration of synthetic opioids with local amide anesthetics in epidural analgesia for labor. While the results of these studies have favored the use of these anesthetics in combination, there still exist inconsistencies in terms of tolerability, effects on obstetric conditions, and optimal drug and dosing combinations. This meta-analysis compared the safety and efficacy of the administration of fentanyl with bupivacaine or ropivacaine in epidural analgesia for the relief of labor-associated pain by analyzing relevant RCTs.

Material and Methods

Literature search

The literature search was performed using multiple electronic databases – Medline/PubMed, Embase, Scopus, CINAHL, OvidSP, EBSCO, Cochrane library, and Google Scholar – using major MeSH terms (bupivacaine, ropivacaine, and fentanyl). Keywords – Analgesia, Anesthesia, Labor, Delivery, Neuraxial, Epidural, Efficacy, Side effects, Motor block, Sensory block, Randomized trial – were used in different combinations and phrases (e.g., bupivacaine-fentanyl epidural labor randomized; ropivacaine-fentanyl epidural labor motor block, etc.). The relevant research articles obtained from the literature search were also explored for cross-references. The search encompassed original research papers published between 1990 and May 2014 in English-language journals.

Inclusion and exclusion criteria

Studies involving the comparative evaluations of bupivacaine and ropivacaine in combination with fentanyl for labor

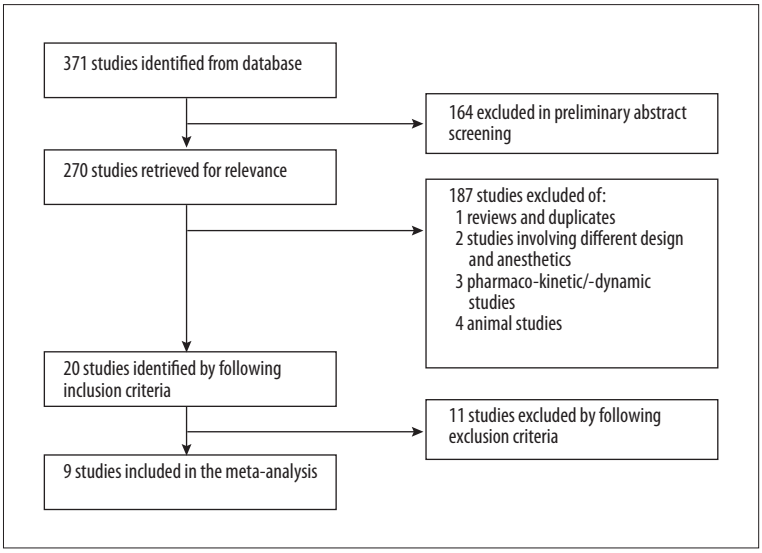

Figure 1. Flowchart of literature screening and study selection process.

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Table 1. Risk of bias assessment in the included studies.

	Other bias	Selective reporting	Incomplete outcome data	Blinding of outcome assessment	Blinding of participants/ personnel	Allocation concealment	Random sequence generator
Asik et al. 2002	L	L	L	U	L	L	L
Atienzar et al. 2008	L	L	L	U	L	L	L
Bolukbasi et al. 2005	L	L	L	U	L	L	L
Fernandez-Guisasola et al. 2001	L	L	L	U	L	L	L
Finegold et al. 2000	L	L	L	U	L	L	L
Girard et al. 2006	L	L	L	U	L	L	L
Meister et al. 1999	L	L	L	U	L	L	L
Owen et al. 2001	L	L	L	U	L	L	L
Pirbudak et al. 2007	L	H	L	U	L	L	L

H – high risk; L – low risk; M – mediocre risk; U – unclear risk.

analgesia were included in this systematic review and meta-analysis. Inclusion criteria were RCTs that: (a) recruited parturient mothers in labor to study the efficacy and safety of epidural analgesia with bupivacaine and ropivacaine in combination with fentanyl (hereinafter BUPI-FEN and ROPI-FEN, respectively), (b) compared at least 3 efficacy and/or safety parameters, (c) infused the combined analgesic solution epidurally to maintain analgesia during labor and delivery, and (d) assessed the effectiveness of analgesia using the visual analog pain score (VAS) where participants entered the trial with a score of at least 40. Exclusion criteria were: (a) studies that used intrathecal administration, (b) single-arm randomized studies examining either BUPI-FEN or ROPI-FEN as labor analgesia or double-arm studies using 1 of these combinations, (c) studies evaluating BUPI-FEN and/or ROPI-FEN combinations for only caesarian section or post-delivery analgesia, (d) studies examining a combination of more than 2 of these anesthetics, and (e) reports of trials providing inadequate information about outcomes and/or efficacy and safety (Figure 1).

Quality assessment of the selected RCTs

The Cochrane Collaboration Risk of Bias Assessment Tool for the assessment of RCTs [14], which evaluates the internal validity of the trial, assessment of the risk of possible bias in different phases of the trial, and conduct and outcome analyses, was used for the qualitative assessment of the included studies using 7 categories of bias possibilities (Table 1).

Data extraction, synthesis, and statistical analysis

The data were extracted from the textual, tabular, and graphic sources of the published research papers regarding the participants' demographic, obstetric characteristics, interventions, and outcomes independently by 2 reviewers (Y.Y.L. and C.H). The outcome measures included analgesia duration, onset of analgesia, mean change in VAS following analgesia throughout labor, incidence of instrumental and cesarean deliveries, incidence of motor blocks, incidence of labor induction, Apgar scores of neonates, maternal satisfaction, and duration of first and second stages of labor.

Meta-analyses were performed using Review Manager (RevMan Version 5.2; Cochrane Collaboration) software with both fixed-effects (FEM) and random-effects (REM) pooled proportions models. Means and standard deviation (MSD) of the variables of interest were calculated and converted into mean differences along with 95% confidence intervals (95% CI) for each constituent study. Subsequently, a calculation of the overall effect size was made. For dichotomous variables, odds ratios were calculated for meta-analyses. The overall effect of the treatment was a weighted average of the inverse variance adjusted to individual effects (mean differences or odds ratios). Statistical heterogeneity was tested using the I^2 index. Where necessary, sensitivity analyses were performed. The assessment of publication bias was made by visual examination of the asymmetry of the funnel plots.

Results

Nine studies meeting the inclusion criteria were selected [15–23]. The characteristics of the included studies (e.g., patients' demographics, obstetrics data, and type and concentration of anesthetics) are presented in Table 2. Overall, the selected studies included 556 parturient women with a mean

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Table 2. Characteristics of the included studies.

Study/design	n	demographics	Obstetric characteristics	Anesthetic dosage: Concentration (w/v)/ overall usage		
				Bupivacaine	Ropivacaine	Fentanyl
Asik et al. 2002/DB-RCT/ Epidural	B 28 R 25	Age: 28 (20–38) *vs.* 27 (19–37) yr Height: 165.1±4.8 *vs.* 163.4±3 cm Weight: 72.8±7.8 *vs.* 70.3±6.7 kg	Gestation: 39.56±1.2 *vs.* 38.9±1.02 wk Cervical dilation: 4.8±0.94 *vs.* 4.06±0.79 cm	0.02%/ 142.2±42.6 mg	0.02%/ 117±36.4 mg	0.0002%/ 117±36.4 (R) *vs.* 142.4±42.6 (B) µg
Atienzar et al. 2008/DB-RCT	B 31 R 34	Age: 31±2.9 *vs.* 31±2.6 yr Height: 164±6 *vs.* 1652±5 cm Weight: 75±9 *vs.* 71±10 kg	Gestation: 39.2±1 *vs.* 39.4±1 wk Cervical dilation: 2.4±1 *vs.* 2.7±0.8 cm	0.125%/ 32.5 (26.7–50) mg IQR	0.2%/ 34.6 (23.3–73.3) mg IQR	0.0001%/ 16.9 (11.7–36.1) R *vs.* 26 (16.7–38.7) B µg
Bolukbasi et al. 2005/DB-RCT	B 20 R 20	Age: 25.5±0.64 *vs.* 25.35±0.96 yr Height: 163.6±1.16 *vs.* 161.9±1.04 cm Weight: 77.35±1.65 *vs.* 76.95±1.75 kg	Gestation: 38.55±0.3 *vs.* 38.95±0.31 wk Cervical dilation: 5.15±0.2 *vs.* 4.95±0.2 cm Nulliparity: 0% *vs.* 0%	0.625%/ 30.17±1.48 mg	0.625%/ 31.2±1.96 mg	0.0002%/ 54.8±5(B) *vs.* 58.2±5 (R) µg
Fernandez-Guisasola et al. 2001/DB-RCT	B 51 R 47	Age: 31±4 *vs.* 30±4 yr Height: 162±5 *vs.* 163±4 cm Weight: 75±11 *vs.* 72±10 kg	Cervical dilation: 3±1 *vs.* 3±1 cm Primipara: 71.7% *vs.* 79.2%	0.625%/NA	0.1%/NA	0.0002%/NA
Finegold et al. 2000/DB-RCT	B 50 R 50	Age: 27.41±3.2 *vs.* 28.1±2.8 yr Height: 164.3±5.8 *vs.* 163.2±5.1 cm Weight: 79.9±9.8 *vs.* 81.8±12.9 kg	Gestation: 39.6±1.5 *vs.* 39.5±1.1 wk Cervical dilation: NA	0.125%/ 69±49.7 ml	0.1%/ 66.8±81 ml	0.0002%/NA
Girard et al. 2006/DB-RCT	B 33 R 27	Age: 29.3±5.2 *vs.* 28.7±5.5 yr BMI: 27.9±3.5 *vs.* 28.4±4.3 kg/m^2	Gestation: 39.5±1.1 *vs.* 39.6±1.5 wk Cervical dilation <4cm 79% *vs.* 66%	0.125%/NA	0.125%/NA	0.0001%/NA
Meister et al. 1999/DB-RCT	B 25 R 25	Age: 27±6 *vs.* 27±6 yr Height: 167±7 *vs.* 166±7 cm Weight: 84±13 *vs.* 83±13 kg	Gestation: NA Cervical dilation: NA Nullipara: 48% *vs.* 48%	0.125%/ 102.5±82.4 mg	0.125%/ 113.0±43.3 mg	0.0002%/ 164.0±82.4 (B) *vs.* 180.8±69.2 (R) µg
Owen et al. 2001/DB-RCT/ Epidural	B 25 R 25	Age: 24±5 *vs.* 27±6 yr Height: 165±3 *vs.* 164±4 cm Weight: 79±10 *vs.* 84±15 kg	Gestation: 39±1 *vs.* 40±1 Cervical dilation: 4±1 *vs.* 4±1	0.075%/ 96±59 ml	0.075%/ 101±45 ml	0.0002%/NA
Pirbudak et al. 2007/DB-RCT	B 20 R 20	Age: 22.9±0.6 vs 23.1±0.7yr Height: 162.9±1.7 *vs.* 162.8±0.9 cm Weight: 68.5±1.7 *vs.* 68.3±1.7 kg	Gestation: NA Cervical dilation: NA	0.05%/ 28.28±10.67 mg (56.5±21.3 ml)	0.05%/ 26.17±10.49 mg (52.35±20.9) ml	0.00015%/NA

B – bupivacaine; R – ropivacaine; L, NA – not available; DB – double blind; IQR – inter-quartile range; RCT – randomized controlled trial; wk – weeks; cm – centimeter; kg – kilogram; yr – years.

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Table 3. Mean differences bases meta-analyses comparing the effectiveness of neuraxial analgesia with ROPI-FEN *vs.* BUPI-FEN for labor pain relief.

Parameter	No. of Studies	No. of mothers	Mean difference [95% CI]; significance level		I^2	Results favor
			Fixed effects	Random effects		
Onset of analgesia	3	218	0.96 [–0.38, 2.30]; P=0.16	1.02 [–0.49, 2.53]; P=0.19	14%	Indifferent
Duration of 1st stage of labour	5	281	12.97 [6.31, 19.63]; P<0.0002	0.93 [–18.19, 20.05]; P=0.92	32%	Indifferent
Duration of 2nd stage of labour	6	393	–5.74 [–7.80, –3.68]; P<0.0001	–6.87 [–10.98, –2.77]; P<0.002	36%	BUPI-FEN
Mean change in VAS from baseline	7	466	0.30 [–0.30, 0.89]; P=0.31	0.00 [–1.31, 1.32]; P=1	30%	Indifferent

Table 4. Odds ratios based meta-analyses comparing the effectiveness of neuraxial analgesia with ROPI-FEN *vs.* BUPI-FEN for labor.

Parameter	No. of Studies	No. of mothers	Total cases		Odds ratio [95% CI]; significance level		I^2	Results favour
			ROPI	BUPI	Fixed effects	Random effects		
Motor blockade	9	556	52/273	115/283	0.30 [0.20, 0.45]; P<0.00001	0.31 [0.18, 0.51]; P<0.00001	27%	ROPI-FEN
Instrumental delivery	8	516	66/253	67/263	1.03 [0.68, 1.57]; P=0.87	1.05 [0.58, 1.92]; P=0.87	46%	Indifferent
Cesarean section	8	516	30/253	33/263	0.92 [0.54, 1.58]; P=0.77	0.92 [0.53, 1.61]; P=0.78	0%	Indifferent
Oxytocin use	7	451	94/192	106/199	0.82 [0.54, 1.25]; P=0.35	0.82 [0.54, 1.25]; P=0.35	0%	Indifferent
Apgar score of <7	4	263	1/101	4/102	0.33 [0.05, 2.14]; P=0.25	0.33 [0.05, 2.14]; P=0.25	0%	Indifferent
Maternal satisfaction*	3	188	88/92	91/96	1.23 [0.33, 4.59]; P=0.76	1.20 [0.31, 4.60]; P=0.79	0%	Indifferent

age range of 23±0.6 to 31±4 years. Mean height and weight of the parturient women ranged between 162±5 and 167±7 cm and 68.5±1.7 and 84±13 kg, respectively.

Gestation period ranged from 38.6±0.3 to 40.5±1 weeks and the cervical diameter at the time of trial entry was between 2.4±1 and 5.15±0.2 cm. Dose concentrations (weight/volume) of the anesthetics were 0.086±0.04% (0.02–0.125) for bupivacaine, 0.98±0.053% (0.02–0.125) for ropivacaine, and 0.00016±0.00009% (0.0001–0.0002) for fentanyl.

The qualitative assessment of the included studies using the Cochrane Collaboration Risk of Bias Assessment Tool revealed that the studies were of generally good quality based on the information provided in the respective papers when assessed against the trial objectives of each study (Table 2). However, in blinding of outcome assessment, no information was available in any report and, although low risk of bias was evident against the item (selective reporting), inconsistencies were frequent in parametric outcome dissemination; therefore, the number of included studies in various parameters ranged between 1 and 9.

The major findings of this systemic review and meta-analysis are presented in Tables 3 and 4. There were no statistically significant differences between the different combinations in the time of analgesic onset, change in VAS during labor, duration of the first stage of labor, incidence of instrumental or cesarean delivery, use of oxytocin for induction, neonate Apgar score, or maternal satisfaction.

The duration of the second stage of labor was significantly shorter in the BUPI-FEN group under both models and decreased by a mean of –5.74 (–7.80, –3.68; *P*<0.0001) in the FEM and by –6.87 (–10.98, –2.77; *P*<0.002) in the REM (Figure 2). Analgesia duration following a single bolus was reported in

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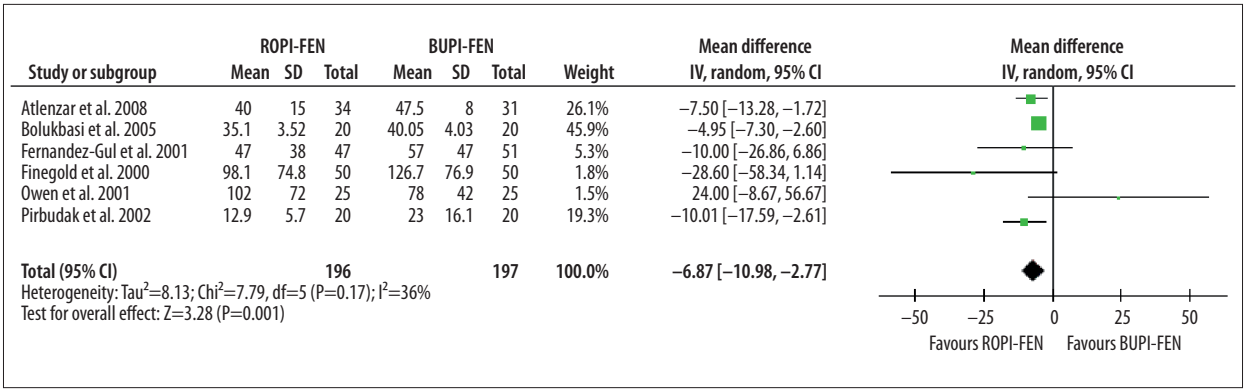

Figure 2. Forest plot showing significantly shorter second stage labor with epidural BUPI-FEN administration using a random-effects model of 6 studies.

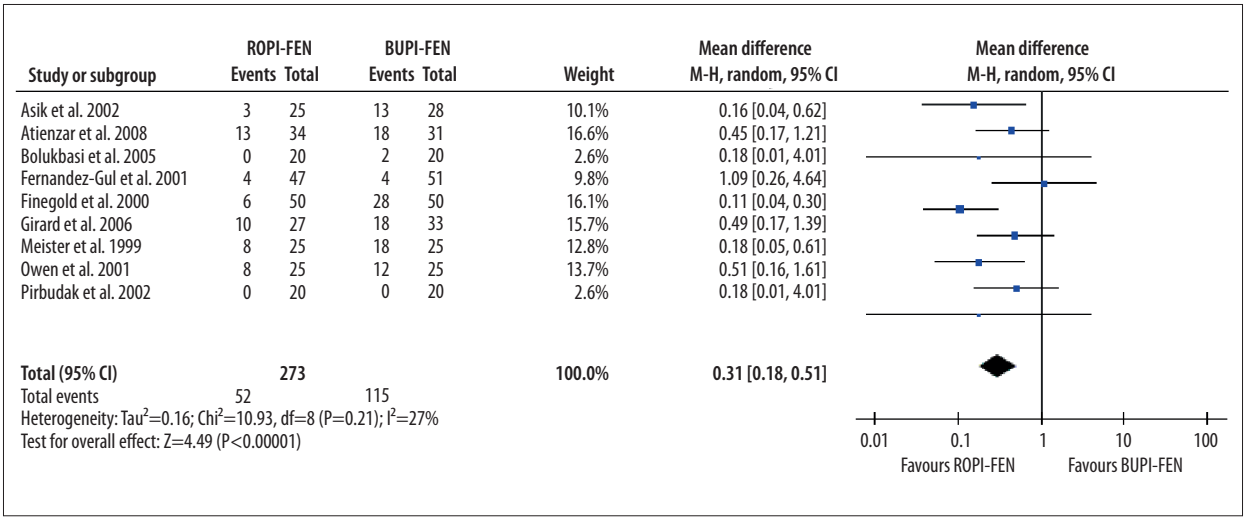

Figure 3. Forest plot showing a significantly lower incidence of motor block in patients administered epidural ROPI-FEN using a random-effects model of 9 studies.

only 1 study, which found significantly longer analgesic duration in the BUPI-FEN group by a mean of –14.10 (–23.61, –4.59; *P*<0.005).

In the overall study population, 52 of the 273 patients in the ROPI-FEN group and 115 of the 283 patients in the BUPI-FEN group experience motor blocks with Bromage scores equal to or greater than 1. Both models found the ROPI-FEN group to be significantly superior to BUPI-FEN group in this regard, with a mean difference of 0.30 (0.20, 0.45; *P*<0.00001) in the FEM and 0.31 (0.18, 0.51; *P*<0.00001) in the REM (Figure 3). Incidence of motor block increased with the concentration of amide anesthetics (bupivacaine, r=0.42; ropivacaine, r=0.65). On the other hand, increased concentration of fentanyl resulted in a decrease in the incidence of motor block (BUPI-FEN, r=–0.6; ROPI-FEN, r=–0.8).

In the ROPI-FEN group, there was a trend towards increased incidence of instrumental deliveries further correlated with increased concentrations of ropivacaine (r=0.550). Conversely, the correlation coefficient between bupivacaine concentration and incidence of cesarean delivery was 0.52 in the BUPI-FEN administered women and only 0.31 in the ROPI-FEN group.

Sensitivity analyses were performed to assess the inter-study dose concentration deviation. In the meta-analyses of the studies wherein 0.125% concentration of both bupivacaine and ropivacaine were used, the results did not differ significantly from the overall results from all studies. This was also the case when studies using 0.125% concentrations of local amide anesthetics were excluded and all other studies with lower concentrations were included.

Observed adverse effects from the combined use of these anesthetics and fentanyl included pruritus, nausea, and hypotension, which were observed in at least 4 of the included studies. Incidence of these adverse effects was similar in both the BUPI-FEN and ROPI-FEN groups (pruritus: 25.2±21.6 *vs.*

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28±19.9; nausea: 6±3.56 *vs.* 6.2±1.9; and hypotension 11.7±11 *vs.* 15.7±17). Backache (10%), shivering (5%), and fetal bradycardia (10%) were also observed in 1 study each.

Discussion

Several measures of efficacy and safety were examined in the present review and the majority of these were comparable between groups. However, the second stage of labor was found to be significantly shorter in the BUPI-FEN group and the incidence of motor block was significantly lower in the ROPI-FEN group; 19.4% of patients in the ROPI-FEN group and 42.4% of patients in the BUPI-FEN group developed motor blocks of equal to or greater than 1 on the Bromage scale. It has been suggested that ropivacaine possess low lipophilic characteristics and is therefore resistant to rapidly penetrating the myelinated nerve fibers and thus is less likely to cause a motor blockade and neurotoxicity [24].

Dose-sparing effects of opioids for local amide anesthetics in epidural analgesia offer a favorable option for pain relief during labor while reducing the incidence of adverse effects [25], because opioids reduce local anesthetic requirements by 19% to 31% [26,27]. Multiple studies have reported that ropivacaine possesses a lower potency (of up to 40%) when compared to racemate bupivacaine [28], which could explain the lower incidence of motor block in ropivacaine-anesthetized patients. Meister et al. speculated that lower hourly ropivacaine doses may lower the incidence of motor blocks. However, this may be due to the drug's effect rather than its potency [29]. In this analysis, only 2 studies used different concentrations of bupivacaine (0.125% and 0.0625%) and of ropivacaine (0.20% and 0.1%). However, the results are consistent with the findings of Gautier et al. that motor block is an effect of the drug and is dependent on potency [29].

Epidural analgesia has been shown not to increase the risk of prolonged labor or the incidence of caesarean delivery [30–32]. Interestingly, the present study found that within the ROPI-FEN group, increased concentration of ropivacaine correlated with increased incidence of instrumental delivery (r=0.55), but a similar correlation could not be found in the BUPI-FEN group (r=0.037). On the other hand, in the BUPI-FEN group, increased bupivacaine concentration increased the incidence of cesarean delivery (r=0.52) but the same was observed, though to a lesser extent, in the ROPI-FEN group (r=0.31). It is hard to definitively state if there is indeed a correlation between the incidence of motor block and dose concentration, because the correlation coefficient between the concentration of the local amide anesthetic and the number of patients experiencing motor block was 0.42 with bupivacaine and 0.65 with ropivacaine.

Severe motor block can prolong the second stage of labor and increase the chance of instrumental delivery [4]. A combination of a low-dose opioid and a local anesthetic has been preliminarily shown to have a low incidence of instrumental deliveries [33–36] and the present study confirms this.

The small overall patient population and the inconsistencies in parametric data reporting are important limitations of this study. For many parameters, only a few studies provided data, making evidence with regards to analgesia duration, onset of analgesia, and maternal satisfaction inconclusive. Additionally, some of the included studies used test doses of other anesthetics such as lidocaine for catheter placement, which might have had a slight, although likely negligible, impact on motor function. However, such a finding would have probably been shared by both the groups.

Conclusions

Ropivacaine in combination with fentanyl leads to significantly reduced motor block events when compared to bupivacaine and fentanyl, but both combinations are comparable in terms of onset of analgesia, VAS score, Apgar score, incidence of oxytocin use for induction, duration of first stage of labor, incidence of instrumental and cesarean deliveries, and maternal satisfaction. Ropivacaine in combination with fentanyl has a safer toxicity profile, making it ideal for use in conditions where motor block poses a greater risk. Complications of both anesthetics appear to be dose-dependent.

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