REVIEW ARTICLE

Safety and efficacy of combined ropivacaine and sufentanil compared with ropivacaine for cesarean sections: A systematic review and meta-analysis

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Abstract

Cesarean sections are the most common operations in the United States and one of the most common worldwide. Using the lowest possible dose of anesthetic that provides painless delivery with the lowest adverse events is a major concern. We investigated the efficacy and safety of combined ropivacaine and sufentanil by pooling data from relevant studies. We searched PubMed, Web of sciences, Scopus, and Cochrane Library until the end of December 2021 and included all records with data about combined ropivacaine and sufentanil. We used Review Manager to pool data as a mean difference for continuous outcomes or risk ratio for dichotomous outcomes with a 95% confidence interval. Methodological quality was appraised using version one of the Cochrane risks of bias tool. Seven Randomized clinical trials with a total sample size of 730 women were included; the mean age of enrolled parturients ranged from 28 to 35 years. We found that combined sufentanil and ropivacaine were significantly associated with decreased risk of being aware and nervous during CS (presented by Sedation level 1) (RR: 0.05, 95%CI [0.01,0.33], P=0.002), decreased risk of shivering (RR=0.29, 95%CI [0.19,0.44], P<0.00001), nausea (RR=0.62, 95%CI [0.41, 0.92], P=0.02), and vomiting (RR=0.27, 95% CI [0.12, 0.61], P=0.002). However, combined sufentanil and ropivacaine slightly were associated with late-onset of sensory blockade (MD=0.41, 95%CI [0.13, 0.68], P=0.004) and less motor blockade of leg flexion at hip joint presented by Bromage Scale 0 (RR=7.15 95%CI [2.71, 18.86], P<0.0001). Combined ropivacaine and sufentanil were associated with a reduction in visceral pain and lower risks of hypotension, shivering, nausea, and vomiting, compared to isolated ropivacaine, with no difference regarding the incidence of bradycardia. Although Combined ropivacaine and sufentanil were associated with a higher risk of pruritus, the incidence of pruritus was reportedly proportionate with the used dose of sufentanil. However, combined ropivacaine and sufentanil may slightly delay the onset of the sensory blockade to pinprick at T10 with less motor blockade but with a smaller probability for women to be aware and nervous during CS. *(Afr J Reprod Health 2023; 27 [1]: 95-106).*

Keywords: Efficacy, ropivacaine, sufentanil, cesarean sections, systematic review, meta-analysis

Résumé

Les césariennes sont les opérations les plus courantes aux États-Unis et l'une des plus courantes dans le monde. L'utilisation de la dose la plus faible possible d'anesthésique permettant un accouchement sans douleur avec le moins d'effets indésirables est une préoccupation majeure. Nous avons étudié l'efficacité et l'innocuité de l'association ropivacaïne et sufentanil en regroupant les données d'études pertinentes. Nous avons effectué des recherches dans PubMed, Web of sciences, Scopus et Cochrane Library jusqu'à fin décembre 2021 et avons inclus tous les enregistrements contenant des données sur la combinaison de ropivacaïne et de sufentanil. Nous avons utilisé Review Manager pour regrouper les données sous forme de différence moyenne pour les résultats continus ou de risque relatif pour les résultats dichotomiques avec un intervalle de confiance à 95 %. La qualité méthodologique a été évaluée à l'aide de la première version de l'outil Cochrane des risques de biais. Sept essais cliniques randomisés portant sur un échantillon total de 730 femmes ont été inclus ; l'âge moyen des parturientes inscrites variait de 28 à 35 ans. Nous avons constaté que le sufentanil et la ropivacaïne combinés étaient significativement associés à une diminution du risque d'être conscient et nerveux pendant la césarienne (présenté par le niveau de sédation 1) (RR : 0,05, IC à 95 % [0,01, 0,33], P = 0,002), une diminution du risque de frissons (RR=0,29, IC à 95 % [0,19, 0,44], P<0,00001), nausées (RR=0,62, IC à 95 % [0,41, 0,92], P=0,02) et vomissements

(RR=0,27, IC à 95 % [0,12, 0,61], P=0,002). Cependant, le sufentanil et la ropivacaïne combinés étaient légèrement associés à un blocage sensoriel d'apparition tardive (DM = 0,41, IC à 95 % [0,13, 0,68], P = 0,004) et à un blocage moteur moindre de la flexion de la jambe au niveau de l'articulation de la hanche présenté par l'échelle de Bromage 0 (RR=7,15 IC95% [2,71, 18,86], P<0,0001). La ropivacaïne et le sufentanil combinés ont été associés à une réduction des douleurs viscérales et à une diminution des risques d'hypotension, de frissons, de nausées, de vomissements par rapport à la ropivacaïne isolée, sans différence concernant l'incidence de la bradycardie. Bien que la ropivacaïne et le sufentanil combinés aient été associés à un risque plus élevé de prurit, l'incidence du prurit aurait été proportionnelle à la dose de sufentanil utilisée. Cependant, la ropivacaïne et le sufentanil combinés peuvent retarder légèrement le début du blocage sensoriel à la piqûre d'épingle à T10 avec moins de blocage moteur mais avec une probabilité plus faible pour les femmes d'être conscientes et nerveuses pendant la césarienne. *(Afr J Reprod Health 2023; 27 [1]: 95-106).*

Mots-clés: Efficacité, ropivacaïne, sufentanil, césarienne, revue systématique, méta-analyse

Introduction

Cesarean section (CS) operations rose tremendously between 1970 to 2016, from 5% to 31.9%. Currently, it is the number-one executed operation in the United States, one of the most common worldwide[1]. Although epidural anesthesia is associated with a lower risk of aspiration and other benefits, It is associated with slower induction of anesthesia, with sometimes patchy asymmetrical effect[2].

Ropivacaine is an intrathecal anesthetic that was found to be effective and safe in CS[3,4]. It was reportedly able to limit the time of motor blockade with a lower intensity, shorten the time of analgesia, and have a low incidence of adverse events, including hypotension[3,5,6]. As ropivacaine has limited lipid solubility and anesthetic potency[7], a high dose was initially required to perform adequate anesthetic effects during CS. However, it was reported to cause unintended epidural spread[8] and a high incidence of hypotension and visceral pain among parturients[9]. Thus, the optimal dose that provides potent anesthesia and low adverse events was controversial; lately was set between 15 and 20 mg that could be lower in combination with spinal analgesics[10,11].

It is well established that intrathecal opioids potentiate the effect of intraspinal anesthetics[12-14]. Sufentanil is an opioid with a high affinity to opioid receptors, leading to early-onset, more potent analgesic effects than morphine[15] and fentanyl[14]. Its high lipid solubility decreased cephalad spread through cerebrospinal fluid and increased clearance rate from neuronal tissue[16].

Although sufentanil exerted an adjuvant effect that caused lowering the dose of ropivacaine[17-19], the literature review shows controversy regarding the effectiveness of combined ropivacaine and sufentanil on the onset of anesthesia during CS. Bachmann-Mennenga *et al.*[17] and Chen *et al.*[18] showed that combined ropivacaine and sufentanil had no significant effect on the onset of anesthesia during CS. However, Parpaglioni and colleagues[19] showed that the combination with sufentanil reduced the onset of anesthesia.

So, we aimed to determine the effect of combined sufentanil and ropivacaine on induction of anesthesia during CS. Also, to investigate the possible effect of the combination on postoperative adverse events.

Methods

We executed this meta-analysis in agreement with "The Cochrane handbook for systematic reviews of interventions" [20]. This study was reported tracking the up-to-date preferred reporting items for systematic review and meta-analysis (PRISMA) checklist [21].

Eligibility criteria

The subsequent criteria were demanded inclusion: (1) population: women undergoing cesarean section; (2) intervention: combination of sufentanil and ropivacaine; (3) comparator: ropivacaine alone (4) outcomes: any outcomes assessing safety and efficacy. We included only randomized clinical trials (RCTs) in English only. We excluded studies that matched the subsequent criteria: animal studies, In vitro studies, studies with an overlapped dataset, conference abstracts, reviews, book chapters, thesis, and editorials.

Literature search

We Performed a broad search in these databases: Cochrane Library, PubMed, Scopus, Web of science, from the inception to the end of December 2021. The following search query was used: (“Cesarean section” OR “abdominal Deliver*” OR “caesarean Section” OR cesarian OR csection OR “surgical delivery” OR “c-section” OR “surgical

birth" OR "c section") AND (Sufentanil OR Sufentanyl OR Dsuvia OR Sufenta OR "Sufentanil-Ratiopharm" OR "Sufentanil-Hameln" OR "R-3073" OR "R 30730") AND (Ropivacaine OR "AL 381" OR "AL-381" OR "LEA 103" OR "LEA-103" OR Naropin OR Naropeine). The search term was modified to match databases requirements (ex: quotation marks in Scopus).

Data extraction

Two authors collected the succeeding data from enrolled studies:

1. Summary: study ID (first author-publication year), study design, country, study groups, sample size, dose, inclusion criteria, outcomes, and conclusion.
2. Baseline: study arms, age (years), height (cm), weight (kg), gestational age at delivery (weeks), and duration of surgery (min).
3. Outcomes: onset time to sensory blockade at T10, Time to the greatest blockade level, motor blockade presented by Bromage scale, sedation level, quality of intraoperative analgesia, the occurrence of hypotension, bradycardia, risk of nausea, vomiting, shivering, pruritis, and ephedrine total dose (mg).

Risk of bias assessment

The methodology of enrolled studies was appraised using version one of the Cochrane risk-of-bias tool that consists of the following domains: selection bias, blinding of participants and personnel, detection bias, attrition bias, selective reporting, and other possible bias resources[22]. Authors judged each domain as low risk, high risk, or unclear.

Data synthesis

Analyses of this study were done by Review Manager (RevMan) version 5.4. continuous data was exhibited as mean difference (MD) and 95% confidence interval (CI), while dichotomous data was exhibited risk ratio (RR) and 95%CI. Heterogeneity was examined using I-squared (I2) and Chi-square (chi2) tests. We considered heterogeneity significant if I2 and the P-value of Chi2 were more than 50% and 0.1, respectively. The random-effect model and sensitivity analysis treated significant heterogeneity.

Results

Literature search and characteristics of the included trials

Our comprehensive search retrieved 424 unique records: 44 from PubMed, 76 from Web of sciences, 74 from Cochrane Library, and 230 from Scopus. Duplicates removal was done before the screening of 301 titles and abstracts. We finally included seven unique studies[17-19,23-26]. (Figure 1). Our included studies were held in China, Italy, and Germany. All the included studies are RCTs, with a total sample size of 730 women. The mean age of the enrolled population ranged from 28 to 35 years. We summarized the enrolled studies in table (1), while baseline characteristics of the enrolled population were summarized in table (2). The quality of the included studies using the Cochrane risk-of-bias tool was ranged from moderate to high. Details of the quality assessment with the authors' judgments of all domains are shown in supplementary table (S1).

1. Efficacy outcomes

Onset time to sensory blockade at T10

The pooled data of 144 parturients showed that combined ropivacaine and sufentanil were associated with significantly delayed onset of the sensory blockade to pinprick at T10 after intrathecal injection than ropivacaine (MD=0.41, 95%CI [0.13, 0.68], P=0.004). Pooled results were homogenous (I2=0%, P=0.32). Figure 2

Time to the highest level of blockade:

The pooled data of 144 parturients showed that combined ropivacaine and sufentanil were associated with more duration to reach the highest level of blockade (MD=1.08, 95%CI [0.17, 2.00], P=0.02). Pooled results were homogenous (I2=0%, P=0.77). Figure 3

Motor block and Bromage Scale:

The pooled data of 284 parturients showed that combined ropivacaine and sufentanil were associated with significant seven-folds less blockade of leg flexion at the hip joints than ropivacaine presented by Bromage Scale 0 (RR=7.15 95%CI [2.71, 18.86], P<0.0001). Pooled results were homogenous (I2=10%, P=0.33). Figure 4

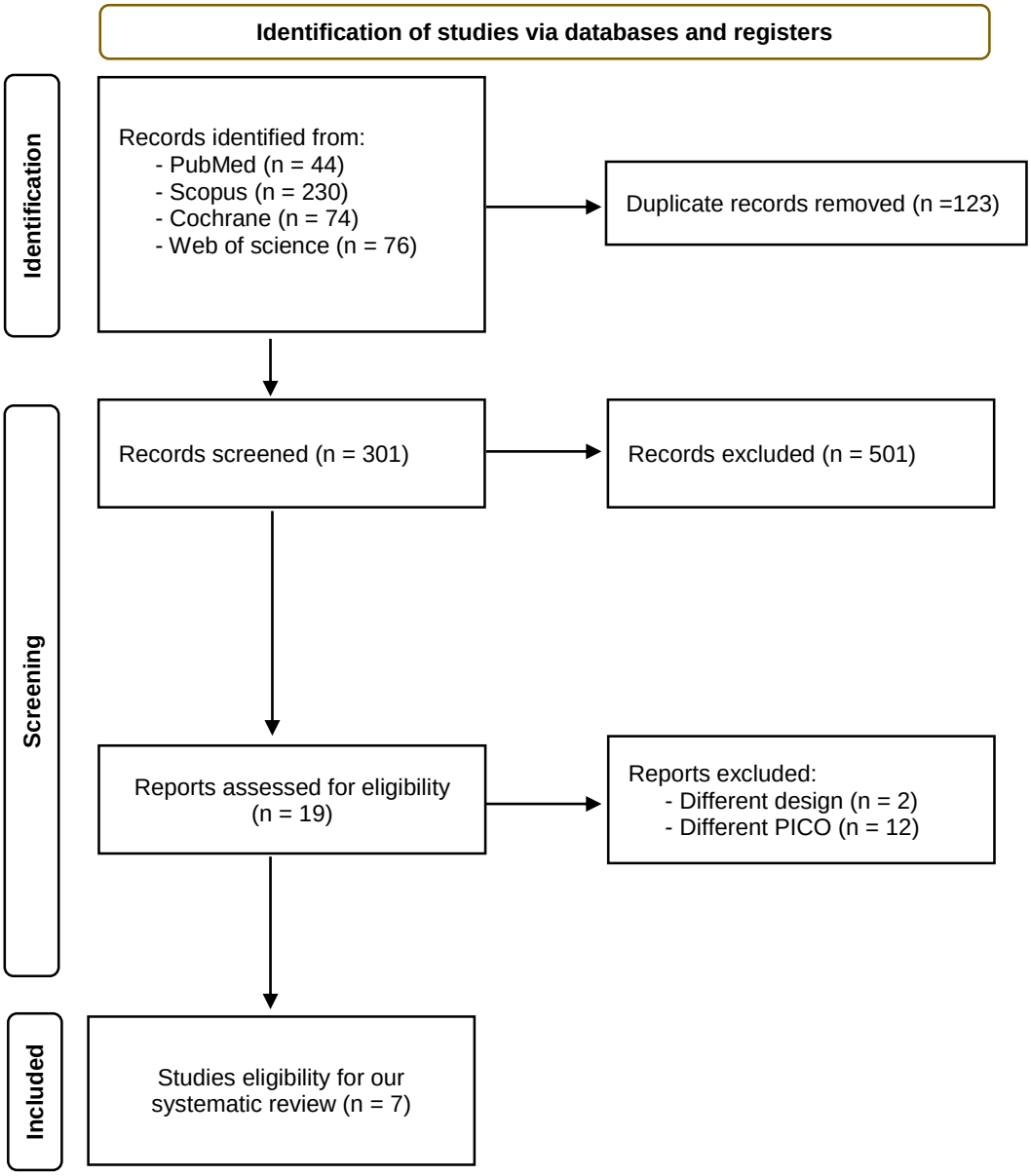

Figure 1: PRISMA flow diagram

The pooled data of 284 parturients showed that combined ropivacaine and sufentanil had no significant difference over ropivacaine regarding motor blockade of knee flexion presented by Bromage Scale 1 (RR=1.92, 95%CI [0.59, 2.82], P=0.52). Heterogeneity could not be resolved (I2=74%, P=0.009). Figure 5

The pooled data of 284 parturients showed that combined ropivacaine and sufentanil were associated with marginally significant less motor blockade of foot movement, presented by Bromage Scale 3 (RR=0.39, 95%CI [0.15,1.01], P=0.05). Figure 6. After resolving the initial heterogeneity (I2=55%, P=0.08) by excluding Parpaglioni *et al.*[19], combined ropivacaine and sufentanil had no significant difference over ropivacaine regarding motor blockade of foot movement, presented by Bromage Scale 3 (RR=0.63, 95%CI [0.20, 2.02], P=0.44) (I2=43%, P=0.18). Figure 7

Maximum sedation levels:

The pooled data of 144 parturients showed that combined ropivacaine and sufentanil were significantly associated with decreased risk of being

Table 1: Summary of the included studies

Study ID	Country	Study groups, (sample size)	Dose	Inclusion criteria	Outcomes	Conclusion
Miao 2021	China	R1, (43) R2, (45) R1S, (43) R2S, (43)	0.1% ropivacaine 0.15% ropivacaine 0.1% ropivacaine +0.5µg/ml of sufentanil 0.15% ropivacaine +0.5µg/ml of sufentanil	1- They were 21–45 years of age after 32 weeks of gestation (If the gestational age is less than 32 weeks, the newborn will be transferred to the children's hospital, which may affect the mother's mood) and 2- At the American Society of Anesthesiology physical status classification I–II), 3- They were scheduled to undergo CS under neuraxial anesthesia.	1-Postoperative NRS Scores 2-Patient Satisfaction 3-Requirements for Concomitant Analgesics 4-Recovery of Motor Function 5-Sedation Scores 6-Adverse Drug Reactions	"Although we observed a higher incidence of pruritus and numbness, coadministration of 0.15% ropivacaine and 0.5µg/ml of sufentanil administered epidurally optimized pain relief after CS, with treated subjects exhibiting lower NRS scores, shorter time to first flatus, and higher patient-satisfaction scores."
Chen 2021	China	R, (56) RS, (56)	0.75% isobaric ropivacaine 0.75% isobaric ropivacaine plus 5µg sufentanil	1- Parturients who were full-term. 2- Parturients who were older than 18 years; and 3- Parturients who had signed informed consent.	1-The maximum sensory block time (minutes) 2-Motorblock time (minutes) 3 -Shivering and visceral traction pain during anesthesia 4-Adverse reactions 5- The newborns Apgar scores	"Adding low-dose sufentanil to ropivacaine can significantly reduce the incidence of shivering and visceral traction pain after spinal anesthesia."
Chen 2010	China	R, (32) RS, (32)	15 mg ropivacaine 15 mg ropivacaine + 5µg sufentanil	1-Elective Caesarean delivery, 2-At full term singleton 3- ASA physical status class I or II	1-The median effective dose (ED50) 2-Sensory block 3-Motor block 4- Quality of intraoperative analgesia 5-Adverse events	"Intrathecal sufentanil 5mg produced a 28% reduction of ED50 of intrathecal hyperbaric ropivacaine for caesarean delivery."
Qian 2008	China	R, (40) RS, (40)	15 mg ropivacaine + 10% dextrose 0.5 mL 10 mg ropivacaine + sufentanil 5 µg	1-Healthy full-term singleton parturients (ASA I or II) 2- Undergoing elective caesarean delivery	1-Sensory block 2- Motor block 3-Incidense of hypotension 4-Ephedrine total dose 5- Quality of intraoperative analgesia 6-Adverse events 7-Duration of complete analgesia 8-Duration of effective analgesia 9-Max sedation level 1-2-3-4	

Parpagolini 2009	Italy	L, (45) R, (45) LS, (45) RS, (45)	12 mg Levobupivacaine 15 mg of ropivacaine 12 mg Levobupivacaine +sufentanil (3 mcg) 15 mg of ropivacaine + sufentanil (3 mcg)	1- Elective caesarean delivery, at term, 2- With an ASA physical status of class I or II, 3- They 156–170 cm in height	1-The minimum local anesthetic dose (MLAD) 2-Sensory block onset time 3-Sensory block regression time 4-The intensity of motor block after 60 min 5-Adverse events	"The addition of sufentanil reduced the MLAD of both the local anesthetics. It did not affect their potency ratio significantly and resulted in enhanced spinal anesthesia"
Bachmann 2004 (R=0.75%)	Germany	R, (20) RS1, (20) RS2, (20)	Ropivacaine 0.75% Ropivacaine 0.75%+10µg of sufentanil Ropivacaine 0.75%+20µg of sufentanil	1-Elective Caesarean section were studied. 2- Patients of age 18 years and above, 3- American Society of Anaesthesiologists class I or II, 4- With a singleton fetus in breech presentation	1-Onset time of anesthesia 2-Pain assessed by VAS 3-Additional analgesics 4-Sensory block 5- Motor block 6-Adverse events	"Our results suggest that addition of 20mgof sufentanil improved the epidural anesthesia with ropivacaine 0.75%for Caesarean section."
Bachmann 2004 (R=1%)	Germany	R, (20) RS1, (20) RS2, (20)	Ropivacaine 1% Ropivacaine 1%+10µg of sufentanil Ropivacaine 1%+20µg of sufentanil	1- Elective Caesarean section were studied. 2- Patients of age 18 years and above, 3- American Society of Anaesthesiologists class I or II, 4- With a singleton fetus in breech presentation	1-Onset time of anesthesia 2-Pain assessed by VAS 3-Additional analgesics 4-Sensory block 5- Motor block 6-Adverse events 7-NeonataL outcome (APGAR)	"Ropivacaine 1%alone provided sufficient analgesia. Sufentanil addition did not significantly improve the quality of epidural anesthesia with ropivacaine 1.0%for Caesarean section."

Table 2: Baseline characteristics of the enrolled patients in the included studies

Study ID	study arms	Age(years)	Height (cm)	Weight (kg)	Gestational age at delivery (weeks)	Duration of surgery (min)
Miao 2021	R1	34.1±4.2	162.9±4.9	79±12.9	38±1.53	44.67±10.74
	R2	34.1±3.7	161.6±4.9	74.3±10.4	38.33±0.77	38±8.42
	R1S	34.4±4.1	161.3±6	76.3±13.9	38±0	44±14.57
	R2S	35.±4.6	162±6	76.8±10.5	38.33±0.77	41±11.5
Parpaglioni 2009	R	34.83±3.69	164±6.29	71.27±9.19	39±1.2	44±13
	R+S	33.25±4.51	164.79±6.94	75.36±12.48	39±1	48±12
Chen 2010	R	28±3	160±5	67±6	39±1	42±6
	RS	28±3	160±4	69±7	39±1	43±7
Chen 2021	R	29.32±6.17	N/A	68.10±4.08	38.23±1.01	43.25±7.23
	RS	29.577±7.35	N/A	68.32±4.12	38.84±1.20	42.25±8.36
Qian 2008	R	29.9±2.8	161±4.9	71.2±6.6	N/A	42±6.4
	RS	28.6±3.2	160±4	70.4±7	N/A	45.3±6.6
Bachmann 2005 (R=1%)	R	28±15.16	167±5.3	88±14	39±1.1	N/A
	RS1	30.67±16.75	168±5.4	81±18	38±1.2	N/A
	RS2	28.33±11.97	170±6.1	85±12	39±1	N/A
Bachmann 2005 (R=0.75%)	R	30±15.16	168±6.1	82±17	38±0.7	N/A
	RS1	30.33±18.35	167±5.9	85±14	38±1.1	N/A
	RS2	28.67±12.77	167±5.8	85±19	38±1.1	N/A

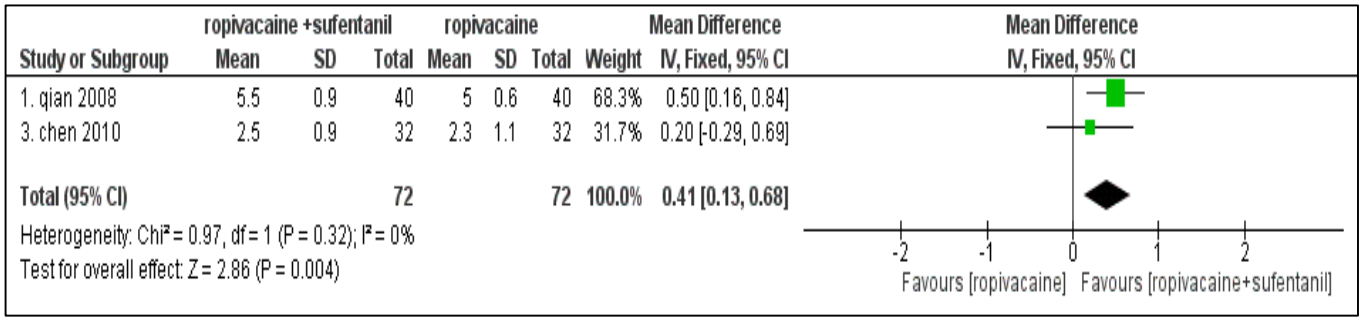

Figure 2: A forest plot of onset of sensory blockade to pinprick at T10

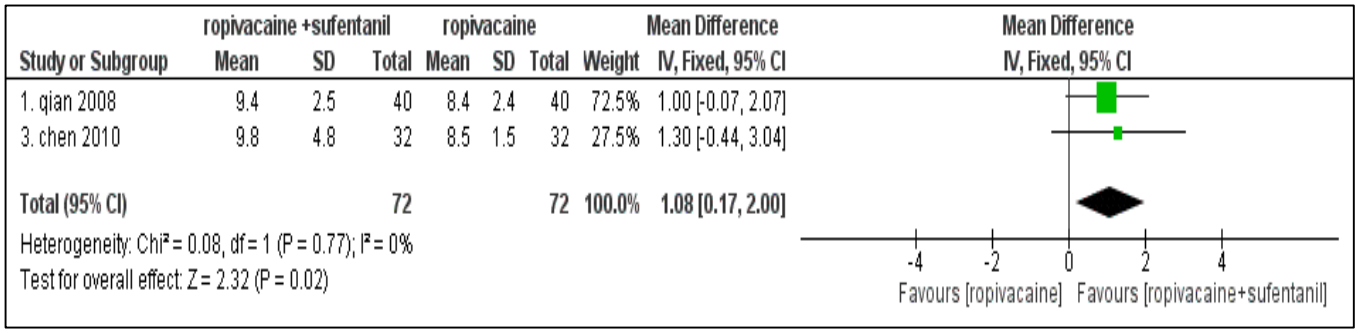

Figure 3: A forest plot of time to highest level of sensory blockade

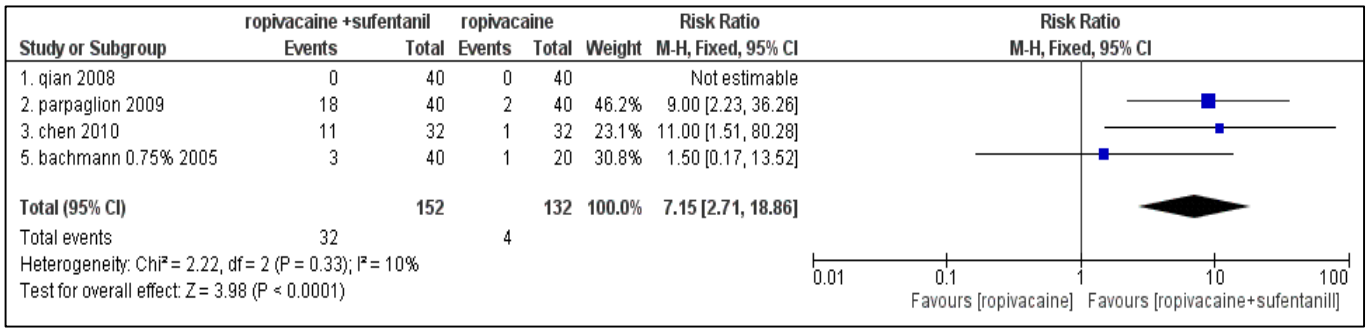

Figure 4: A forest plot of motor block of leg movement at hip joint, presented by Bromage scale 0

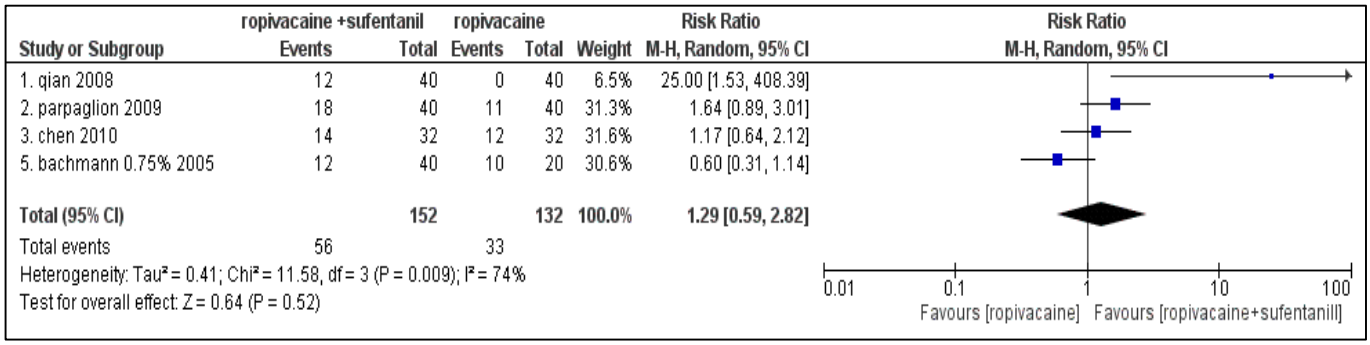

Figure 5: A forest plot of motor blockade of knee movement, presented by Bromage scale 0

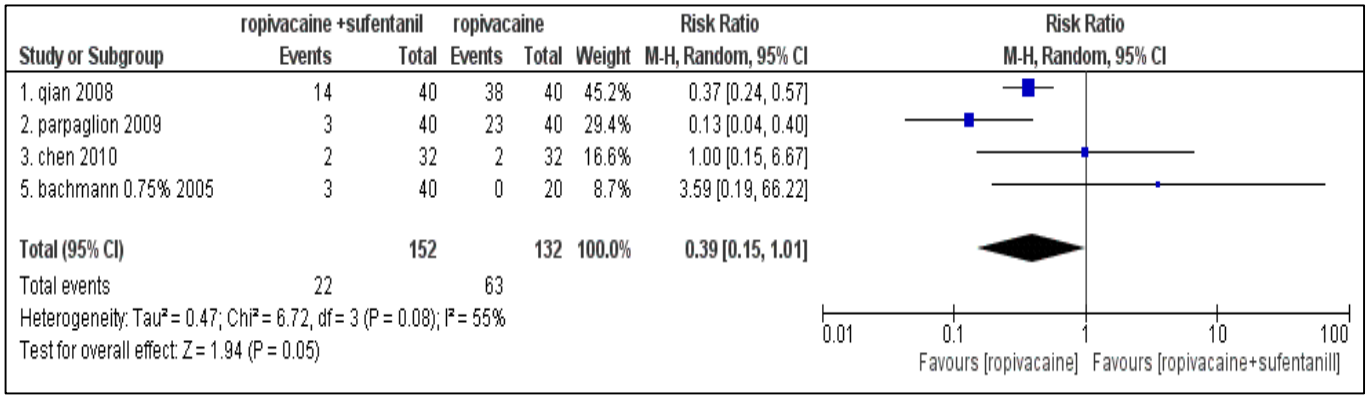

Figure 6: A forest plot of motor blockade of foot movement presented by Bromage scale 3; before resolving of heterogeneity

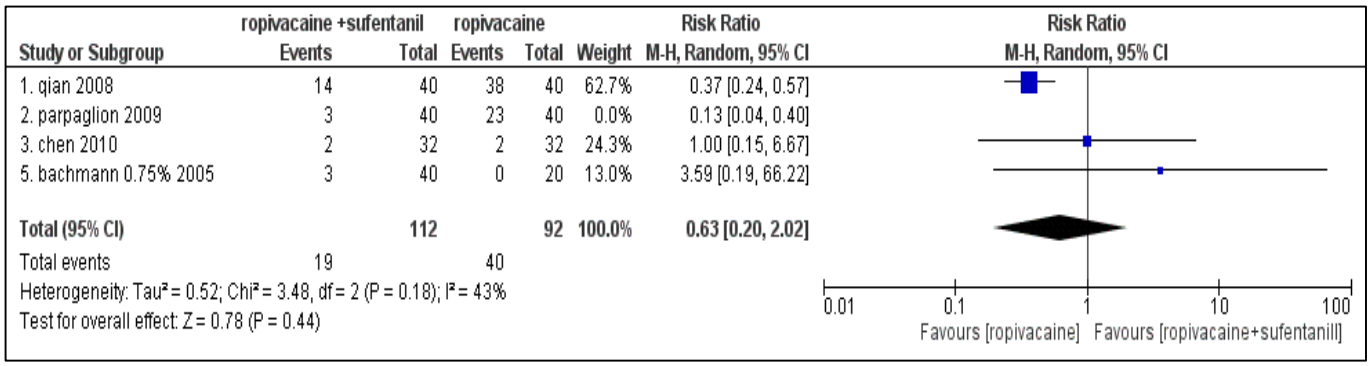

Figure 7: A forest plot of motor blockade of foot movement presented by Bromage scale 3; after resolving of heterogeneity

aware and nervous during CS (presented by Sedation level 1) by 95% (RR=0.05, 95%CI [0.01,0.33], P=0.002). Pooled results were homogenous (I2=9%, P=0.29). Supp.1

The pooled data of 144 parturients showed no significant difference between combined ropivacaine and sufentanil and isolated ropivacaine regarding the risk of being aware and calm during CS (presented by sedation level 2) (RR=0.85, 95%CI [0.43,1.68], P=0.64). The detected heterogeneity could not be resolved (I2=81%, P=0.02). Supp.2

The pooled data of 144 parturients showed that the association between the combined ropivacaine and sufentanil and the high risk of being sleepy but easily arousable during CS (presented by sedation level 3) was significant (RR=33.00, 95%CI [4.64,234.95], P=0.0005). Pooled studies were homogenous (I2=0%, P=1.00). Supp.3

2. Safety outcomes

Hypotension:

The pooled data of 515 patients showed that the difference between the combined ropivacaine and sufentanil and isolated ropivacaine was not significant regarding the incidence of hypotension (RR=0.65, 95%CI [0.39,1.09], P=0.10). Supp.4. However, when initial heterogeneity (I2=62%, P=0.03) was resolved by the exclusion of Bachmann-Mennenga *et al.*[17], the pooled data of 455 parturients showed that occurrence of hypotension had a significantly lower association with the combined ropivacaine and sufentanil by 46% than isolated ropivacaine (RR=0.54, 95%CI [0.37, 0.78], P=0.001) (I2=27%. P=0.25). Supp.5

Total ephedrine dose:

The pooled data of 224 parturients showed that the total ephedrine dose for hypotension was

significantly lower in the combined ropivacaine and sufentanil group than isolated ropivacaine (MD=-2.12, 95%CI [-3.79, -0.46], P=0.01).
The heterogeneity between studies could not be resolved (I2=69%, P=0.07). Supp.6

Shivering:
The pooled data of six homogenous studies (I2=17%, P=0.31) showed that combined ropivacaine and sufentanil were associated with decreased risk of shivering by 71% (RR=0.29, 95%CI [0.19,0.44], P<0.00001). Supp.7

Pruritus:
The pooled data of 550 parturients showed that combined ropivacaine and sufentanil were significantly associated with a higher risk for pruritus than ropivacaine (RR=16.56, 95%CI [5.00, 54.86], P<0.00001). Pooled studies were homogenous (I2=0%, P=0.47). Supp.8

Nausea:
The pooled data of seven homogenous studies (I2=17%, P=0.30) showed that combined ropivacaine and sufentanil were significantly associated with less risk of nausea than isolated ropivacaine by 38% (RR=0.62, 95%CI [0.41, 0.92], P=0.02). Supp.9

Vomiting:
The pooled data of five homogenous studies (I2=0%, P=0.64) showed that combined ropivacaine and sufentanil were significantly associated with less risk of vomiting by 73% (RR=0.27, 95% CI [0.12, 0.61], P=0.002). Supp.10

Bradycardia:
The pooled data of 344 parturients showed no significant difference between combined ropivacaine and sufentanil over isolated ropivacaine (RR=0.95, 95%CI [0.58, 1.57], P=0.85). studies were homogenous (I2=0%, P=0.53). Supp.11

Qualitative evidence about postoperative pain:
A study by Bachmann Mennenga *et al.*[23] showed that combined sufentanil 20 mcg with ropivacaine were associated with a significant reduction in visual analogue pain scale (VAS) score for skin incision, from (5±22) to (4±12), (P=0.028). another study by Chen and colleagues[25] reported that combined sufentanil and ropivacaine were associated with a significantly lower incidence of visceral traction pain (14.29%) than ropivacaine (46.43%), (P=0.03).

Miao *et al.*[26] used numerical rating scale (NRS) in reporting the difference regarding pain during rest, movement, or uterine massage, six hours after closing skin among parturients administered sufentanil in addition to different doses of ropivacaine. They found that addition of sufentanil to ropivacaine 0.1 was reported with NRS score at rest 3 [2–3] that was significantly lower than what was reported with using of ropivacaine 0.1 (3 [3–4] P<0.05) and ropivacaine 0.15 (3 [2–4], P<0.05). Likewise, the addition of sufentanil to ropivacaine 0.15 was reported was NRS score 2 [1-3] that was significantly lower than what was reported with ropivacaine 0.1 (3 [3–4], P<0.001), and ropivacaine 0.15 (3 [2–4], P<0.01). Regarding NRS score about any movement six hours after closing skin, the addition of sufentanil to ropivacaine 0.1 was reported with a lower NRS score (4 [3–5]) than what was reported with ropivacaine 0.15(5 [4–6], P<0.05); addition of sufentanil to ropivacaine 0.15 was reported was NRS score (4 [3–5]) that was significantly lower than what reported with using of ropivacaine 0.1 (5 [4–6], P<0.05) and ropivacaine 0.15 (5 [4–6], P<0.01).

Regarding NRS score about uterine massaging six hours after closing skin: the addition of sufentanil to ropivacaine 0.15 was reported with lower NRS score (6 [5–6]) than what was reported with using of ropivacaine 0.1 (7 [6–8], P<0.01).

Discussion

We found that regarding efficacy outcomes, the combined ropivacaine and sufentanil were associated with significant later onset of the sensory blockade to pinprick at T10 level with more duration to reach the highest level of sensory blockade (Figure1,2). However, Parpaglioni *et al.*[19] and others[27,28] reported earlier onset of sensory blockade with sufentanil at T5. In contrast, Bachmann-Mennenga *et al.* [17] reported no significant difference regarding the onset of the sensory blockade to T10 level.

Parturients administered combined ropivacaine and sufentanil were seven-folds less likely to have a motor blockade of leg flexion at the hip joint, with no significant difference between the combination and ropivacaine alone regarding motor

blockade of knee flexion and foot movement (presented by Bromage scales 0, 1 and 3, respectively). Our result was consistent with what was reported by Fournier *et al*.[29]

The parturients administered combined ropivacaine and sufentanil during CS were significantly more likely to be sleepy but easily arousable and less likely to be aware and nervous but have the same possibility of being aware and calm parturients administered ropivacaine only. We think that being sleepy but easily arousable may benefit relieving anxiety in the case of CS. Also, combined sufentanil and ropivacaine was associated with a significant reduction in visceral pain, as reported by Miao *et al.*[26] and others[23,25].

Regarding safety outcomes, parturients administered combined ropivacaine and sufentanil were significantly associated with lower risk of hypotension, shivering, nausea, vomiting and had a smaller indication for ephedrine. Spinal anesthesia was reportedly associated with a high incidence of shivering that ranged from 38% to 85%[24,30]. Shivering of parturients causes hypoxia that may lead to lactic acidosis or even arrhythmia. A meta-analysis by Liu et al. [31] and other studies[27,32] were consistent with our results, that an appropriate dose of sufentanil intrathecally could decrease incidence and degree of shivering. Our positive result about the low risk of nausea and vomiting associated with combined ropivacaine and sufentanil was based on data of 630 and 344 parturients, respectively. We think that other reports of high risk of nausea and vomiting [4,33,34] with combined ropivacaine and sufentanil may be due to smaller sample size, longer duration of fasting before CS, or tight suturing of peritoneum after CS.

Combined ropivacaine and sufentanil were significantly associated with a higher risk for pruritus, which was inconsistent with Chen *et al*.[25], but consistent with Miao *et al*.[26] and many other studies. By extrapolation of literature, the risk of pruritus with sufentanil administration may depend on the dose of sufentanil. A study by Cai *et al.*[35]. showed that the incidence of pruritus was only about 3% when a lower dose (0.3 mcg) of sufentanil was administered, which was more than Miao *et al.* [26] that reported an incidence of pruritus of 9.3% with administration of 5 mcg of sufentanil.

We think that discrepancy of results between previous studies may be due to different doses of ropivacaine and sufentanil, short duration of observation after labor, and small sample size. The pooling of included studies provided us with a relatively higher sample size than all individual studies giving our results higher weight than reported by discrete studies. However, this study had some limitations: small sample size of the included studies. Doses of ropivacaine and sufentanil were not identical among the included studies. Also, there were not enough data about the time to first flatus, the safety of newborns, and preoperative confounding factors.

We recommend high-quality multicenter RCTs to determine the dose of sufentanil that effectively reduces the dose of ropivacaine with the most negligible incidence of adverse events and complications, including pruritus and visceral pain.

Conclusion

The pooled data of the included studies showed that combined ropivacaine and sufentanil were associated with lower risks of hypotension, shivering, nausea, vomiting compared to isolated ropivacaine, with no difference regarding the incidence of bradycardia. Although Combined ropivacaine and sufentanil were associated with a higher risk of pruritus, the incidence of pruritus was reportedly proportionate to the used dose of sufentanil. Also, combined ropivacaine and sufentanil were reported to have a significant effect in reducing postoperative visceral pain. However, combined ropivacaine and sufentanil may slightly delay the onset of the sensory blockade to pinprick at T10 with less motor blockade but with a smaller probability for parturients to be aware and nervous during CS.

Competing interests

There are no conflicts of interests to declare.

Contribution of authors

Conception and design: all the authors. Acquisition of data: MSA, HAF, and AME. Analysis and interpretation of data: HKM, AMA, and MYE. Drafting of manuscript: AME, M.S.A, H.A.F. EIE, and FMA. Reviewing and editing: all the authors.

Ethical approval

Ethical approval was not required because the data were secondary data obtained from the databases.

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