A META-ANALYSIS ON THE EFFECTIVENESS OF POSTOPERATIVE ANALGESIA WITH INTRATHECAL NALBUPHINE VERSUS INTRATHECAL FENTANYL AS NEURAXIAL ADJUVANTS IN CESAREAN SECTION

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ABSTRACT

Background: Inadequately treated postoperative pain can contribute significantly to morbidity in women undergoing cesarean section. Recent studies showed that nalbuphine and fentanyl has promising result as neuraxial adjuvants in terms of postoperative analgesia and with lower incidents of adverse effect when use in cesarean section.

Objective: To compare postoperative analgesia with intrathecal nalbuphine versus intrathecal fentanyl as neuraxial adjuvants in cesarean section.

Methods: A meta-analysis following the PRISMA guidelines was performed. Articles were searched through the Cochrane Library, PubMed.Gov and Pubmed Central, Google Scholar, HERDIN, WPRIM and ProQuest Guideline Central using different search strategies such as keywords and MeSH term. Cochrane version 2 risk-of-bias tool for randomized trials (RoB 2) was used to assess for quality. Quantitative data were pooled and analyzed using Review Manager 5.4.

Results: A total of four trials, involving 425 full term pregnant women were compared. The pooled mean difference showed significantly longer duration of postoperative analgesia (MD=21.12 minutes, 95%CI=11.13,31.11, I^2=73%), pooled risk ratio showed lesser risk for pruritus (RR=0.09, 95%CI=0.02,0.50, I^2 = 0%) and postoperative nausea and vomiting (RR=0.38, 95%CI= 0.19,0.78, I^2 = 11%) who received intrathecal nalbuphine compared to intrathecal fentanyl.

Conclusions: The results of this meta-analysis demonstrates that the use of intrathecal nalbuphine appears to have longer duration of postoperative analgesia and lesser incidence of PONV and pruritus than fentanyl. However, due to the presence of heterogeneity it warrants that the results should be treated with caution especially with the possibility of publication bias.

Recommendations: Better literature search through inclusion of high-quality studies from relevant databases and strict adherence on the uniformity of the dosage and methods used are very crucial to achieve the target clinical outcomes and minimize the publication bias.

Keywords: *Cesarean section; Nalbuphine; Fentanyl; Meta-analysis*

INTRODUCTION

In most cesarean section, spinal anesthesia is the preferred anesthetic due to its simplicity and safety. Its advantages include a conscious mother during delivery, minimal anesthetic exposure to the neonate, and avoiding the possible complications that may be caused by general anesthesia.(1) The main limitation, however, of spinal anesthesia is its short duration of action. It does not provide prolonged postoperative analgesia when it is only performed with local anesthetics. Inadequately treated postoperative pain can contribute significantly to morbidity of surgical patients, resulting in the delay of patients' recovery, functional capacity and ultimately additional hospital stay. Adding adjuvant drugs to intrathecal local anesthetics improves quality and duration of spinal blockade, and prolongs postoperative analgesia. It is also possible to reduce dose of local anesthetics, as well as total amount of systemic postoperative analgesics. It has been almost 40 years since neuraxial opioids first underwent rigorous clinical study for use in humans.(2). Preservative-free morphine is perhaps the most popular adjuvant administered via intrathecal or epidural route in many countries. It provides proven and significantly prolonged postoperative analgesia with a reduction in postoperative analgesic requirement. However, the estimated incidents of the adverse effects such as, pruritus, nausea, vomiting and respiratory depression are significantly high. Recent studies showed that the use of neuraxial opioids such as nalbuphine and fentanyl have a promising result in terms of postoperative analgesia and with lesser side effects when used in cesarean section. The findings of this study will give additional evidence-based information which can support and guide the administration of neuraxial opioids for pregnant patients to ensure an ideal balance of risks and benefits.

Nalbuphine is a mixed synthetic agonist antagonist which attenuates the μ-opioid effects and enhances the κ-opioid effects (3). Reports show that nalbuphine has no established neurotoxicity.(4) In a study conducted by Mukherjee et al. (2011), it was seen that intrathecal nalbuphine 0.4 mg used as an adjuvant

in subarachnoid block prolongs postoperative analgesia without increased side-effects.[5] Another study reported that intrathecal nalbuphine 0.8 mg can provide good intraoperative and early postoperative analgesia without significant side effects of postoperative nausea and vomiting (PONV) or pruritus.[6] In a more recent study, adding 1 mg nalbuphine to 12.5 mg hyperbaric bupivacaine is an effective postoperative analgesia with non-significant adverse effects in patients undergoing elective cesarean section. The rapid onset of sensory and motor block (1.95±.44 min) with slow regression of sensory block and time to Bromage I (211.6± 13.2 min) was seen in patients who received nalbuphine. Also, the analgesic time was noted to be 263.7± 16.3 with a high sedation score (1.78± 0.63).[7] On the other hand, fentanyl improves duration of sensory anesthesia and postoperative analgesia without causing significant side effects.[8],[9] In one study consisting of healthy parturients (n=70) with singleton pregnancy scheduled for elective cesarean section, it was found out that the duration of sensory block was prolonged in group which received adjuvant fentanyl (p-value < 0.05) with bupivacaine as compared to the group which received subarachnoid block with 0.5% bupivacaine alone. Also, effective analgesia (134 ± 5.6 minutes versus 164 ± 9, p-value =0.00) were also prolonged in the fentanyl group. It was then concluded that addition of fentanyl to intrathecal bupivacaine during cesarean section increases the duration of postoperative analgesia without increasing risk for maternal or neonatal complications.[10] In another study, women scheduled for cesarean section (n= 40) received either 0.5% bupivacaine or isobaric bupivacaine with fentanyl added. Results showed that peak sensory level was lower and motor block was less intense in the bupivacaine-fentanyl group. On the other hand, patients from standardized bupivacaine groups were more likely to require treatment for hypotension (75% versus 15%) and had more persistent hypotension (4.6 versus. 1.0 hypotensive measurements per patient) than patients in the bupivacaine-fentanyl group. Also, more emetic effects were reported in the bupivacaine group than the bupivacaine-fentanyl

group. It was concluded that bupivacaine plus fentanyl can provide better spinal anesthesia for CS with less hypotension and vasopressor requirements.[11] However, as of this writing there has been no pooled data on the comparison of intrathecal nalbuphine versus intrathecal fentanyl as neuraxial adjuvants in cesarean section published. This study aims to compare the effectiveness of postoperative analgesia with intrathecal nalbuphine versus intrathecal fentanyl as neuraxial adjuvants to cesarean section.

METHODOLOGY

This meta-analysis conducted the following guidelines of Cochrane Handbook and reported following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Guidelines. All studies with a target population of female adult patients (at least 18years old, ASA Physical Status I and II, term pregnancy) who underwent elective cesarean section under spinal anesthesia were included. However, studies whose participants were less than 18 years old, preterm pregnancy, with known fetal abnormality, cardiovascular and cerebrovascular disease, renal disease, allergy to study medication and refused to participate were not included in the analysis. The primary intervention dose used was of 0.8 mg to 1 mg of intrathecal nalbuphine combined with 2ml 0.5% hyperbaric bupivacaine or 2ml 0.75% isobaric ropivacaine given during induction of spinal anesthesia. The comparator dose used was 20 mcg to 25 mcg intrathecal fentanyl combined with 2 ml 0.5% hyperbaric bupivacaine or 2ml of 0.75% isobaric ropivacaine. Both groups did not receive any other intervention that interfered in the outcome of the study. The primary outcomes were duration of analgesia in minutes and total analgesic requirement. Secondary outcomes were onset of sensory block, onset of motor block, incidence of maternal side effects (postoperative nausea and vomiting (PONV), pruritus and hypotension) and fetal side effects (Apgar score)

Randomized controlled trials comparing the effectiveness of post-operative intrathecal nalbuphine versus intrathecal fentanyl in cesarean section were included. Non-comparative clinical trials, outcomes research or real-world data,

animal experiments, and reviews were not included. Duplicate studies or those that were republished, observational studies, case reports or series, and other types of publications were removed. Two review authors independently screened the abstracts and titles of yielded studies with reference to the specified eligibility criteria (see Annex A). No disagreements happened between the reviewers. Assessment for risk of bias was preformed using the Review Manager program, and version 2 of the Cochrane risk-of-bias tool for randomized trials tool (RoB 2.0). Each included article was independently appraised by the primary investigator and co-investigator based on 5 bias domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Discrepancies in the included studies were resolved by reexamination of the original articles and through discussion. Investigator and co-investigator performed data extraction. Extracted data on study design, patient population, facility location, comparator, intervention, and all outcomes measured were tabulated (Table 2). A literature search from various search engines and electronic databases such as PubMed, Cochrane CENTRAL, Google Scholar, Proquest, Guideline Central, WPRIM, and local websites such as Herdin Plus were done. Included studies were also searched for relevant citations. The database medRvix was searched. Grey literature was searched to identify studies not indexed in the databases listed above. Anesthesia consultants were asked for possible reference articles or unpublished studies. Reference and citation lists of the eligible studies have been reviewed also to further look for relevant articles. To assess heterogeneity between studies for the outcome, chi-square test was used as included in the forest plot of RevMan program, with $P<0.10$ indicating significant heterogeneity, and I^2 with suggested thresholds for low (24-49%), moderate (50-74%) and high (>75%) values. Heterogeneity was explored by performing a sensitivity analysis excluding outlier studies if they were methodologically different from other studies. Risk of publication bias was detected with the use of funnel plot. The meta-analysis was performed using the Reviewer

Manager Software, version 5. (Cochrane Collaboration, UK). All data were analyzed using a random-effects model due to clinical or methodological heterogeneity. Mean difference for mean duration of analgesia between the groups was used. Relative risk for nausea, vomiting, pruritus and hypotension were estimated. Forest plots of the outcomes of interest were generated to display effect estimates and confidence intervals for both individual studies and meta-analysis. The level of statistical significance was set at $p<0.05$ values with a 95% confidence interval. To assess heterogeneity between studies for the outcome, chi-square test was used as included in the forest plot of RevMan program, with $P<0.10$ indicating significant heterogeneity, and I^2 with suggested thresholds for low (24-49%), moderate (50-74%) and high(>75%) values. Heterogeneity was explored by performing a sensitivity analysis excluding outlier studies if they were methodologically different from other studies. Risk of publication bias was detected with the use of funnel plot.

RESULTS

The initial search through databases and other sources yielded 1,128 references. Most articles were excluded due to different study designs, population, and other outcomes used. Twelve full text articles were reviewed for eligibility. Out of the twelve, six full text articles were excluded due to different surgical procedures, two were excluded due to incomplete data. A total of four (4) studies were then included in the analysis. A flowchart of study selection is summarized in Figure 1 below.

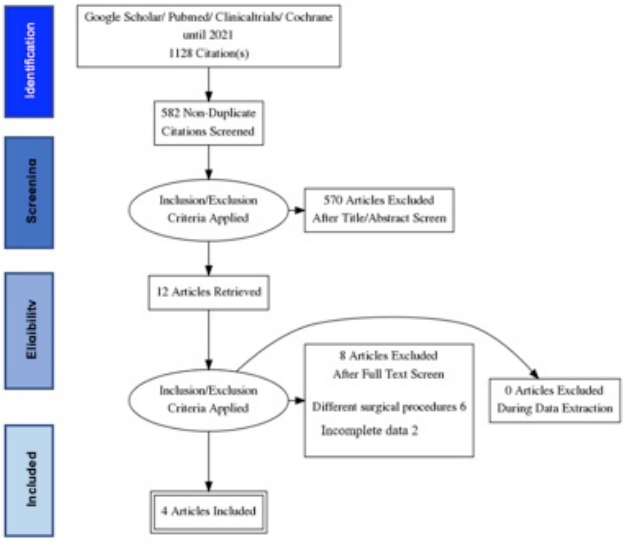

Figure 1. PRISMA diagram for study screening and selection

This meta-analysis included 4 randomized controlled trials (RCT), comparing the effect of postoperative analgesia of intrathecal nalbuphine versus intrathecal fentanyl as neuraxial adjuvants in caesarean section. Population, intervention, control and other details of the study are included in Table 2.

This study encompasses data for 425 women, wherein 165 of them were randomized to nalbuphine, while 165 were randomized to fentanyl and the remaining 95 fall into placebo arm. The population of these trials range from 60 (Gomaa et al) to 150 (Bindra et al) full term pregnant women scheduled for elective caesarean section.

Table 2. Characteristics of Studies Included in the Meta-Analysis

STUDY ID Author, Year, Location	Study Title	Population	Method/Design	Group Sample Sizes	Comparator	Intervention	Placebo arm	Study Outcomes
A Mohamed, etal 2021 Egypt (Department of Anesthesia, Surgical ICU and Pain Management, Cairo University	A comparison between intrathecal nalbuphine and fentanyl for intraoperative pain management during uterine exteriorization in cesarean section: a randomized	Inclusion: Full term parturients, ASA I and II, aged 20-45 years, weight 60-100 kgs, height 160-180 cm, for elective cesraean section under spinal anesthesia Exclusion: ASA III and IV, coagulopathies, uncooperative, allergy to local anesthetics, cardiac disorder, cns illness, preterm, small birthweight	Randomized controlled trial	Nalbuphine = 45 Fentanyl = 45 Normal saline = 45	0.5% hyperbaric bupivacaine + nalbuphine 800 mcg (Volume of 0.5% hyperbaric bupivacaine was determined by patient's weight and height table 1.3 ml -2.2 ml)	0.5% hyperbaric bupivacaine + fentanyl 25 mcg (Volume of 0.5% hyperbaric bupivacaine was determined by patient's weight and height table 1.3ml -2.2 ml)	0.5% hyperbaric bupivacaine + 0.5 ml normal saline (Volume of 0.5% hyperbaric bupivacaine was determined by patient's weight and height table)	Duration of effective analgesia, VAS for visceral abdominal, total fentanyl used as rescue analgesia, number of patients required rescue fentanyl, onset of sensory and motor block, hypotension,brady cardia, pruritus, nausea, vomiting shivering, APGAR score
B Ahmed 2019 Egypt (Department of Anesthesia and Surgical Intensive Care, Zagazig University)	Intrathecal nalbuphine versus fentanyl as an adjuvant to bupivacaine in spinal anesthesia for elective cesarean section: a randomized double blind study	Inclusion: full term singleton parturients, ASA I and II, aged 20-40 years, for elective cesarean section under spinal anesthesia Exclusion: Aged <20 or >40 years, contraindications to spinal anesthesia, morbid obesity, emergency cs, complicated pregnancy, intrauterine fetal compromise	Randomized double blind study	Nalbuphine = 40 Fentanyl = 40	12.5 mg of 0.5% hyperbaric bupivacaine + fentanyl 25 mcg	12.5 mg of 0.5% hyperbaric bupivacaine + nalbuphine 800 mcg	None	Duration of postoperative analgesia and consumed analgesic dose post op, onset of sensory and motor block, incidence of pruritus, shivering, PONV, sedation, hypotension, bradycardia and neonatal APGAR score
C Bindra, etal. 2018 Punjab, India (Department of Anesthesia and Critical Care, GMC, Paitala)	Postoperative Analgesia with Intrathecal Nalbuphine versus Intrathecal Fentanyl in Cesarean Section: A Double-Blind Randomized Comparative Study	Inclusion: Full term parturients, ASA I and II, aged 20-45 years, normal coagulation profile, for elective cesarean section under spinal anesthesia Exclusion: Contraindication for spinal anesthesia	Randomized double-blind, controlled study	Nalbuphine = 50 Fentanyl = 50 Normal saline = 50	2 ml 0.5% hyperbaric bupivacaine (10mg) + 0.4 ml fentanyl (20 mcg)	2 ml 0.5% hyperbaric bupivacaine (10mg) + 0.4 ml nalbuphine (0.8mg)	2ml 0.5% hyperbaric bupivacaine + 0.4 ml normal saline	Duration of effective analgesia, number of rescue analgesics, onset of sensory and motor block
D Gomaa, etal. 2014 Egypt (Kasr Al Ainy Hospital, Cairo University, Ahmed Maher Hospital, Cairo University)	A comparison between post-operative analgesia after intrathecal nalbuphine with bupivacaine and intrathecal fentanyl with bupivacaine after cesarean section	Inclusion: Full term parturients. ASA I and II, Aged 20-45 years, weight 60-90 kgs, height 160-180 cm, normal coagulation profile, for elective cesarean section under spinal anesthesia Exclusion: ASA III and IV, patient refusal, infection at the injection site, coagulopathy, anticoagulant medications, pre existing neurological disease, uncooperative patients, cardiac or respiratory system failure, allergy to local anesthetics	Double Blind Randomized Comparative Study	Nalbuphine = 30 Fentanyl = 30	2 ml 0.5% hyperbaric bupivacaine + 0.5 ml fentanyl (25 mcg)	2ml 0.5% hyperbaric bupivacaine +0.5 ml nalbuphine (0.8 mg)	None	Duration of analgesia, sensory and motor block, effective analgesic time, incidence of hypotension, nausea, vomiting, pruritus, shivering, and fetal APGAR score

Risk of bias of the selected articles was judged based on Risk of bias tool (ROB 2.0) and Review Manager 5.0 bias assessment tool. Two out of the four included studies in this paper had minimal risk of bias while the other two studies had high risk of bias based on five different domains as summarized in Figure 2. Sensitivity analysis performed for the primary outcome by excluding the studies with high risk of bias did not affect the conclusion.

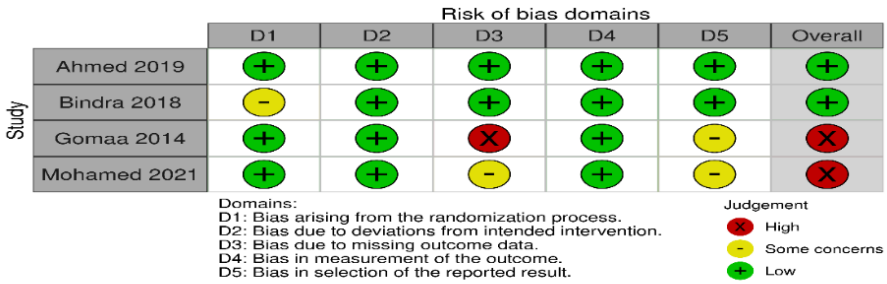

Figure 2. Risk of bias summary of included studies

Comparison of Outcomes

Primary Outcome: *Effect on the duration of postoperative analgesia*

Mean duration of effective analgesia (in minutes) for both intervention group and comparator were primarily pooled in this study, in which the overall effect estimate was calculated as the mean difference with 95% confidence interval. Pooled summary estimates were derived using the random effects model. Figure 3 indicates that patients who had **intrathecal nalbuphine as neuraxial adjuvant during cesarean section had significantly longer duration of analgesia** compared to fentanyl group (MD=21.12 minutes, 95%CI=11.13,31.11, p-value<0.0001). Intrathecal nalbuphine used as a neuraxial adjuvant in cesarean section can prolong the duration of postoperative analgesia by an average of 21.12 minutes compared to intrathecal fentanyl. The level of heterogeneity using I^2 was 73% (moderate) although the forest plot showed that all included studies leaned more towards nalbuphine than fentanyl group. (Figure 3)

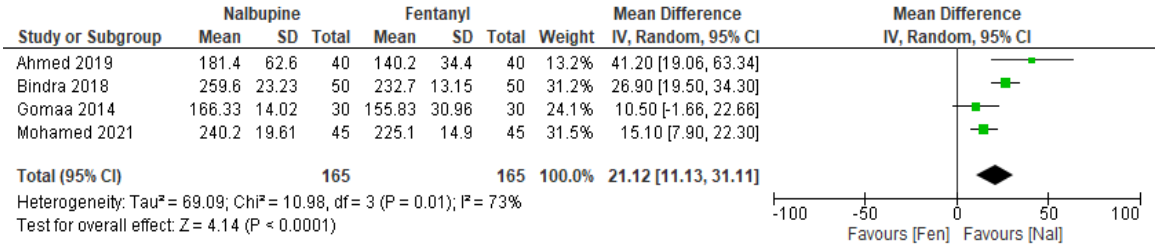

Figure 3. Meta-analysis on the effect on duration of postoperative analgesia

A sensitivity analysis omitting 1 study at a time was done to check for possible causes of heterogeneity by: 1) bupivacaine hyperbaric spinal dose 2) fentanyl dose and 3) high risk of bias. Ahmed's trial used a higher spinal dose of bupivacaine hyperbaric (12.5 mg), Bindra's used a different fentanyl dose (20 mcg), and Gomaa's trial and Mohamed trial due to 3) high risk of bias. Ahmed's trial, Bindra's trial, Gomaa's trial and Mohamed's trial were removed from the sensitivity analysis as shown in Figure 4,5,6 and 7 in which none of the individual studies eliminated the heterogeneity.

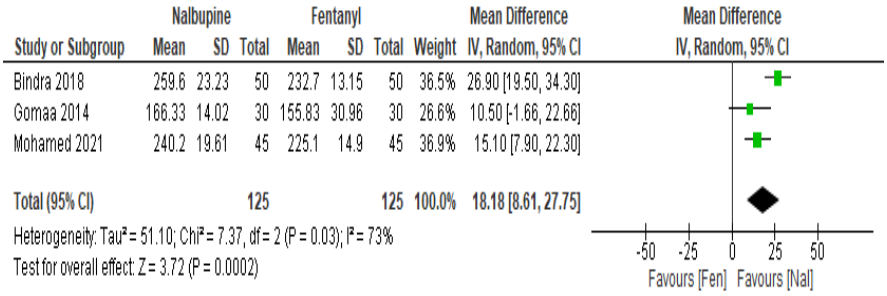

Figure 4. Sensitivity analysis on the effect on duration of postoperative analgesia excluding Ahmed's trial

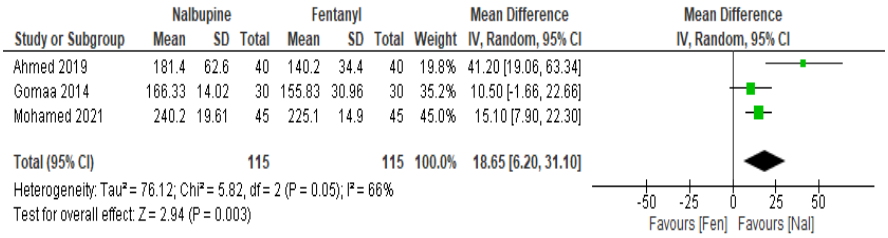

Figure 5. Sensitivity analysis on the effect on duration of postoperative analgesia excluding Bindra's trial

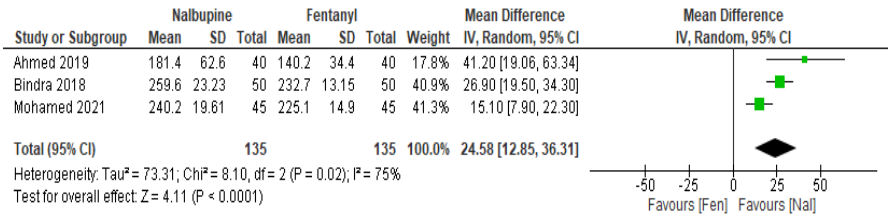

Figure 6. Sensitivity analysis on the effect on duration of postoperative analgesia excluding Gomaa's trial

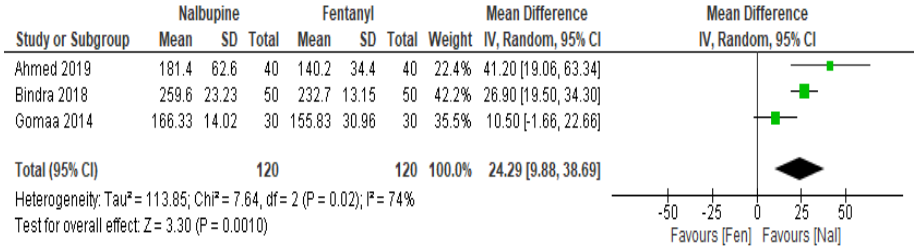

Figure 7. Sensitivity analysis on the effect on duration of postoperative analgesia excluding Mohamed's trial

Secondary Outcome 1: *Effect on time for the onset of sensory block*

Mean onset of sensory block for both intervention group and comparator group were primarily pooled. The overall effect estimate was calculated as the mean difference with 95% confidence interval. Pooled summary estimates were derived using the random effects method. All the included studies reported the mean time for onset of sensory block among patients who received intrathecal nalbuphine and intrathecal fentanyl during cesarean section. As shown in Figure 8, the overall the pooled mean difference between the two groups was comparable. (MD=0.22minutes,95%CI—0.03,0.46,pvalue=0.08). The studies demonstrated high heterogeneity (I^2=98%). Sensitivity analysis was performed to detect the possible cause of heterogeneity. When the study by Goma was identified as an outlier due to high risk of bias, the heterogeneity on the effect on the onset of sensory block between the nalbuphine group versus fentanyl group was removed (MD= 0.29 minutes 95%CI 0.27,0.31, p value <0.001, I^2=0%) and none of the remaining studies eliminate the heterogeneity.

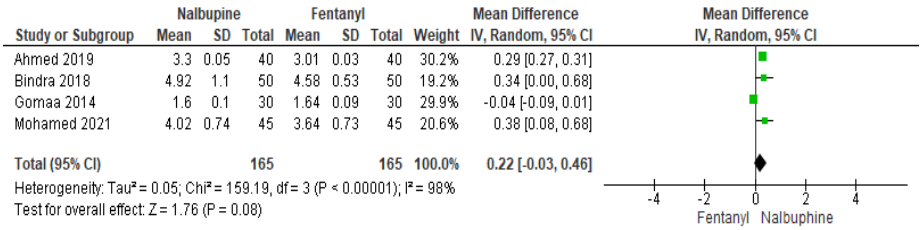

Figure 8. Meta-analysis on the effect on time for onset of sensory block

Secondary Outcome 2: *Effect on time for the onset of motor block*

Mean onset of motor block for both nalbuphine group and fentanyl group was primarily pooled in this study. The overall effect estimate was calculated as the mean difference with 95% confidence interval. Pooled summary estimates were derived using the random effects method in Review Manager 5.3. All the included studies reported the mean time for onset of motor block among patients who received intrathecal nalbuphine and intrathecal fentanyl during cesarean section. Overall, the pooled mean difference showed no significant difference between the two groups (MD=0.30, 95%CI -0.05,0.65, p value = 0.09). The studies demonstrated high heterogeneity (I^2=85%). Sensitivity analysis was also performed to detect the possible cause of heterogeneity. When Ahmed's trial was identified as an outlier due to different spinal dose of bupivacaine hyperbaric (12.5 mg) used, the heterogeneity on the effect on the onset of sensory block between the nalbuphine group versus fentanyl group was reduced (MD = 0.16 minutes 95%CI -0.03,0.35, p value = 0.09, I^2 = 38%) and none of the remaining individual studies eliminated the large heterogeneity.

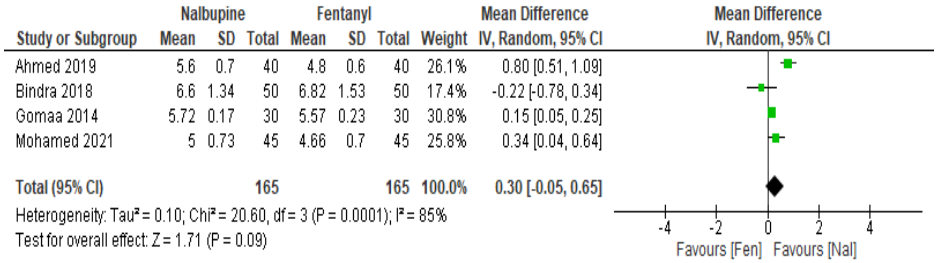

Figure 9. Meta-analysis on the effect on time for onset of motor block

Secondary Outcome 3: *Effect on the APGAR scores*

Three studies reported the effect on 1- minute APGAR scores between the nalbuphine and fentanyl group. The effect on the 1- minute APGAR scores for both intervention group and comparator group was primarily pooled. The overall effect estimate was calculated as mean difference with 95% confidence interval. Pooled summary estimates were derived using the random effects method in Review Manager 5.3. The pooled mean difference between the two groups was comparable as shown in Figure 10.

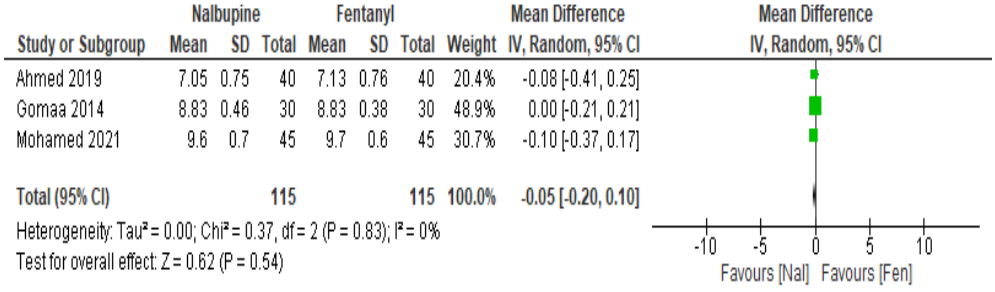

Figure 10. Meta analysis on the effect on postoperative hypotension

Secondary Outcome 4: *Effect on the postoperative hypotension*

Three studies measured the risk of postoperative hypotension as their outcome.

Relative risk for incidence of postoperative hypotension and random effects method was used to estimate the pooled effect with 95% confidence interval. Pooled risk ratio as presented in Figure 11 showed no significant difference between the two groups in terms of risk of postoperative hypotension (RR=0.78,95%CI=0.38,1.60, p value = 0.50).

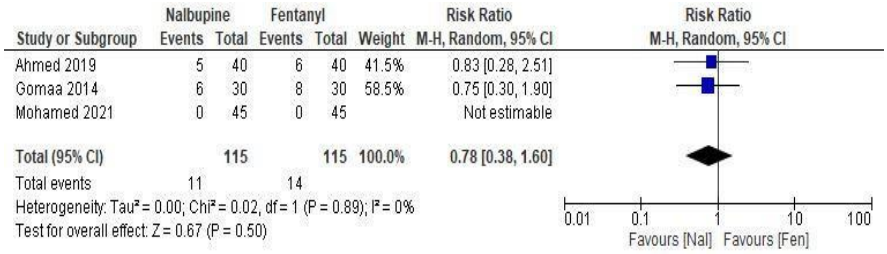

Figure 11. Meta analysis on the effect on postoperative hypotension

Secondary Outcome 5: *Effect on the postoperative nausea and vomiting* Three out of four studies measured the risk of postoperative nausea and vomiting as one of their outcomes. The relative risk for incidence of postoperative nausea and vomiting and random effects method was used to estimate the 95% confidence interval. Pooled data as presented in Figure 12 showed that the use of intrathecal **nalbuphine reduced the risk of PONV by 62%** compared to fentanyl (RR=0.38,95%CI= 0.19,0.78, p value = 0.008 I^2 = 11%).

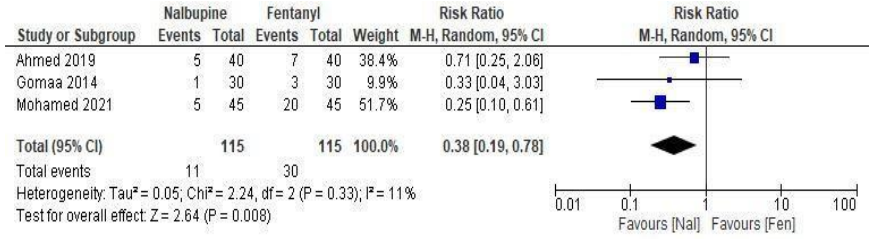

Figure 12. Meta-analysis on the effect on postoperative nausea and vomiting Secondary

Outcome 6: *Effect on postoperative pruritus*

Only three studies included the risk for postoperative pruritus between the two groups. The relative risk for incidence of postoperative pruritus and random effects method was used to estimate the 95% confidence interval. Pooled risk ratio as shown in Figure 13 showed that **nalbuphine group decreased the risk of pruritus by 91%** compared to the fentanyl group (RR=0.09, 95%CI=0.02, 0.50, p value = 0.006 I^2 = 0%). Funnel plot to address any publication bias was not done as there were <10 studies for each outcome.

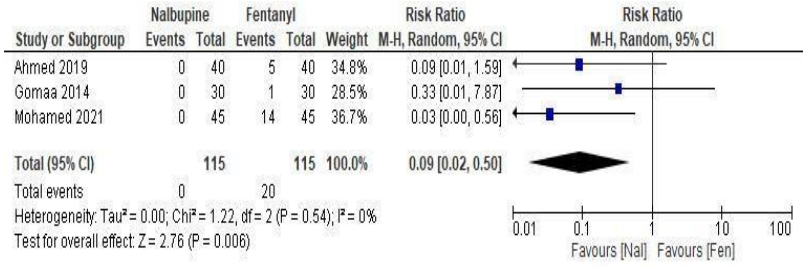

Figure 13. Meta-analysis on the effect on postoperative pruritus. Additional Analysis

DISCUSSION

After pooling the results of the study, pregnant women who were given intrathecal nalbuphine had longer a duration of postoperative analgesia compared to the fentanyl group. A longer duration of postoperative analgesia for even just 21.12 minutes will be beneficial to patients and anesthesiologists which can lead to possible lesser analgesic requirement, early postop recovery, lesser hospital stay and a satisfactorily childbirth experience. This result can be comparable to to the systematic review and meta-analysis by Yu et al [12] about the effect of nalbuphine as an adjuvant to local anesthetics in spinal anesthesia and concluded that the use of intrathecal nalbuphine can prolong the duration of analgesia (MD=118.11; 95%CI = 71.34-164.89, p<0.0001) without increasing the incidence of adverse reactions in comparison to control group (normal saline). Analysis on the

duration of postoperative analgesia of intrathecal nalbuphine versus intrathecal fentanyl in this review showed moderate heterogeneity (I^2=73%) however. the forest plot showed that majority leaned more towards nalbuphine than fentanyl. The following factors can contribute to the heterogeneity of the review. 1) different fentanyl dose (20 mcg) in Bindra et al study 2) higher spinal dose of hyperbaric bupivacaine (12.5mg) as seen in Ahmed's trial and 3) high risk of bias in Gomaa's and Mohamed's trial. Sensitivity analysis was conducted omitting one study at a time but the pooled result remained heterogenous. The presence of heterogeneity involving this outcome reduce the robustness of the result and it warrants that the result should be treated with caution. Initially, the pooled data on the effect on time for onset of sensory block showed that there was no difference between the nalbuphine group and fentanyl group (MD=0.22 minutes, 95%CI— 0.03,0.46, p value = 0.08 I^2=98%). When sensitivity analysis was conducted omitting 1 study at a time, the significant heterogeneity was eliminated after excluding the study by Gomaa et al due to high risk of bias, [13] in which the original finding was substantially changed and there was a statistical difference in the results (MD= 0.29 minutes, 95%CI 0.27,0.31, p value <0.001, I^2=0%). However, a difference of 0.07 minutes on the onset of sensory block has no clinical significance. In a study by Yu et al [12] it showed that nalbuphine group had no difference when compared to control group on the effect on onset of sensory block and supports the initial findings of this outcome. Pooled results on the effect on time for onset of motor block demonstrated that nalbuphine group were comparable to fentanyl group (MD=0.30 minutes, 95%CI -0.05,0.65, p value = 0.09 I^2=85%). After sensitivity analysis was done in which Ahmed study was excluded due to a higher spinal dose of bupivacaine hyperbaric used (12.5mg) it removed the heterogeneity. Nevertheless, the pooled results remained unchanged from the original finding (MD = 0.16 minutes (95%CI -0,03,0.35, p value = 0.09 I2=38%). Pooled results also showed that nalbuphine group reduced the risk of PONV by 62% compared to fentanyl group (RR=0.38, 95%CI= 0.19,0.78, p value = 0.008,

I^2= 11%). Similarly, the risk of pruritus was also reduced by 91% among the nalbuphine group compared to the fentanyl group (RR=0.09, 95%CI=0.02, 0.50, p value = 0.006 I^2=0%). With regards to this results, Yu's review [12] showed that the risk of pruritus (RR=0.23, 95% CI = 0.10-0.53, p<0.01) was lower in nalbuphine than the potent opioid group. In lieu of these results, Uppal et al study [14] concluded that the addition of intrathecal fentanyl was associated with higher incidence of pruritus (RR=5.89, 95%CI=2.07-16.79; p<.001; I2=0%). However, in contrast with the results of this meta-analysis, Uppal's review [14] also concluded that the risk of PONV (RR=0.41; 95%CI, 0.24-0.70; p<.001;I2 35%) was lesser in fentanyl compared to potent opioid group. Pruritus and PONV had the highest prevalence among the adverse effects of lipophilic opioids. Based on literatures and pooled data from multiple randomized trials it showed that fentanyl being a mu agonist usually have a mu receptor-based side effects like nausea, vomiting and pruritus and on the contrary, nalbuphine a mixed agonist-antagonist opioid provides analgesic effects and exhibits lesser mu adverse effects like nausea, vomiting and pruritus due to its kappa agonistic action [15] and supports the findings of this review.

Pooled results on the effect on the 1-minute APGAR scores between intrathecal nalbuphine and intrathecal fentanyl based on pooled mean difference showed that there was no significant difference between the 2 groups (MD -0.05, 95%CI= -0.20, 0.10, p value = 0.54). It should, however, be noted that none of the studies included in this meta-analysis were powered to demonstrate differences in the neonatal outcomes assessed. Similarly, none of the studies had sufficient power to detect the risk of postoperative hypotension between the two groups (RR=0.78, 95%CI=0.38,1.60, p value = 0.50).

This review also included the effect on the total analgesic requirement between nalbuphine group and fentanyl group. Ahmed et al, [16] compared the consumed total ketorolac dose (mg/patient over 24 hours) (Nalbuphine (N=40) SD= 39.8 + 14.2, Fentanyl (N=40) SD = 49.5 +14.5 p value =

0.003) and total pethidine dose (mg/patient over 24 hours) (Nalbuphine (N=40) SD=39.8 + 14.2, Fentanyl (N=40) SD=49.5 +14.5 p value= 0.005) between the two groups. While, Bindra et al [3] compared the administered intramuscular diclofenac (75mg) as rescue analgesic and the total number of rescue analgesics postoperatively in 24 hours between the two groups. (Nalbuphine (N=50) SD=1.54+ 0.705, Fentanyl (N=50) SD=2.06 +0.682 p value = <0.001). Lastly, Mohamed et al [15] compared the total fentanyl used as rescue dose (Nalbuphine (N=45) SD=5.6 95%CI 1-10.2, Fentanyl (N=45) SD=3.3 95%CI 0.4-7 p value = 0.49) and the number of patients required rescue fentanyl between the nalbuphine (Nalbuphine(N=45) SD=5 (11.1%), Fentanyl (N=45) SD=3 (6.7%) p value = 0.45). However, due to the inconsistency on how this outcome was reported in the 3 studies since 1) there was nonuniformity of pain medications used as rescue analgesics and 2) different methods were used in comparing the total analgesic requirement between the two groups, hence meta-analysis cannot be performed on the said outcome.

CONCLUSION AND RECOMMENDATION

The results of this meta-analysis demonstrates that the use of intrathecal nalbuphine appears to have a better outcome in increasing the duration of postoperative analgesia and with lesser incidence of PONV and pruritus than fentanyl. However, due to the presence of heterogeneity it warrants that the results should be treated with caution especially with the possibility of publication bias. It is heterogenous due to the nonuniformity of the dosage and method used together with the inclusion of high risk of bias studies. It has a low power to determine the significant publication bias since there are only four studies included in this review. Better literature search through inclusion of high-quality studies from relevant databases and strict adherence on the uniformity of the dosage and methods used are very crucial to achieve the target clinical outcomes and minimize the publication bias.

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