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The Used of Fentanyl as Adjunction Bupivacaine in Spinal Anaesthesia, is it Better?

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I. INTRODUCTION

Regional anaesthesia is a major factor in patient safety during Caesarean delivery. Resurgence of spinal anaesthesia as a popular technique was possible due to the development of small-bore needles with pencil-point tips and has become the preferred method of anaesthesia for elective and for many emergency Caesarean deliveries.1 A survey of Society for Obstetric Anesthesia and Perinatology members found that spinal anesthesia is most commonly used for elective cesarean delivery (85% respondents), with 90% of these respondents preferring hyperbaric 0.75% bupivacaine. Further, 79% of responders added fentanyl, 77% added morphine, and 54% added both fentanyl and morphine to the intrathecal bupivacaine for spinal anesthesia. 2

Bupivacaine is the most commonly used local anesthetics in spinal anesthesia, in The Anaesthesia textbooks recommend bupivacaine in a dose of between 12 and 15 mg. 3 A number of studies have sought an optimal dose of bupivacaine, but produced dissimilar findings with doses ranging from 5 to 20 mg. The use of a lower dose aims to decrease maternal side-effects (hypotension, intraoperative nausea/ vomiting), reduce the time to discharge from the post-anaesthesia care unit, and improve maternal satisfaction.1

Intrathecal opioid and local anesthetic combinations are popular for analgesia because of rapid, effective pain relief, but the duration of analgesia is limited. 4 Fentanyl has been used as an adjunct to bupivacaine for spinal anaesthesia for elective caesarean section as it has been shown both to improve the quality of block and reduce the need for intraoperative supplementation of opioids. 5.

Fentanyl, a lipophilic opioid, has a fast onset and is 10–20 times more potent when administered intrathecally compared to the IV route. Eventhough, a “ceiling effect” has been observed in intrathecal doses >0.25 μg/kg, implying that higher doses of intrathecal fentanyl do not improve intra-operative analgesia and may increase side effects. 6 Moreover, spinal route for fentanyl and sufentanil have not been approved by the United States Food and Drug Administration (FDA). In FDA’s labels, only intravenous or intramuscular routes are predicted for fentanyl citrate ampoules and intravenous or epidural routes for sufentanil. 7

This systematic literature review aimed to compare bupivacaine single dose with bupivacaine fentanyl combination in spinal anaesthesia.

II. METHODS

A. Search Strategy

We performed a systematic literature search from the databases PubMed, Medline, Cochrane and Google scholar with the keywords Bupivacaine, Fentanyl and Spinal Anesthesia from 1999 to 2021 and found limited search in access and language.

Total of 663 articles were identified in the initial search. After removing duplicates, 347 were screened by titles and abstracts. Obviously irrelevant articles were excluded. The remaining 103 journals were retrieved for full text assessment. After qualitative synthesis, we excluded 90 articles. In this study, total 13 articles were entered which consist of 3 Review, 3 Meta Analysis , 1 Textbook and 6 RCT.

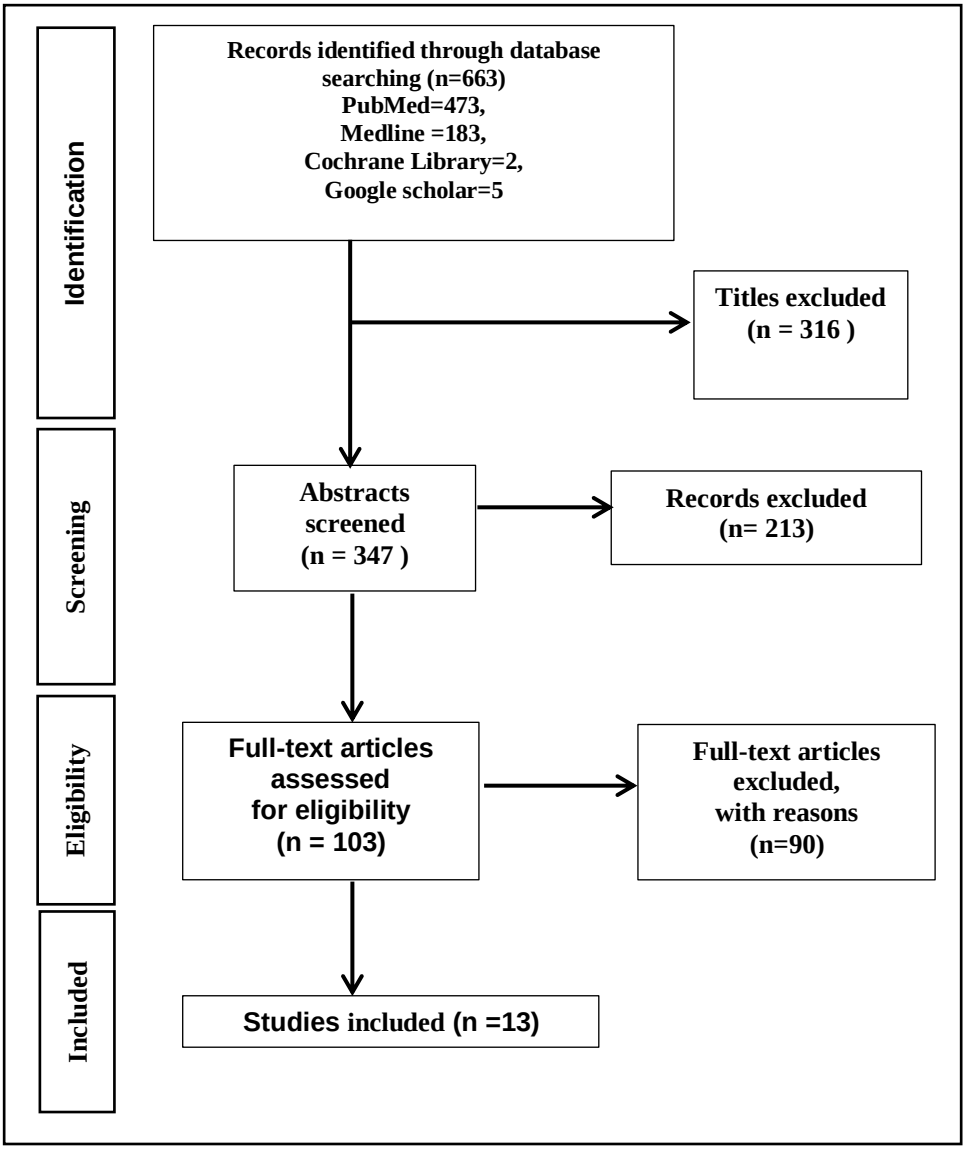

Fig. 1: Flowchart of the included studies

B. Study Selection

Articles were included in this systematic review if they fulfilled the following inclusion criteria: random allocation to treatment, have 2 group randomized receive Spinal Anesthesia Bupivacaine or Bupivacaine with Fentanyl. We applied no restriction in the type of control treatment (eg, same dosages or criteria patients). We excluded trials performed Bupivacaine with other drugs, studies on overlapping population (ie, secondary analyses of a previously published trial), studies not reporting outcome or adverse event data, studies published as abstract only, and animal studies.

In this study we used PICO for study selection technic to find out articles that are eligible and fulfilled the following inclusion criteria. Table 1

Population	Adult patients who received spinal anesthesia
Intervention	Bupivacaine
Comparation	Bupivacaine with Fentanyl
Outcome	Comparisson between Bupivacaine and Bupivacaine Fentanyl combination (eg Blood pressure, Recovery Time and Adverse Event)

Table 1: PICO

Patients were eligible for study inclusion if they met the following criteria: Adult, received Bupivacaine or Bupivacaine with Fentanyl as agent of spinal anesthesia, ASA I-III. Exclusion criteria included the following: receipt other drugs than Fentanyl as adjunction in spinal anesthesia or study who used Isobaric Bupivacaine in spinal anesthesia.

III. DISCUSSION

The search yielded 103 hits. 13 studies fulfilled the inclusion criteria and 6 RCT were included in this study. These studies included total of 413 patients who received spinal anesthesia for surgery. All patients presented ASA I-III with Caesarean surgery as type of operation. All included studies provided dose, mean age, weight and height, length of operation, outcome, adverse event and APGAR score.

A. Baseline characteristics of Patients

In this systematic literature review, Dosage, Age, Weight, Height, Length of operation, type of operation and ASA were included. Most of the studies used 9mg to 15 mg of Bupivacaine and only 1 study used a very low dose of bupivacaine which is 2,5 mg and all the patients in this study was ASA I-III. Table 2.

Baseline Patients	Drug	Dose	Age (yr)	Weight (kg)	Height (cm)	Length of the operation (min)	Type of Operation	ASA
Johana 1999 N=76	Bupivacaine	9 mg	31 ± 5	74 ± 8	164 ± 7	36 ± 9	Elective SC	I-II
	Bupivacain + Fentanyl	9 mg + 20 μg	34 ± 5	76 ± 10	165 ± 5	35 ± 7		
Choi 2000 N=40	Bupivacaine	10 mg	30 ± 4	65 ± 8	159 ± 5	45 ± 10	Elective SC	I-II
	Bupivacain + Fentanyl	10 mg + 10 μg	31 ± 4	65 ± 8	158 ± 4	48 ± 12		
Wendy 2003 N=37	Bupivacaine	2,5 mg	28 ± 4,3	74 ± 15	158 ± 5	NR	Cito SC	I-II
	Bupivacain + Fentanyl	2,5 mg + 25 μg	27 ± 5	66 ± 10	156 ± 6	NR		
Meyer 2012 N=138	Bupivacaine	15 mg	34	83 ± 3	163	NR	Elective SC	I-II
	Bupivacain + Fentanyl	12 mg + 15 μg	34	77 ± 5	163	NR		
Sun 2014 N=60	Bupivacaine	10 mg	29 ± 4	73 ± 8	165 ± 5	42,8 ± 9	Elective SC	I-II
	Bupivacain + Fentanyl	10 mg + 25 μg	30 ± 5	75 ± 9	163 ± 5	43,2 ± 8		
Farrarezi 2021 N=62	Bupivacaine	10 mg	26,9 ± 7	83,8 ± 14	163	74,6 ± 19	Elective SC	II-III
	Bupivacain + Fentanyl	10 mg + 7,5 μg	30,7 ± 7	86,5 ± 14	162	70,4 ± 18		

Table 2: Baseline Characteristic of Patients

ASA: American Society of Anesthesiologist, SC : Sectio Caesarean, NR : Not Recorded

IV. RESULTS

Johana et al found that the median onset time of anesthesia at dermatome T5 was 10 minutes, 7 and 22 minutes for Bupivacaine alone and 10 and 30 minutes for Bupivacaine with Fentanyl and both groups can reach T2-T3. Bupivacaine group has longer duration time of recovery than Bupivacaine with Fentanyl group eventhough there is no significant differences in APGAR score.8 It was a little contrast with Choi et al, they found a significant difference in dermatome block levels which Bupivacaine group has lower sensory block (T2-T3) and Bupivacaine with Fentanyl had T1 in sensory block level. This study found that when the doses of bupivacaine were increased, sensory and motor recovery times were prolonged and adding fentanyl to the intrathecal bupivacaine can delay the onset of postoperative pain, especially in sensory level without hindering the motor recovery.9 Other study found there were no significant differences among sensory latency time, maximal level of sensory block and degree of motor block in both groups Bupivacaine alone and Bupivacaine with Fentanyl. The maximum level of sensory block ranged from T2 to T6 with predominance of level at T4 in both groups. In this study observed, that the time for full motor block recovery was significantly longer in Bupivacaine alone, it is demonstrating the importance of using opioids when used lower doses of Bupivacaine.10

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Study	Drug	Dose	Distributoion of Maximal Sensory Level		Blood Pressure			Complete Recovery (min)	APGAR Score
			Highest Blok Level	Time (min)	Initial SBP (mmHg)	Lowest SBP (mmHg)	MAP		
Johana 1999 N=76	Bupivacaine	9 mg	T3	19 (7-30)	NR	NR	NR	110 ± 27	9,2 ± 0,4
	Bupivacain + Fentanyl	9 mg + 20 μg	T2	19 (10-30)	NR	NR	NR	92 ± 24	9,2 ± 0,4
Choi 2000 N=40	Bupivacaine	10 mg	T3	NR	NR	NR	NR	131 ± 31	NR
	Bupivacain + Fentanyl	10 mg + 10 μg	T1	NR	NR	NR	NR	130 ± 31	NR
Wendy 2003 N=37	Bupivacaine	2,5 mg + 25 μg	NR	NR	127 ± 17	115 ± 13	NR	NR	NR
	Bupivacain + Fentanyl	2,5 mg + 25 μg + 8% Glucose	NR	NR	130 ± 14	109 ± 11	NR	NR	NR
Meyer 2012 N=138	Bupivacaine	15 mg	T1	NR	136 ± 14	NR	101 ± 11	NR	8,6 ± 1,4
	Bupivacain + Fentanyl	12 mg + 15 μg	T1	NR	131 ± 15	NR	98 ± 10	NR	8,7 ± 0,9
Sun 2014 N=60	Bupivacaine	10 mg	T4	9,1	NR	NR	74,6 ± 6,5	127,5 ± 25,7	8
	Bupivacain + Fentanyl	10 mg + 25 μg	T4	8,47	NR	NR	75,2 ± 7,1	130,6 ± 29,8	8
Farrarezi 2021 N=62	Bupivacaine	10 mg	T4	NR	NR	NR	NR	71,4 ± 38	9 ± 1,5
	Bupivacain + Fentanyl	10 mg + 7,5 μg	T4	NR	NR	NR	NR	115,8 ± 50,9	9 ± 1,5

Table 3: Comparison Bupivacaine with Bupivacaine + Fentanyl

Meyer et al found there was no difference in sensory levels for loss of sensation to cold at 2 , 10 and 20 minutes between Bupivacaine group and Bupivacaine with Fentanyl group and there was no difference in the proportion of patients with peak sensory levels above T1 or with a significant motor block.11 In contrast with Sun et al who found that the sensory block duration was significantly higher in Bupivacaine with Fentanyl compared with Bupivacaine alone. 12

Several studies found there is no significant differences in blood pressure changes between Bupivacaine group and Bupivacaine with Fentanyl groups, eventhough low dose Bupivacaine can decrease the blood pressure. 8,9, 11,12,13 Meyer et al describe a statistically significant difference in the decrease of systolic blood pressure which Bupivacaine with fentanyl group shows less potent to decrease the blood pressure (BP fell 39 mmHg) than Bupivacaine alone (BP fell 47 mmHg) eventhough there is no differences in the incidence of hypotension.11

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Study	Drug	Dose	Vasopressor	Adverse Event					
				PONV	Hypotension	Bradycardia	Pruritus	LBP	Shivering
Johana 1999 N=76	Bupivacaine	9 mg	18	4	-	-	-	5	-
	Bupivacain + Fentanyl	9 mg + 20 μg	22	3	-	-	3	11	-
Choi 2000 N=40	Bupivacaine	10 mg	NR	16	9	-	-	-	6
	Bupivacain + Fentanyl	10 mg + 10 μg	NR	6	9	-	-	-	1
Wendy 2003 N=37	Bupivacaine	2,5 mg	NR	2	1	-	10	-	1
	Bupivacain + Fentanyl	2,5 mg + 25 μg	NR	-	3	-	11	-	6
Meyer 2012 N=138	Bupivacaine	15 mg	69	44	NR	-	3	-	-
	Bupivacain + Fentanyl	12 mg + 15 μg	69	25	NR	-	8	-	-
Sun 2014 N=60	Bupivacaine	10 mg	NR	1	4	1	1	-	1
	Bupivacain + Fentanyl	10 mg + 25 μg	NR	3	4	2	1	-	5
Farrarezi 2021 N=62	Bupivacaine	10 mg	20	12	20	-	-	-	-
	Bupivacain + Fentanyl	10 mg + 7,5 μg	17	20	17	-	1	-	-

Table 4: Adverse Event of the Studies

PONV: Post Operative Nausea and Vomiting, LBP : Low Back Pain, NR : Not Recorded

All the studies define decreased blood pressure as the major adverse event in Bupivacaine or Bupivacaine with Fentanyl when used in spinal anaesthesia. 8-13 However, some studies reported that PONV incidence was higher in Bupivacaine alone while pruritus and shivering were higher in Bupivacaine with Fentanyl group 9-12

Authors	Year	Study	Patients	Type of Surgery	Drugs	Outcome	Adverse Event
Johanna et al.[8]	1999	RCT	76 patients	Elective SC	Bupivacaine 9mg and Bupivacaine 9mg + Fentanyl 20 μg	Bupivacaine and Bupivacaine with Fentanyl induced satisfactory anesthesia for caesarean surgery lasting than an hour without any difference in the speed of onset or maximal level of sensory block	PONV higher in the Bupivacaine alone than Bupivacaine with Fentanyl
Choi et al.[9]	2000	RCT	40 patients	Elective SC	Bupivacaine 10mg and Bupivacaine 10mg + Fentanyl 10 μg	There is a significant difference in dermatome block levels, Bupivacaine group has lower sensory block (T2-T3) and Bupivacaine with Fentanyl had T1 in sensory block level.	PONV higher in the Bupivacaine alone than Bupivacaine with Fentanyl
Wendy et al.[10]	2003	RCT	37 patients	Cito SC	Bupivacaine 2,5mg + Fentanyl 25 μg and Bupivacaine 2,5mg + Fentanyl 25 μg + Glucose 8%	No significant differences among sensory latency time, maximal level of sensory block and degree of motor block in both groups	No significant differences, but pruritus is common

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Meyer et al.[11]	2012	RCT	138 patients	Elective SC	Bupivacaine 15mg and Bupivacaine 12mg + Fentanyl 15 μg	No difference in sensory levels for loss of sensation to cold at 2 , 10 and 20 minutes between Bupivacaine group and Bupivacaine with Fentanyl group	PONV higher in the Bupivacaine alone than Bupivacaine with Fentanyl
Sun et al.[12]	2014	RCT	60 patients	Elective SC	Bupivacaine 10mg and Bupivacaine 10mg + Fentanyl 25 μg	Sensory block duration was significantly higher in Bupivacaine with Fentanyl compared with Bupivacaine alone	PONV & Shivering higher in the Bupivacaine with Fentanyl than Bupivacaine alone
Farrarezi et al.[13]	2021	RCT	62 patients	Elective SC	Bupivacaine 10mg and Bupivacaine 10mg + Fentanyl 7,5 μg	There were no significant differences among the groups for sensory latency time, maximal level of sensory block and degree of motor block. The maximum level of sensory block ranged from T2 to T6, with a predominance of level T4 in the both groups	PONV higher in the Bupivacaine with Fentanyl than Bupivacaine alone

Table 5: Summary of Studies

RCT: Randomized Control Trial, SC : Sectio Caesarean, PONV : Post Opera Nausea and Vomiting

V. CONCLUSION

There are no significant differences in hemodynamic changes in the use of Bupivacaine with Fentanyl compared with bupivacaine alone for spinal anesthesia, eventhough Bupivacaine with Fentanyl had an advantage when used in operations requiring a longer duration of analgesia and Bupivacaine alone has more advantages in cesarean surgery especially patients with ASA I-II because of better recovery time and fewer adverse events when used in the right dose than bupivacaine with fentanyl combination.

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