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A comparative study of intrathecal morphine and fentanyl as additives to of 0.5% hyperbaric bupivacaine in lower segment caesarean section: A prospective randomized double blind clinical trial

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ABSTRACT

Background And Aims- Addition of small doses of opiods to intrathecal bupivacaine solution improves the quality of sensory blockade and provides better postoperative pain relief. Morphine and fentanyl are the opioids commonly used for this purpose. We aimed to compare analgesic efficacy in terms of post-operative analgesia and adverse effects associated with intrathecal morphine and fentanyl in patients undergoing Lower segment caesarean section.

Materials and Methods: - This was Prospective randomized double blind clinical trial, invoving 120 patients undergoing elective lower segment caesarean section under spinal anaesthesia. They were randomly divided into 2 groups, 60 patients in each group, group A received 0.5% hyperbaric bupivacaine 1.8ml with Morphine 100mcg, group B received 0.5% hyperbaric bupivacaine 1.8ml with Fentanyl 25mcg. Primary objective is to measure time taken for request of first rescue analgesic dose secondary objectives is to compare incidence of side effects between both groups.

Results: Onset of sensory, onset of motor block was not statistically significant between both groups. Time taken for 2 segment regression of sensory block was significantly higher in morphine group 242.83 ± 28.94 compared to fentanyl group 172.33 ±20.70, p <0.0001,time taken for regression of motor block to bromage 0 was significantly higher in morphine group 216.33 ±117.76 compared to fentanyl group 155.00 ±29.31, p<0.0002. Duration of analgesia that is time for request of first rescue analgesic at VAS score of 4 is significantly higher in morphine group with mean duration of 885.67 ± 216.41 compared to fentanyl group 356.68 ±123.48, incidence of nausea , vomiting , pruritis, shivering did not differ in patients of either group.

Conclusion: -We concluded that addition of 100 mcg morphine to intrathecal 0.5% hyperbaric bupivacaine resulted in significantly prolonged duration of postoperative analgesia compared to fentanyl 25mcg without significant side effects.

Keywords: *Spinal anaesthesia, Morphine, Fentanyl, Lower segment caesarean section, Post-operative analgesia.*

1. INTRODUCTION

Number of caesarean sections are steadily rising, spinal anaesthesia is ideal method for caesarean section, which is easy to administer, affordable and results in a quick onset of anaesthesia and lowers obstetric mortality associated with anaesthesia[1].

Spinal anaesthesia has high degree of efficacy, requires less pharmacological dosage, results in minimal neonatal depression, awake mothers, and has fewer cases of aspiration pneumonitis, however lasts for the set amount of time. Opioids and Local anaesthetics work synergistically to intensify sensory blockade without impacting sympathetic blockade, analgesia is dose dependent[2].

Intrathecal opioids reduce the dose of Local anaesthetics, improve anaesthesia and prolong surgical analgesia without causing more side effects. Beneficial analgesia has to be balanced against known adverse effects, agent and dosage selection are known to influence this risk-benefit balance. Morphine and Fentanyl, especially had been used for this purpose[3].

Morphine- A hydrophilic phenanthrene derivative, it has slower onset of action and prolonged duration compared to lipophilic opiods, nonetheless it also causes delayed respiratory depression, which necessitates vigilante attention and careful patient selection[4].

Fentanyl - Fentanyl is derivative of phenylpiperidine, it is a synthetic opiod agonist, and highly lipid soluble has a rapid onset of action and relatively short half-life.

2. METHODOLOGY

This prospective randomized double blind clinical trial was carried out in patients undergoing lower segment caesarean section under spinal anaesthesia at a tertiary care hospital, permission from hospital ethical committee was taken, study was registered in CTRI (CTRI/2021/11/037876) 120 patients were included in this study were randomly divided into two groups containing 60 patients by sealed envelope method.

Sample size calculated based on article-Comparison of Morphine with Fentanyl Added to intrathecal 0.5% Hyperbaric Bupivacaine for Analgesia After Caesarean Section.done by Salmah G S,Choy Y C.,et al

Alpha Error (%) = 1 Power (%) = 95 Sample size of 59 was obtained in each group Keeping in mind dropouts of 1 in each group we planned to take sample size of 60 in each group a total of 120 patients.

The study was conducted in patients undergoing elective lower segment caesarean at tertiary care hospital, all the patients falling under inclusion criteria were numbered

Patients posted for elective LSCS, aged between 20 and 35 years , belonging to ASA II , weighing between 40–80 kg,hight of More than 145cm , having singleton pregnancy were included in the study, patient who refused to give consent, belonging to ASA III and IV, posted for emergency procedures , patients with coagulopathies and increased intracranial tension, known allergy to study drugs and having contraindications to spinal anesthesia were excluded from the study.

Study period- April 2021-January 2023

Informed and written consent was obtained from each patient after explaining study procedure, in pre-operative room patients baseline parameters Heart rate, blood pressure, and SpO2 were measured , IV line was secured with a wide diameter cannula and injection Ondansetron 4 mg IV was given.

Using the sealed envelope procedure, the patients were divided randomly into two groups of 60 each and assigned to receive either Group A received 1.8ml of Hyperbaric Bupivacaine 0.5% + 100mcg of morphine diluted in 0.5ml NS(2.3ml).

Group B received 1.8ml of Hyperbaric bupivacaine 0.5% + Fentanyl 25mcg (2.3ml). This sterile drug was prepared by trained anesthesiologist who is not involved in intraoperative and postoperative management of patient.

Intravenous crystalloid fluids were started in the operating room vital parameters were recorded Under aseptic precautions the subarachnoid block was carried out in sitting position with a 26G Quincke spinal needle at L3-L4 or L4-L5 interspace.

All subsequent measurements were made starting from the instant the preloaded sterile drug solution was fully injected into the subarachnoid space, which was marked as the study's zero time.

Sensory level was checked every minute with 26G blunt needle until highest sensory level achieved and the time required to achieve T6 sensory block was recorded motor block was assessed using modified Bromage score. The time taken to reach modified Bromage 3 was recorded.

After subarchnoid block vital parameters - heart rate, SBP, DBP, MAP, and use of ephedrine, atropine were recorded and documented during the first 120 min at intervals of 0min,1min, 2min,3min,4min,5min,10min,15min,20min, 25min, 30min,40min,50min,60min,70min,80min, and 90min till the end of surgery.

Intravenous Ephedrine or Intravenous Phenylephrine was administered if the systolic blood pressure reduces ≥ 20% of the baseline value or if the MAP ≤60 mm Hg.

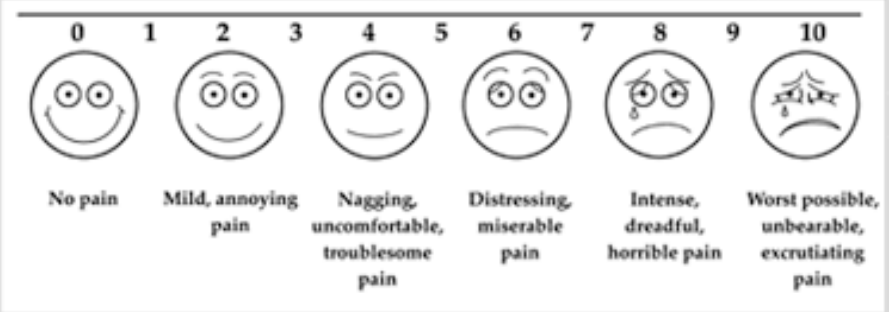
Intravenous atropine 0.6 mg was administered if the HR ≤50 bpm. Patients were not received any additional analgesic in the intra-operative period, incidence of any adverse effects such as hypotension, bradycardia, shivering, nausea,vomiting, pruritus, respiratory depression were noted.

Time for 2 segment regression of sensory block, regression of motor block to modified bromage zero was recorded.

All the patients were monitored in the post anaesthesia care unit for two hours and in ward for 24 hours till patients request for first rescue analgesic, monitored by an anaesthesia resident who is blinded in this study.

Post-operative pain assessment done at the intervals of 1st , 2nd , 4th , 8th, 16th & 24th hour by visual analogue scale (0 to 10) duration of analgesia was taken from the time of intrathecal drug administration to the first supplementation of rescue analgesic when the patient complained of pain or visual analogue score of ≥4.

Visual analogue scale



Injection Diclofenac 75 mg IV was administered if the patient complained of pain and had visual analogue scale ≥4.

Respiratory depression was defined as respiratory rate of less than 8 breath/minute.

Motor block was assessed using Modified Bromage Scale.

Bromage 0 – patient is able to move hip, knee and ankle.

Bromage 1 – not able to move hip but able to move knee and ankle.

Bromage 2 – not able to move hip and knee, but able to move ankle.

Bromage 3 – not able to move hip, knee and ankle

Sedation - measured by Ramsay sedation scale and the patient is considered sedated if the score is >/= 4.

Ramsay sedation scale

1. Patient anxious, agitated or restless
2. Patient co-operative, oriented and tranquil alert
3. Patient responds to commands
4. Asleep, but with brisk response to light, glabellar tap or loud auditory stimulus.
5. Asleep, sluggish response to light, glabellar tap or loud auditory stimulus.

Data analysis

Statistical software- SPSS 2020, and Microsoft word and Excel have been used to generate graphs, tables.

Age, height, weight, BMI, duration of surgery, hemodynamic parameters, onset of sensory block, onset of motor block, regression of 2 segment sensory block , regression of motor block, duration of post-operative analgesia compared between two groups by independent student ' t' test.

Postoperative bromage score and VAS score were compared between both groups by Mann Whitney U test.

Incidence of nausea, vomiting, pruritis, shivering were compared between both goups by chi-square test.

P value of < 0.05 is taken as significant.

3. RESULTS

Addition of morphine 100mcg along with 0.5% hyperbaric bupivacaine intrathecally produced appreciable prolongation of time to first request of postoperative analgesic requirement compared to fentanyl group morphine group- 885.67 ±216.41min, Fentanyl group-356.68 ±123.48min (table 2, graph 2)

Time taken to achieve highest sensory level of T6 and motor block of modified bromage 3 were similar between both groups (table 3, graph 3)

Time taken for 2 segment regression is significantly longer in Morphine group n(242.83 ±28.94 min) compared to Fentanyl group (172.33 ±20.70 min) and

time taken for regression of motor block (Modified bromage 0) was significantly longer in morphine group 216.33 ±117.76 min, compared to Fentanyl group 155 ±29.31min (table 4,graph 4)

Incidence of adverse effects pruritis was significantly higher in morphine group. Incidence of Nausea vomiting shivering no significant difference between both groups.

Respiratory depression was not observed in any patient of both groups.

4. DISCUSSION

In this study we compared Morphine and Fentanyl as additive to intrathecal hyperbaric Bupivacaine in Lower segment caesarean section.

We used morphine 100mcg or Fentanyl 25mcg as additive to 0.5% hyperbaric bupivacaine to compare duration of analgesia by visual analogue score as primary objective and associated side effects as secondary objectives, we observed longer time to first request of postoperative analgesic requirement in intrathecal morphine group compared to intrathecal fentanyl.

A modern meta-analysis conducted by Seki H et al.,[5] comprised 4400 participants who were undergoing elective caesarean sections in 66 placebo-controlled randomised controlled trials they established that Intrathecal opioids (fentanyl, sufentanil, and morphine) significantly extended the analgesic duration compared to the placebo by 96,96, 190 min respectively. Uppal A et al.,[6] Conducted meta-Analysis in 17 randomized clinical trials including 1064 participants they found that addition of Fentanyl to intrathecal bupivacaine reduced the need for intraoperative supplemental analgesia (relative risk, 0.18; 95% CI, 0.11–0.27; number needed to treat, 4) and the incidence of nausea or vomiting (relative risk, 0.41; 95% CI, 0.24–0.70; number needed to treat, 6.5), with increased duration of first postoperative analgesia request (mean difference, 91 minutes; 95% CI, 69–113).

In 2 clinical trials addition of fentanyl to intrathecal bupivacaine-morphine offered a similar effect compared to intrathecal bupivacaine-morphine alone, with a noticeably decreased requirement for intraoperative supplementary analgesia (relative risk, 0.16; 95% CI,0.03–0.95; number needed to treat, 9). In a meta-Analysis conducted by Sultan P et al.,[7] comparing low-dose morphine (LD; 50–100µg) with higher-dose (HD;>100–250 µg) morphine in patients undergoing elective caesarean section under spinal anaesthesia. Inclusion criteria were met by eleven articles. In total, 480 patients were enrolled in the study groups. When compared to the LD group, the HD group had a longer mean time to first analgesic request (MD, 4.49 hours [95% CI, 1.85-7.13]; P = 0.0008).In the LD group, there were fewer cases of nausea, vomiting, and pruritis.

Refika Kılıçkaya, Yavuz Orak et al.,[8] conducted double blind randomised control study to compare intrathecal morphine 0.1 mg and Fentanyl 25mcg added to 0.5% hyperbaric bupivacaine 12.5mg in 50 patients undergoing inguinal hernia repair, found that time taken for requirement of first analgesic dose was significantly prolonged in morphine group compared to fentanyl group and postoperative pain scores were significantly lower in morphine group compared to fentanyl group , our study also established similar results.

They also found that there is no statistically significant difference in incidence of nausea and vomiting between both groups which is comparable to finding of our study.

A randomised, unmasked, parallel-group control trial conducted by El Aish KA, Tafish R et al.,[9] they compared morphine 0.2 mg and Fentanyl 20mcg combined with 2ml of 0.5% hyperbaric bupivacaine for postoperative analgesia in caesarean section , they concluded that intrathecal morphine significantly increased the time needed for requirement other analgesic to 9.03 hours compared to intrathecal fentanyl 2.46 hours which was similar to our study results.

Ebrie AM, Woldeyohanis M et al., [10] Conducted prospective cohort study to evaluate effect of fentanyl added to intrathecal hyperbaric bupivacaine in caesarean section, three study groups were included as follows. Group CBF- intrathecal 0.5% of 10 mg bupivacaine +25 mcg fentanyl Group LBF- intrathecal 0.5% of 8 mg bupivacaine +25 mcg fentanyl Group CB- intrathecal 0.5% of 10 mg bupivacaine They found that Time taken for first rescue analgesia in CBF 294.6±99.5 and LBF 294.6±99.5 Group was almost similar , comparing to CB Group 177±25.88 . Results of intrathecal 25mcg fentanyl are almost similar to our study results.

Karaman S, Kocabas S et al.,[11] did a prospective randomized double blind study in 54 females undergoing caesarean section under spinal anaesthesia with 0.5% bupivacaine, they compared time to the first analgesic request which was 19.5 ±4.7 hours in morphine 0.2mg group and 6.3 ±5.2 hours sufentanil 5mcg . 86 our study established similar results, however we used intrathecal fentanyl because of easy availability. Time to onset of sensory block was comparable in both groups similar to our study Time to 2 segment regression and motor regression was longer in morphine but it was not statistically significant which is contrary to our study results.

A study titled Comparison of the Efficacy and Safety of Morphine and Fentanyl as adjuvants to Bupivacaine in Providing Operative Anesthesia and Postoperative Analgesia in Subumblical Surgeries Using Combined Spinal Epidural Technique. Which was conducted by Shah O M, Bhat K M et al., [12] In this study they included 60 patients undergoing subumbilical surgery, they were randomized in to two groups Group A- intrathecal 0.5% heavy bupivacaine 2.5 ml plus morphine 2.85 µg/kg (200 µg equated in 0.5 ml in average adult) Group B - intrathecal 0.5% heavy bupivacaine 2.5 ml plus fentanyl 0.35 µg/kg (25 µg equated in 0.5 ml in average adult). Epidural bolus was given when sensory block regressed to T11 0.25% isobaric bupivacaine 8ml with 0.04 mg/kg of morphine was given in group A, 0.25% isobaric bupivacaine 8ml with 0.7 µg/kg of fentanyl was given in group B. In this study group A, had significantly lower vas scores postoperatively and required less number of epidural bolus in first 24 hours (1.93 ±0.254) Compared to group B (4.33 ±0.606).

Duration required to achieve highest sensory block and complete motor block after spinal anaesthesia was not significant

statistically which is similar to our study results Duration required for regression of sensory block to T11 and regression of motor block after spinal anaesthesia was statistically significant , which is similar to our study results, when compared with incidence of nausea, vomiting , pruritis, shivering between two groups they found no significant difference statistically, which is similar to our results. None of patients in both groups had respiratory depression which is similar to our results.

In support of our study Gupta A, Chatterji R et al[13] found that mean duration of analgesia in Group M was 996.03 ±25.3 min and Group F was 203.88 ± 25.20 min, ,after intrathecal administration of morphine 100mcg or Fentanyl 25mcg along with 0.75% isobaric ropivacaine 2ml in caesarean section. Onset of sensory and motor block had no significant difference which is similar to our study results. Duration of 2 segment sensory and motor regression had no significant difference in both groups which is contrary to our results. Incidence of side effects nausea, vomiting, shivering, pruritis were comparable in both groups these are in same line with our results.

Salmah G S et al.,[14] conducted a prospective randomized , single-blind study in 60 parturients undergoing caesarean section , Group 1 received 0.1mg morphine while Group 2 received fentanyl 25mcg in addition to 0.5% hyperbaric bupivacaine for 88 spinal anaesthesia, length of time needed for first PCA morphine as rescue analgesic was significantly longer in morphine group compared to fentanyl group. Incidence of pruritis was comparable in both groups which is in support of our result however higher frequency of nausea vomiting in morphine group which is contrary to our results.

Consort flow diagram

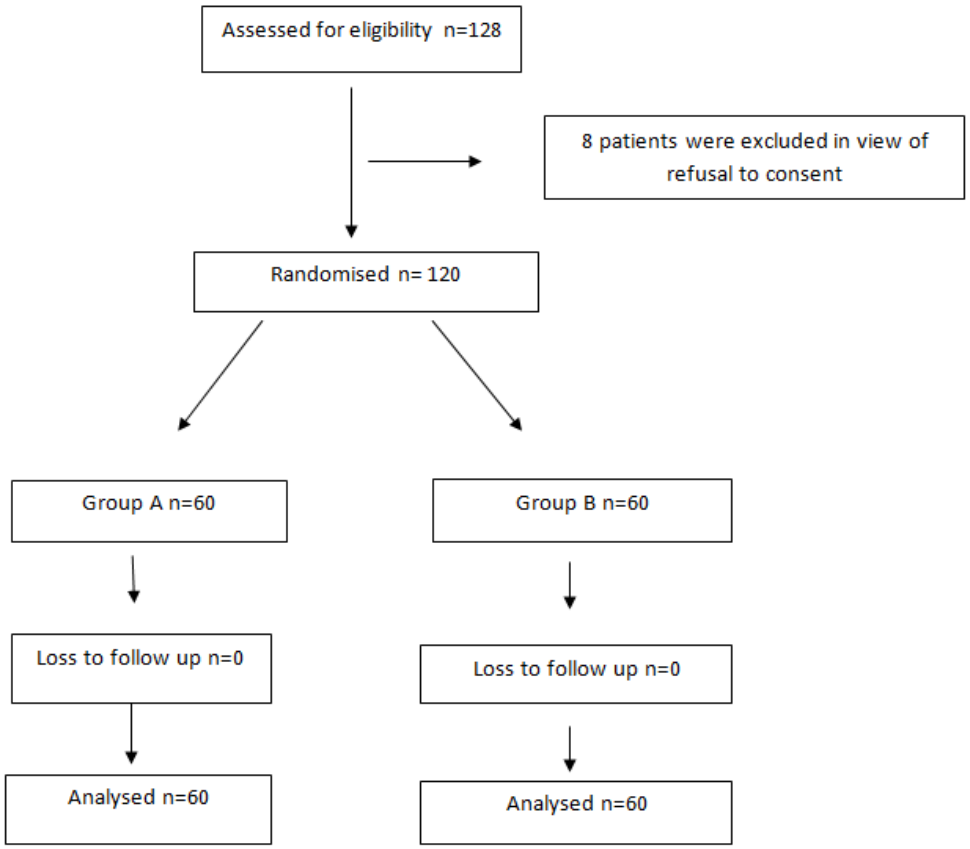
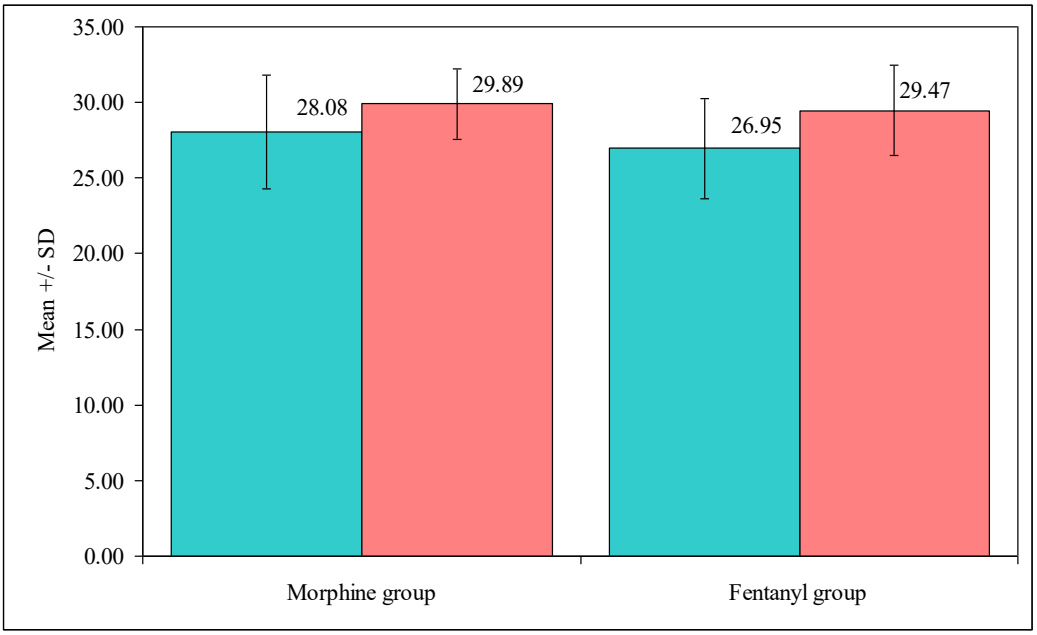


Table 1: Comparison of Morphine group and Fentanyl group with mean age and BMI by independent t test

Parameters	Morphine group			Fentanyl group			t-value	p-value
	N	Mean	SD	n	Mean	SD		
Age in yrs	60	28.08	3.76	60	26.95	3.32	1.7508	0.0826
Height in cms	60	160.28	3.20	60	159.87	6.21	0.4622	0.6448
Weight in kgs	60	76.82	6.87	60	74.95	4.40	1.7730	0.0788
BMI	60	29.89	2.37	60	29.47	2.96	0.8599	0.3916

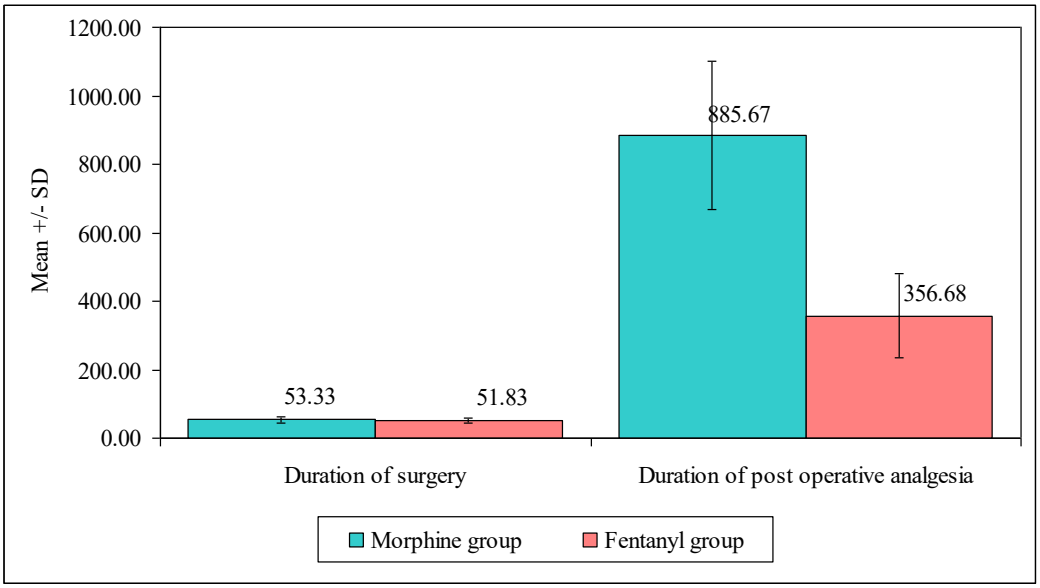


Graph 1: Comparison of Morphine group and Fentanyl group with mean age and BMI

Table 2: Comparison of Morphine group and Fentanyl group with mean duration of surgery and duration of post-operative analgesia by independent t test

Parameters	Morphine group			Fentanyl group			t-value	p-value
	N	Mean	SD	N	Mean	SD		
Duration of surgery	60	53.33	7.74	60	51.83	6.76	1.1306	0.2605
Duration of post-operative analgesia	60	885.67	216.41	60	356.68	123.48	16.4456	0.0001*

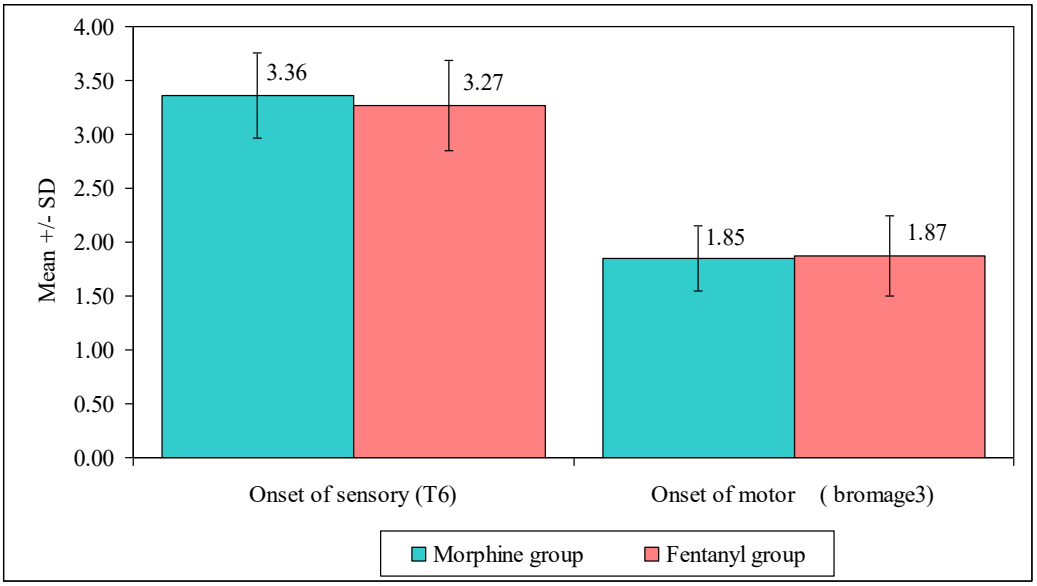
*p<0.05



Graph 2: Comparison of Morphine group and Fentanyl group with mean duration of surgery and duration of post-operative analgesia

Table 3: Comparison of Morphine group and Fentanyl group with mean Onset of sensory block, T6 (Sec) and Onset of motor block, Bronage 3 (Sec) by independent t test

Parameters	Morphine group			Fentanyl group			t-value	p-value
	n	Mean	SD	N	Mean	SD		
Onset of sensory (T6)	60	3.36	0.40	60	3.27	0.42	1.2152	0.2267
Onset of motor (bromage3)	60	1.85	0.30	60	1.87	0.37	-0.2703	0.7874

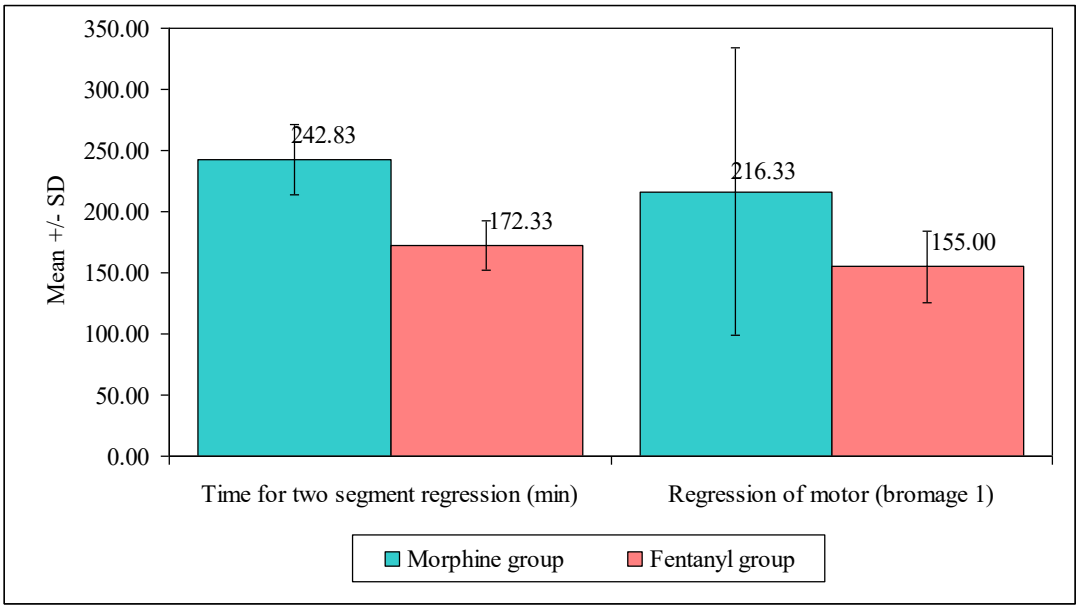


Graph 3: Comparison of Morphine group and Fentanyl group with mean Onset of sensory block, T6 (Sec) and Onset of motor block, Bronage 3 (Sec)

Table 4: Comparison of Morphine group and Fentanyl group with mean Time for two segment regression (min) and Time for rescue analgesia (min) by independent t test

Parameters	Morphine group			Fentanyl group			t-value	p-value
	n	Mean	SD	N	Mean	SD		
Time for two segment regression (min)	60	242.83	28.94	60	172.33	20.70	15.3481	0.0001*
Regression of motor (bromage 1)	60	216.33	117.76	60	155.00	29.31	3.9148	0.0002*

*p<0.05

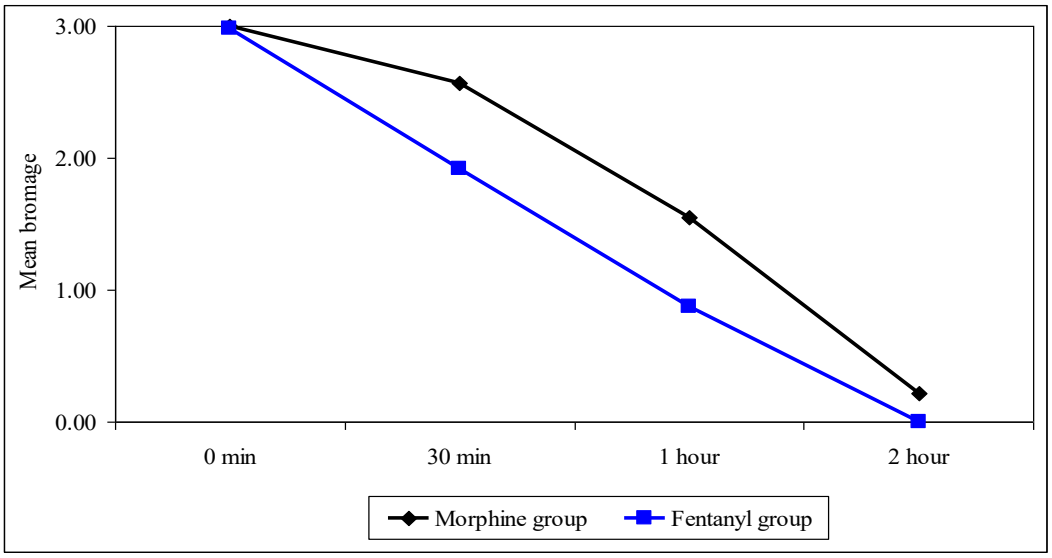


Graph 4: Comparison of Morphine group and Fentanyl group with mean Time for two segment regression (min) and Time for rescue analgesia (min)

Table 5: Comparison of Morphine group and Fentanyl group with bromage scores at different treatment time points by Mann-Whitney U test

Treatment time points	Morphine group			Fentanyl group			Z-value	p-value
	Mean	SD	Mean rank	Mean	SD	Mean rank		
0 min	3.00	0.00	61.00	2.98	0.13	60.00	0.1548	0.8770
30 min	2.57	0.50	77.17	1.92	0.50	43.83	5.2460	0.0001*
1 hour	1.55	0.57	76.48	0.87	0.57	44.52	5.0308	0.0001*
2 hour	0.22	0.49	57.29	0.00	0.00	47.50	1.6308	0.1029

*p<0.05

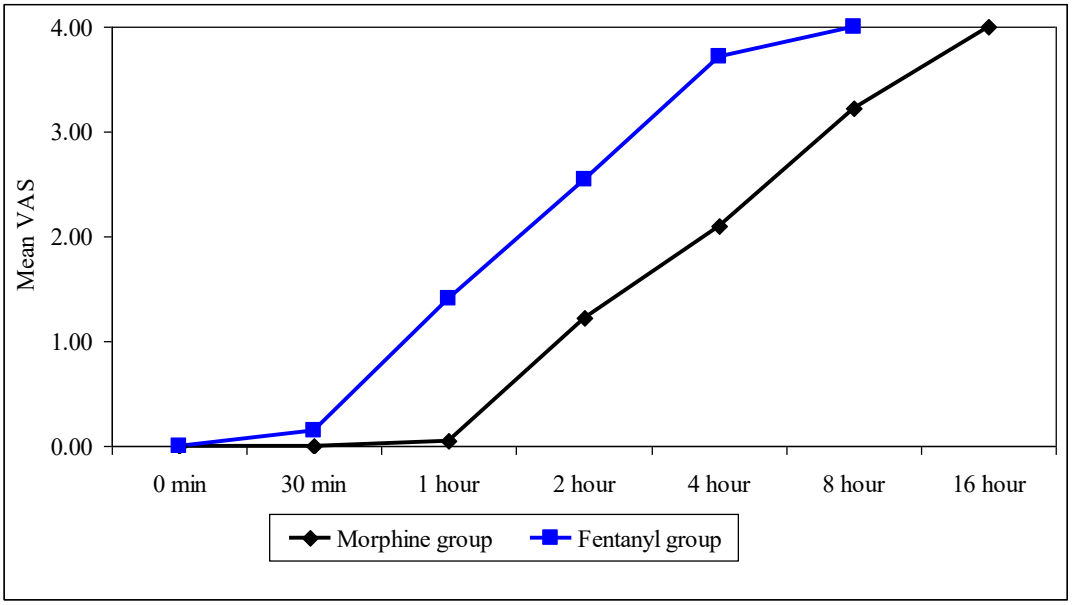


Graph 5: Comparison of Morphine group and Fentanyl group with bromage scores at different treatment time points

Table 6: Comparison of Morphine group and Fentanyl group with VAS scores at different treatment time points by Mann-Whitney U test

Treatment time points	Morphine group			Fentanyl group			Z-value	p-value
	Mean	SD	Mean rank	Mean	SD	Mean rank		
0 min	0.00	0.00	60.50	0.00	0.00	60.50	-0.0026	0.9979
30 min	0.00	0.00	56.00	0.15	0.36	65.00	-1.4145	0.1572
1 hour	0.05	0.22	31.38	1.41	0.50	89.11	-9.1258	0.0001*
2 hour	1.22	0.49	34.00	2.54	0.54	86.44	-8.2886	0.0001*
4 hour	2.10	0.35	32.36	3.71	0.53	87.58	-8.7636	0.0001*
8 hour	3.22	0.52	32.50	4.00	0.00	60.00	-4.3643	0.0001*
16 hour	4.00	0.00	-	-	-	-	-	-

*p<0.05

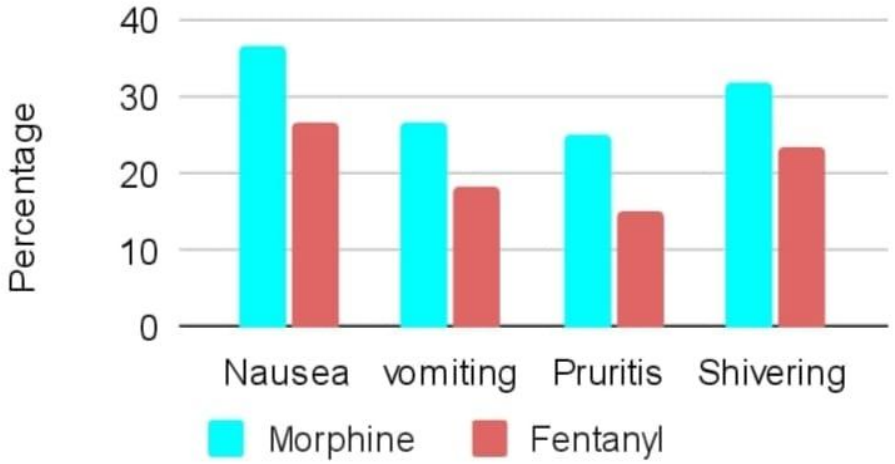


Graph 6: Comparison of Morphine group and Fentanyl group with VAS scores at different treatment time points

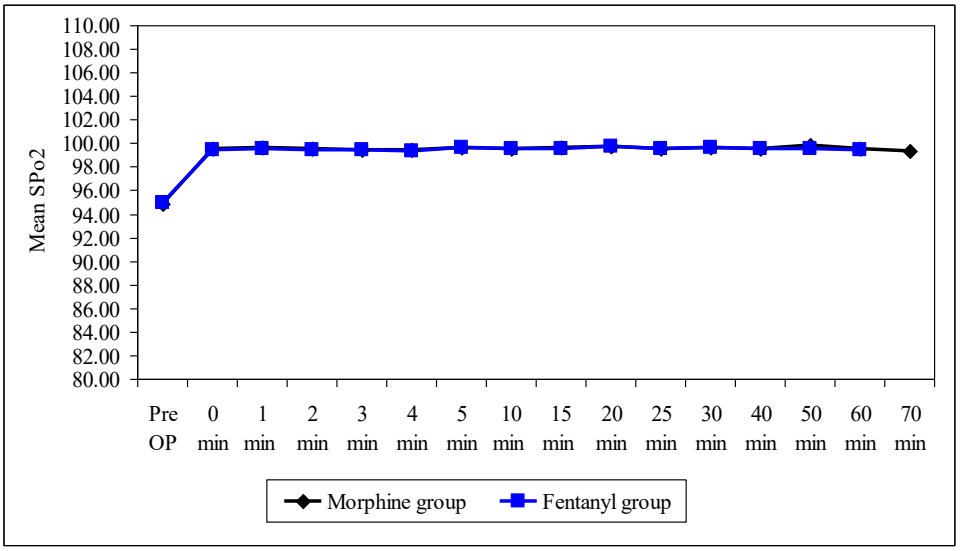
Table 7: Comparison of Morphine group and Fentanyl group with status of side effcets

Side effects	Morphine	%	Fentanyl	%	Total	%	Chi- square	p-value
Nausea								
No	38	63.3	44	73.3	82	68.3	1.3864	0.39015
Yes	22	36.6	16	26.6	38	31.6		
Vomiting								
No	44	73.3	49	81.6	93	77.5	1.1947	0.274375
Yes	16	26.6	11	18.3	27	22.5		
Pruritis								
No	45	75	51	85	96	80	1.875	0.170904

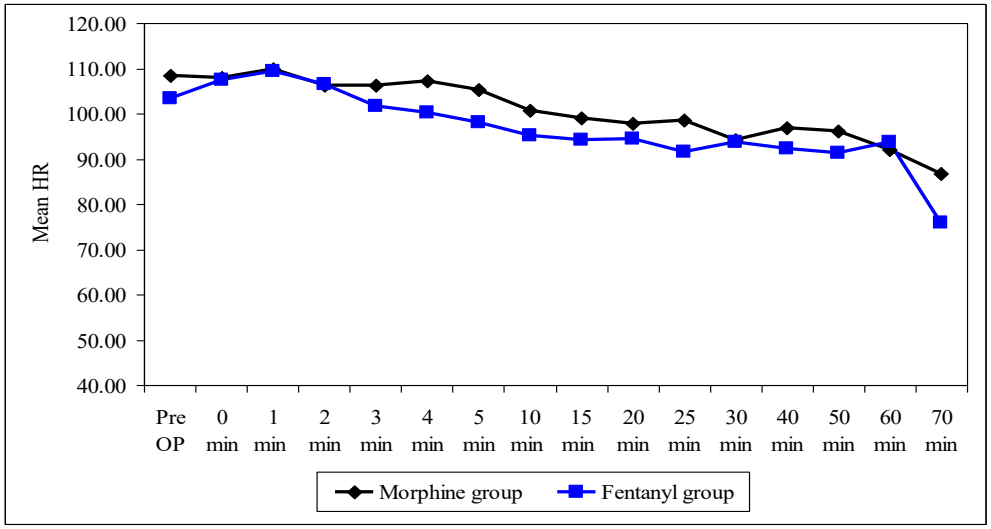
Yes	15	25	9	15	24	20		
Shivering								
No	41	68.33	46	76.67	87	72.50	1.0450	0.3070
Yes	19	31.67	14	23.33	33	27.50		
Total	60	100.00	60	100.00	120	100.00		



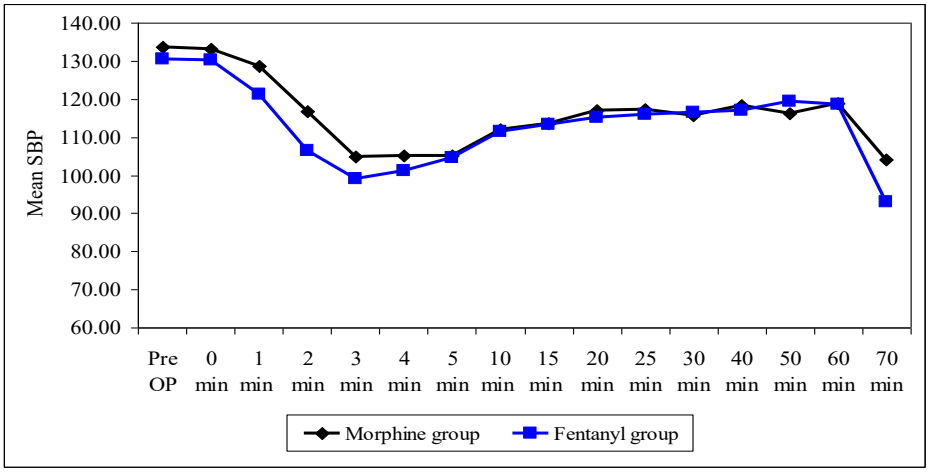
Graph 7: Comparison of Morphine group and Fentanyl group with status of side effcets



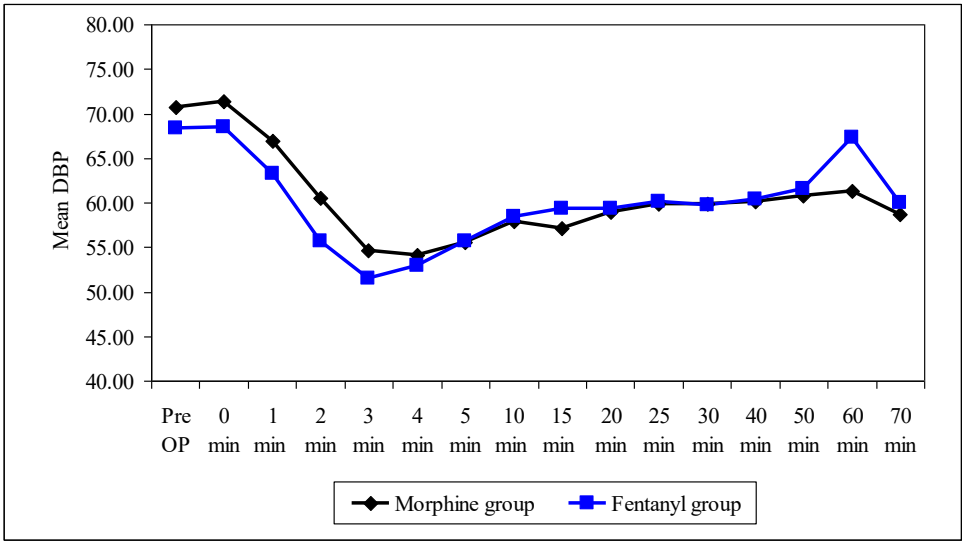
Graph 8: Comparison of Morphine group and Fentanyl group with mean SPo2 at different treatment time points



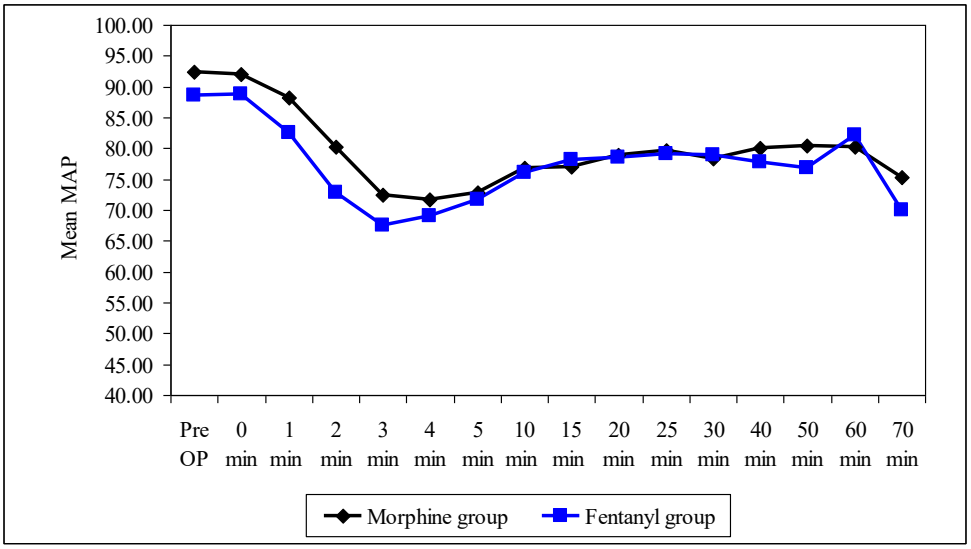
Graph 9: Comparison of Morphine group and Fentanyl group with mean HR at different treatment time points



Graph 10: Comparison of Morphine group and Fentanyl group with mean SBP at different treatment time points



Graph 11: Comparison of Morphine group and Fentanyl group with mean DBP at different treatment time points



Graph 12: Comparison of Morphine group and Fentanyl group with mean MAP at different treatment time points

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