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Effect of Fentanyl and Buprenorphine on post-operative analgesia when administered via different routes- A Prospective Randomized double-blind Study.

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ABSTRACT

Background and objectives

Spinal analgesia can also be prolonged by administration of drugs via intravenous route. This study aims to evaluate the effectiveness of fentanyl and buprenorphine given by intravenous route and intrathecal route on spinal analgesia and to compare the side effects of each.

Materials and methods

One hundred and fifty ASA I/II patients aged between 18-65 years posted for elective surgery under spinal anaesthesia were randomly allocated into 5 groups of 30 each. Group A(Control Group) received 2.5ml of bupivacaine heavy 0.5% with 0.2 ml normal saline(NS) intrathecally(IT) and 10 ml of IV NS over 1min. Group B(IVF) received 2.5 ml of bupivacaine heavy 0.5% with 0.2 ml NS by IT route and IV fentanyl at 2 mcg /kg diluted to 10 ml with NS. Group C (ITF) received 2.5 ml of bupivacaine 0.5 % H with 10 mcg of fentanyl IT and 10 ml of IV NS. Group D (ITB) received 2.5 ml of bupivacaine 0.5 % H with 60 mcg of Buprenorphine IT and 10 ml of IV NS . Group E (IVB) received 2.5 ml of bupivacaine heavy 0.5% with 0.2 ml normal saline IT and IV buprenorphine at 2 mcg /kg diluted to 10 ml with NS.

Results

Demographic data were comparable in all groups. the onset of sensory block at L1 was least in group C(2.47±0.5), the VAS scores were significantly low in opioid groups compared to control from 2-12h, with lowest scores in group D. HR and MAP ,were significantly less ($p<0.05$) in group B and group E during intraoperative period and patients were better sedated than in other groups. The time for first analgesic request (VAS >4) was longest with group D (7.5±0.49), followed by group C and E (5.95±0.67 and 5.6±0.56) which were comparable, followed by group B (4.46±0.47), and least in group A.

Conclusion

Onset of sensory block was significantly early in intrathecal fentanyl group. Intrathecal Buprenorphine by far provided the longest duration of analgesia though intraoperative opioids given intravenously also increase the duration of analgesia postoperatively. Patients who received intravenous opioids were better sedated and maintained lower HR and MAP compared to other groups.

Keywords: intrathecal, intravenous, fentanyl, buprenorphine, bupivacaine.

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INTRODUCTION

Upto 75% of patients after surgery have poor or minimal pain relief. The pain is unpleasant and is associated with arterial hypoxaemia, venous thrombosis, tachycardia, myocardial ischaemia and a more florid hormonal response to surgery. Postoperative analgesia can be achieved by adding adjuvant to spinal anesthesia, epidural analgesia,IV opioids,NSAIDS etc. Despite advances in the management of postoperative pain, many patients still suffer from postoperative discomfort, probably due to difficulties in balancing a reliable, prolonged, and effective pain regimen with acceptable side effects.

Spinal anaesthesia can be prolonged after adding adjuvants to local anaesthetics or by intravenous route such as alpha 2 agonists such as clonidine and dexmedetomidine(1). Although IT opioids supplement spinal anesthesia, that fact alone does not prove that the drug site of analgesic action resides in the spinal cord. An experimental study showed that a significant amount of an IT administered lipophilic opioid, such as fentanyl, is lost by diffusion into the epidural space and subsequently into the plasma[2].

However literature pertaining to intravenous supplementation of opioids to increase duration of spinal analgesia is sparse.Fentanyl is a phenylpiperidine synthetic opioid with strong agonist at μ receptors and has rapid onset and short duration of action with lesser incidence of respiratory depression Buprenorphine is a mixed agonist antagonist with high affinity at mmu and kappa receptors. Intravenous opioids act as agonists at stereospecific opioid receptors in brainstem, spinal cord and outside the CNS in peripheral tissue on primary afferent neurons[6]. Based on this, we hypothesized that fentanyl and buprenorphine which are highly lipophilic when given intravenously, will prolong the computer-generated randomization table.
Allocation concealment was performed using sequentially numbered, coded, sealed.

spinal analgesic effect. The additional advantage with intravenous opioids is that it provides sedation and maintain hemodynamics especially in anxious cardiac patients.

OBJECTIVES

The primary objective was to evaluate the total duration of analgesia. The secondary objectives were to evaluate the time for sensory block at L1, time to Bromage 3, time for first rescue analgesia, post-operative VAS scores, effect on hemodynamics and side effects if any.

MATERIALS AND METHODOLOGY

This prospective, double blind, randomized clinical trial was conducted from August 2019 to June 2021, after obtaining Institutional Ethical Committee approval and registered in Clinical Trial Registry of India with registration number CTRI/2019/08/020760. The clinical study was done following the ethical principles for medical research involving human subjects in accordance with the Helsinki Declaration 2013. The study included 150 adult patients of either gender belonging to ASA Grade I and II aged 18 to 65 years undergoing elective perianal surgeries under spinal anaesthesia. Written informed consent was taken from each patient. All the patients were taught VAS scoring during pre-anaesthetic evaluation. Pregnant women, patients with contraindications to opioids and spinal anesthesia such as patient refusal, haemorrhagic disorders, local infection at the site of lumbar puncture, raised intracranial tension, chronic headache and chronic backache, known hypersensitivity to drugs, autonomic neuropathy were excluded from thetrial

Patients were randomly allocated to group A(control group), group B(IV Fentanyl), group C(IT Fentanyl), group D(IT Buprenorphine), groupE (IV Buprenorphine), using a envelopes by an anaesthesiologist who was not involved in data collection. Decoding was done at the end of the study.

Patients were premedicated with oral alprazolam 0.25 mg night before surgery and kept nil per oral for at least 6 hours prior to surgery. In the patient holding room, an 18G intravenous cannula was inserted for drug and continuous fluid administration. All patients were preloaded with a 10 ml/kg ringer lactate solution.

On arrival in the operating room, routine standard monitors such as continuous ECG, NIBP and pulse oximeter were established and the patients' baseline heart rate, blood pressure and oxygen saturation (SpO_2) were recorded after 5 min settling in the operative room, this time point was considered as baseline. IV Ondansetron 4mg was given to all patients.

Spinal anaesthesia was administered in lateral decubitus position at the level of L4-5 interspace by using 25 G Quincke spinal needle under aseptic precaution. Once CSF tap was obtained, the stilette was placed back, IV infusion pump containing respective IV study drugs in each group were started at 10ml/min by another anaesthesiologist, this time point was noted as 0 min, 15 seconds after starting the IV infusion pump, stilette was removed from spinal needle and the IT study drugs were administered after aspiration free flow of CSF, at the rate of 0.2ml/s and immediately patient was turned to supine posture. Those patients with no free flow of CSF or in whom the intrathecal drug administration was delayed for any other reason were excluded from the study. Oxygen at the rate of 4l/min was administered to all patients.

Patients in Group A (Control Group) received intrathecal bupivacaine heavy 0.5% 2.5ml with 0.2 ml NS and 10 ml normal saline IV. Group B (IVF) received IT bupivacaine heavy 0.5% 2.5 ml with 0.2 ml normal saline and IV fentanyl at 2 mcg /kg diluted to 10 ml with NS. Group C (ITF) received 2.5 ml IT Bupivacaine 0.5 % H with 10 mcg of Fentanyl and 10 ml of IV NS. Group D (ITB) received 2.5 ml IT Bupivacaine 0.5 % H with 60 mcg of Buprenorphine and 10 ml of IV normal saline. Group E (IVB) received IT Bupivacaine H 0.5% 2.5 ml with 0.2 ml NS and IV Buprenorphine at 2 mcg /kg diluted to 10 ml with NS.

The parameters noted were duration of surgery, time for sensory block at L1 min, time for Bromage grade III, heart rate and mean arterial pressure, intraoperative hypotension, time for request for first analgesic in hours, total duration of analgesia (h), sedation, VAS scores,nausea, vomiting, pruritis, respiratory depression.

Time for sensory block (loss of temperature sensation to cold swab test) at L1and time taken to Bromage Grade 3, tested at 2,3,4 and 5 mins after the end of administration of IV study drugs. Intraoperative HR and MAP was measured and monitored according to minimum standard guidelines at every 3mins and recorded at 0, 2, 5, 10, 15, 30 45mins and 1, 2, 4, 6, 8, 12, 24 hours. The total duration of surgery was recorded in minutes.

Patients were shifted from recovery room to post operative ward after Aldrette score of 9 and above. The VAS, HR, MAP was recorded at 1, 2, 4, 6, 8, 12 and 24 h in the postoperative ward. Total duration of analgesia was defined as the time taken from the onset up to the point where patient complaints of pain at operated site, time for request of first analgesia was defned as VAS 4 when the patient first complained of pain.The surgeons and nursing staff were intimated not to give routine analgesics for all the stydy participants. All patients received Inj diclofenac 75mg when VAS >4.

Other side effects such as hypotension, bradycardia, nausea, vomiting, pruritis, dry mouth, sedation , respiratory depression were recorded . Hypotension was defined as decrease in MAP >20% of baseline. Bradycardia was defined as a fall in heart rate >20% from baseline. Hypotension was treated with bolus of fluid followed by Inj ephedrine 6mg aliquots if not responding to bolus fluid administration. Bradycardia associated with hypotension was treated with Inj atropine 0.6mg IV. Respiratory depression was defined as RR< 10/min or fall in saturation < 94%. Sedation was assessed throughout surgery by 4 point Sedation Scale of Filos with Grade 1- Awake and alert; Grade 2- Awake and drowsy; Grade 3- Drowsy, but arousable responding to physical stimulus;

Grade 4- Unarousable, not responding to physical stimulus. The anaesthesiologist blinded to study drugs documented all the parameters.

Considering the power at 80% and confidence interval at 95% to detect at least 15% difference in duration of analgesia , minimum sample size required was 26 participants in each group, which was rounded to 30 participants in each group taking drop outs into consideration . The data were entered in an excel sheet and analysed using Statistical Package for Social Sciences (SPSS) Version 20. Descriptive statistics with mean, standard deviation and proportions (%) were calculated. To test the hypothesis ANOVA, independent sample t test and Chi Square test were used appropriately. p value <0.05 was considered as statistically significant.

RESULTS

Intraoperative HR and MAP was measured and monitored according to minimum standard guidelines at every 3mins and recorded at 0, 2, 5, 10, 15, 30 45mins and 1, 2, 4, 6, 8, 12, 24 hours. The total duration of surgery was recorded in minutes.

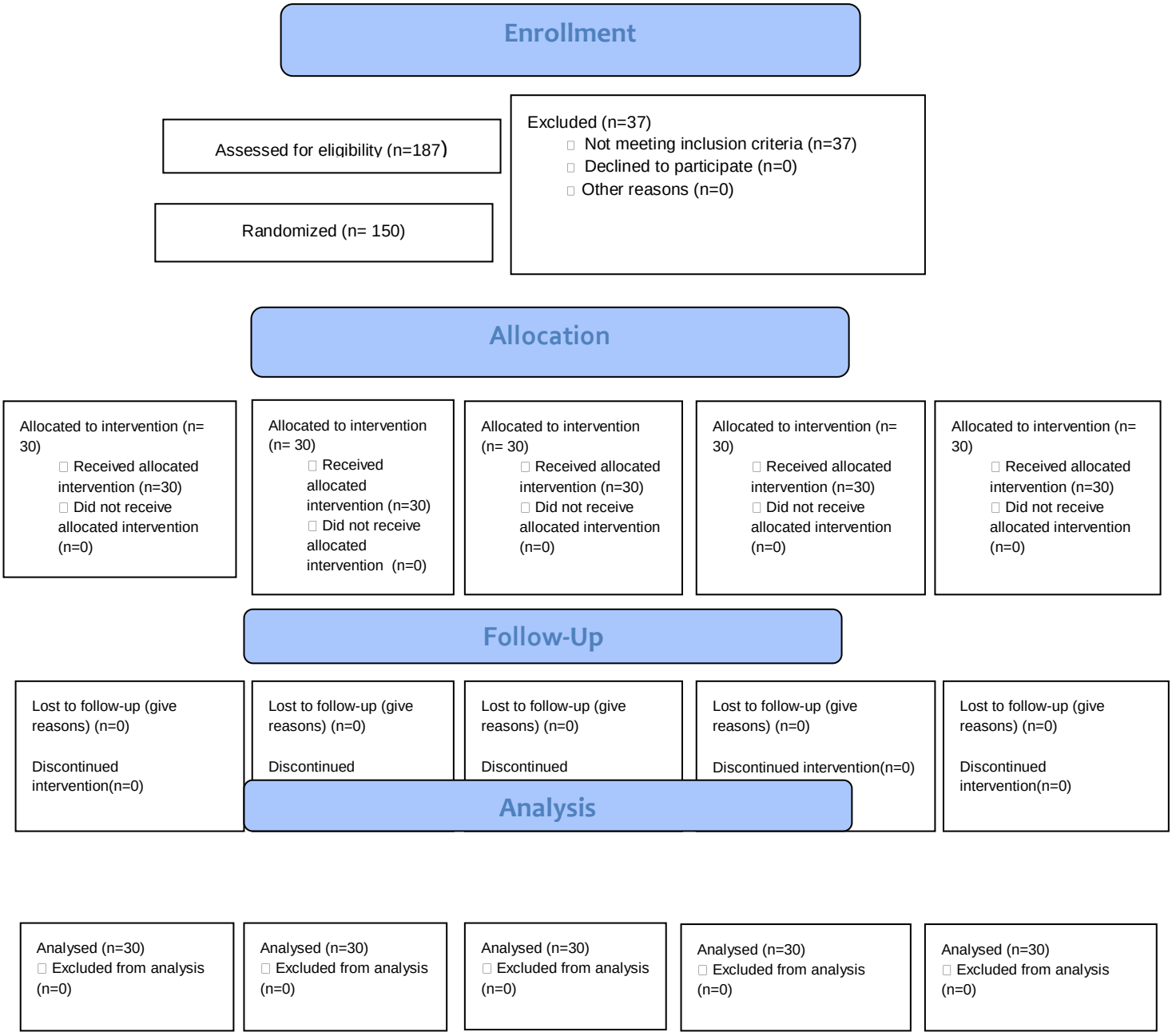
Figure 1 shows a flow diagram for this study where 187 patients were assessed for eligibility and 150 patients were included and their results were analysed. The demographic data were comparable in all the groups and are presented in Table 1.

Table 1: Comparison of Demographic Data

Parameters	Group A	Group B	Group C	Group D	Group E	P value
Age in years	42.8±11.99	41.23±11.69	40.97±11.43	41.5±12.66	42.73±10.92	0.958
Gender Male Female	12.0% 8.0%	12.0% 8.0%	13.3% 6.7%	12.7% 7.3%	12.7% 7.3%	0.98
ASA I/II	26/4	26/4	27/3	25/5	26/4	0.966
Height in cm	164.33±7.98	162.1±6.46	163.6±7.7	164.1±6.01	164.03±7.84	0.76
Weight in kg	62.93±6.716	63.8±5.9	63.2±7.45	63.07±7.07	64.27±7.94	0.94
Duration of surgery(mins)	37.67±10.64	39.47±9.26	40±9.28	37.8±7.28	39±8.44	0.819
Type of surgery Hemorroidectomy with lateral sphincterotomy Fissurectomy with LAS Fistulectomy	10.7% 4.0% 5.3%	11.3% 4.0% 4.7%	11.3% 3.3% 5.3%	11.3% 4.0% 4.7%	11.3% 4.0% 4.7%	1.000

**The data are in mean, standard deviation and proportions (%)*

Figure 1: **CONSORT 2010 Flow Diagram**



Time for sensory block at L1 and time for Bromage grade 3 was significantly faster in group C (2.47±0.5 and 2.96±0.49 min) compared to the rest of the groups.The duration of analgesia, time for first analgesic request was significantly prolonged in all the Optoid groups, and was highest with group D (7.13±0.62, 7.5±0.49 respectively).

The baseline heart rate and MAP were comparable in all the groups. There was a statistically significant decrease in HR and MAP in group B and E during the intraoperative and postoperative period till 12h compared to other groups (Figure 2 and 3).

Figure 2:Comparison of HR between the groups

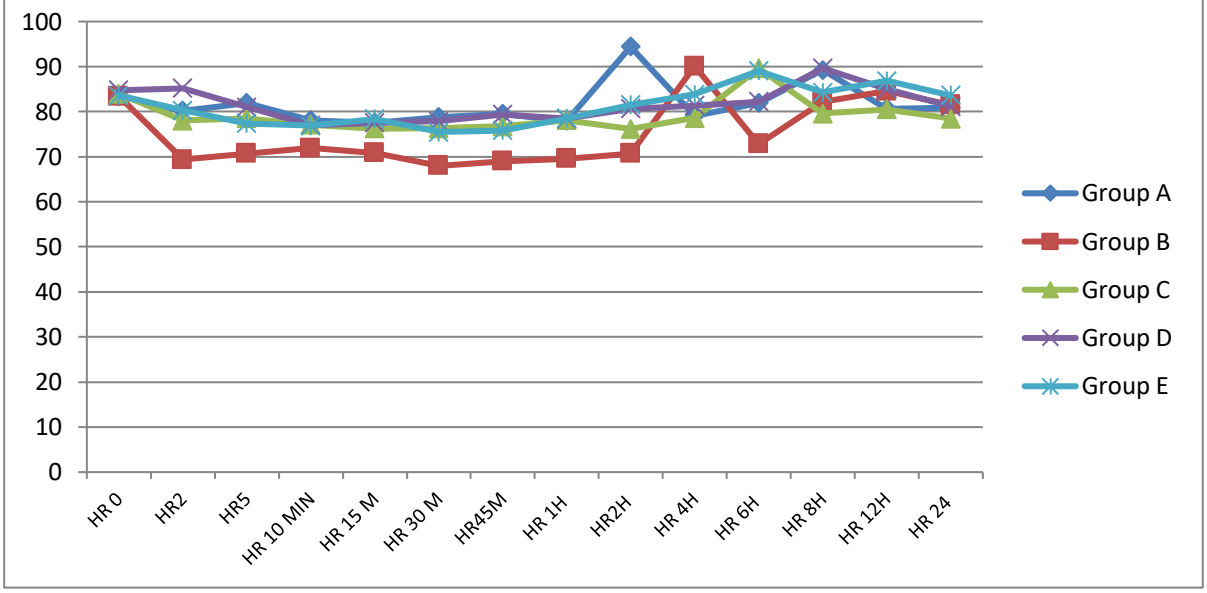
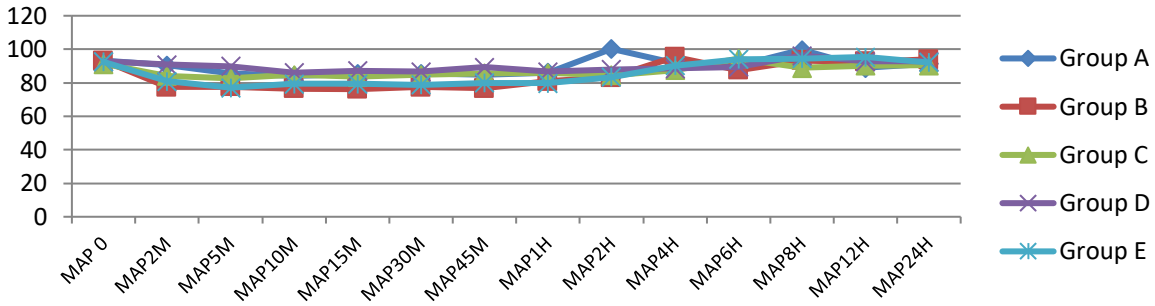


Table 1 Interoperative Parameters

Parameters	Group A	Group B	Group C	Group D	Group E	Significance
Time for sensory block at L1 mins	3.87± 0.35	3.37±0.49	2.47±0.5	3.43±0.5	3.4±0.65	0.000
Time for Bromage grade 3(mins)	4.23±0.34	3.71±0.55	2.96±0.49	3.76±0.43	3.83±0.42	0.000
Total duration of analgesia (h)	2.42±.456	3.67±.6	5.3±0.65	7.13±0.62	5.13±0.73	0.000
Time for request of first analgesia (h)	2.91±0.52	4.46±0.47	5.95±0.67	7.5±0.49	5.6±0.56	0.00
Intraoperative hypotension	2	4	2	2	2	0.00

Intraoperative hypotension was noted in 4 ($p<0.05$) patients in group B and 2 in each of the other groups, which was corrected with fluid bolus and IV ephedrine 6mg. Patients in group B and group E were significantly sedated compared to other groups during the intraoperative period.

Figure 3: Comparison of MAP between the groups



None of the study participants had postoperative hypotension, shivering, nausea, vomiting, respiratory depression, pruritis or dry mouth (Table 3).

Table 3: Side Effects

Parameters		Group A	Group B	Group C	Group D	Group E	Significance
Post-operative hypotension		0	0	0	0	0	NS
Intraoperative sedation	Score 1	20.0%	0.0%	20.0%	0.0%	20.0%	P 0.00(S)
	Score 2	0.0%	14.7%	0.0%	18.0%	0.0%	
	Score 3	0.0%	5.3%	0.0%	2.0%	0.0%	
Nausea		0	0	0	0	0	NS
Vomiting		0	0	0	0	0	NS
Pruritis		0	0	0	0	0	NS
Dry mouth		0	0	0	0	0	NS
Respiratory depression		0	0	0	0	0	NS

NS= not significant , S= significant

The VAS was comparable at 1h and 24h after surgery, but was statistically significant from 2nd hour till 12 hours with least in group D (Table 4).

Table 4 Comparison of VAS between the groups

	Group A	Group B IVF	Group C ITF	Group D ITB	Group E IVB	P value	IVF vs ITF B vs C	IVF vsITB B vs D	IVF vs IVB B vs E	ITF vs ITB C vs D	ITF vs IVB C vs E	ITB vs IVB D vs E
VAS 1	0	0	0	0	0	-	-	-	-	-	-	-
VAS 2H	7.57±0.93	2.63±1.21	0.0±0.0	0.0±0.0	0.3±0.9	0.000	0.00	0.00	0.06	-	0.07	0.07
VAS 4H	4.63±1.45	5.67±1.66	0.33±1.02	0.40±1.07	1.9±2.2	0.000	0.00	0.00	0.00	0.8	0.06	0.002
VAS 6H	3.97±1.32	4.63±0.55	6.7±0.83	1.1±1.86	5.67±1.02	0.000	0.07	0.00	0.05	0.00	0.08	0.000
VAS 8H	7.63±0.99	4.37±0.99	4.0±0.643	5.43±0.97	3.53±0.993	0.000	0.09	0.02	0.07	0.001	0.09	0.000
VAS 10 H	5.5±1.13	4.63±0.55	5.17±0.71	3.64±0.56	4.13±0.77	0.000	0.09	0.01	0.06	0.04	0.1	0.01
VAS 12H	4.2±0.70	3.5±1.32	3.6±0.47	3.5±1.0	3.67±0.8	0.000	0.1	0.25	0.09	0.05	0.2	0.09
VAS 24H	4.43±0.56	4.20±0.88	4.1±0.84	4.4±0.56	4.4±0.62	0.273	0.6	0.3	0.3	0.2	0.1	0.1

DISCUSSION

Subarachnoid block is a widely used regional anaesthetic technique, [2,3] The intrathecal local anaesthetic 0.5% bupivacaine with dextrose, is appropriate for surgeries lasting for 2-2.5 h.[4]Many drugs are administered via different routes to increase the sensory block effect of spinal anesthesia[5,6].

Fentanyl is a synthetic opioid with strong agonist at μ receptors. It is preferred as an adjuvant in spinal anesthesia due to its rapid onset and short duration of action with lesser incidence of respiratory depression.[7]Warwick D et al concluded that The pharmacologic interaction between intrathecal fentanyl and bupivacaine is synergistic, which provide a theoretical basis and support for the clinical practice of combining intrathecal opioids and local anesthetics.[8]

Buprenorphine is a partial agonist at the mu receptor. It is also a weak kappa receptor antagonist and delta receptor agonist. Due to this, the analgesic effect plateaus at higher doses, and then its effects become antagonistic. These multifaceted properties of buprenorphine formed the basis for comparison with the traditionally established fentanyl for use as an adjuvant in subarachnoid block with bupivacaine.

The appropriate dose of buprenorphine equivalent to fentanyl was determined by the results of studies in which the researchers used different doses of buprenorphine. There was prolongation of analgesic effects up to 8 h with 60 μg of buprenorphine due to ceiling effect[9,10]

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Siddik[11] et al compared fentanyl 12.5mcg via IV and IT route in Pregnant women undergoing LSCS and found IT fentanyl was far more effective in terms of longer time to first request for analgesia. We chose to use analgesic dose of opioids in non-pregnant patients undergoing perianal surgeries. We administered the spinal drug after 15 sec owing for arm brain circulation time, so that the opioid would deposit on spinal receptors through systemic diffusion and correspond to spinal local anaesthetic administration. We hypothesized that IV opioids would prolong spinal sensory block owing to their action on spinal receptors and also due to their supraspinal and peripheral effects would provide prolonged postoperative analgesia.

In our study, we found that fentanyl and buprenorphine at the dose of 2mcg/kg given via intravenous route , prolonged the duration of analgesia compared to control.

Singh et al used buprenorphine and fentanyl with ropivacaine and found sensory block and time for first analgesia were prolonged with 60 ug buprenorphine (215.8±24.36 and 7.44±1.69 respectively) compared to fentanyl (196.00±29.48 and 5.68±1.19). The duration of sensory block differed from our study due to use of bupivacaine in our study and the time for first rescue analgesia were comparable to their study suggesting that buprenorphine prolongs the time for first rescue analgesia when used with either ropivacaine or bupivacaine [12]

Khan[13] and Hamdani used 0.75% hyperbaric bupivacaine with buprenorphine 30 μg and compared with 10 μg of fentanyl in elderly patients undergoing urological surgery. The time of onset of sensory anesthesia was lesser in the fentanyl group, but the duration of sensory anesthesia was prolonged in the buprenorphine group. The results were similar to our study. Moreover, their study had higher incidence of nausea and vomiting which is contradictory findings to our study as we used prophylactic IV ondansetron in all patients according to our OT protocol.

Whereas Biswas[14] et al. found that 12.5 μg fentanyl with hyperbaric bupivacaine 0.5% increased the duration of first rescue analgesia to a mean of 248 min. Similar results have been shown in a study conducted by Thomas et al. and Chan et al. and others [15-18] We also used fentanyl in a dose of 10 μg, and our results are almost similar to all the above studies.

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The duration of analgesia was comparable between intrathecal fentanyl and intravenous buprenorphine. The hypotension was significantly increased in the intravenous fentanyl group due to systemic effects but was easily corrected. The patients were more satisfied with intravenous fentanyl and buprenorphine, due to their sedative effect.

We found that VAS was comparable between ITF and IVB from 6-24 postop hours due to prolonged duration of action of buprenorphine. There was a significant difference between ITB compared to all groups till 8h.

Our hypothesis of opioids when given systemically will prolong the duration of analgesia was proven right by increasing the duration of analgesia, VAS<4, and increased time for first rescue analgesic requirement compared to control group.In this study we found that intrathecal buprenorphine produces significantly longer duration of analgesia and longer time for request of first analgesic compared to intravenous buprenorphine and intrathcal and intravenous fentanyl/ control group.

CONCLUSION

Opioids in both intravenous and intrathecal routes prolonged analgesia compared to the control group. Patients in both IV fentanyl and IV buprenorphine were well sedated. The HR and MAP were lower in IV fentanyl and IV buprenorphine group. The intrathecal buprenorphine prolonged duration of analgesia and time for first analgesic request, far more than other groups.

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