

Original Research Article**Post-operative analgesia of Butorphanol and Buprenorphine with levo-bupivacaine in Transversus Abdominis Plane Block in lower abdominal surgeries: A randomized triple blind controlled trial****Neha Chauhan¹, Akash Gupta², Asma Rahat^{3*},**¹ Junior Resident, ²Associate Professor, ³Assistant Professor, Dept of Anaesthesia, Rohilkhand Medial College and Hospital Bareilly UP India***Corresponding Author and reprint request to:** Dr Asma Rahat, Assistant Professor, Dept of Anaesthesia, Rohilkhand Medial College and Hospital Bareilly UP India**ABSTRACT**

Introduction:The ultrasound guided TAP block is an alternate and more modern technique for post-operative analgesia following lower abdominal procedures. Various adjuvants including opioids are being used along with local anaesthetics to prolong analgesic efficacy, in TAP block.

Aim: To compare two drugs in terms of duration of analgesia and time of first request for analgesia.

METHODS: This was a randomized triple-blind controlled study which was carried out in 84 patients, 18-60 years of age of both sexes posted for lower abdominal surgery. Patients were randomly divided in two groups, each comprising 42. Group A received 20ml of 0.25% levo-bupivacaine + 0.3mg (1ml) buprenorphine and Group B received 20ml of 0.25% levo-bupivacaine + 1mg (1ml) butorphanol. Patients were assessed for pain by VAS and any side effects at intervals of 30 minutes, 2 hours, 4, 6, 8, 12, 24 hours. A chi-square test was performed to find associations in different variables between the 02 groups and student independent t-test was performed to find significant differences in mean in different variables between the two groups.

RESULTS: The study groups were comparable in demographic data such as age, sex, weight and ASA grades and it was found that there were no significant difference in age, gender, ASA Grade, weight, Heart rate, SBP, DBP, MAP, SPO₂ among Group A and Group B.

The mean Duration of analgesia and mean time of the first request of analgesia in GROUP A was 718.3±41.44 minutes and 725.33±40.68 minutes while in the GROUP B was 442.6

± 38.77 minutes and 448.2 ± 30.75 minutes. In comparison to GROUP B, GROUP A had a higher mean time for the initial request for analgesia and a longer mean duration of analgesia, and this difference was statistically significant.

CONCLUSIONS:Buprenorphine as an adjuvant to levobupivacaine in TAP block following lower abdominal surgeries improves the resultant effect of block and increases the duration of post-operative analgesia and reduce the opioid requirement as compared to butorphanol.

We came to the conclusion that adding 0.3 milligram of buprenorphine as an adjuvant to levobupivacaine in the TAP block significantly improves the quality of analgesia postoperatively and also reduced the need for analgesics without causing any significant side effects.

Keywords:Anaesthetics, Pain Management,Ultrasonography.

INTRODUCTION

The main apprehension to surgery is pain which is an unpleasant sensation that causes surgical anxiety, slow recovery, protracted hospital stay and many other complications [1, 2]. The primary cause of patients' pain following lower abdominal surgery is an incision made in the abdominal wall. This pain is usually more intense in the first twenty-four hours period. It has been proposed that the best combination for pain control in the multimodal approach to post-operative pain management after surgery is the use of opioids, non-steroidal anti-inflammatory medicines, and local anesthetic infiltration. Each of these drugs acts at a different region of the pain pathway [3, 4].

An alternate and more modern technique for post-operative analgesia following lower abdominal procedures is ultrasound guided transverse abdominis plane block (TAP) [5]. In aTAPBlock, a local anaesthetic solution is deposited in the plane between internal oblique muscle (IO) and transversus abdominis muscle (TA). It blocks the thoracolumbar nerves that arises from T6- L1 spinal roots that operates in this field and supplies the parietal peritoneum, skin, and muscle of the antero-lateral abdominal wall [6,7,8].

Usually, a greater volume of local anaesthetic is needed inTransverse abdominis plane block because of large potential space in abdominal wall. Bupivacaine when given in large volume has potential for systemic toxicity in terms of cardiac and neurotoxicity. Nowadays, levobupivacaine has become one of the most often

utilized local anesthetics due to its reduced cardiotoxic adverse effects; nonetheless, its analgesic duration is limited [9].

The synergistic improvement of the quality and duration of the analgesia is achieved through the addition of diverse adjuvants to it and provides dose-sparing effect to decrease the potential for systemic toxicity. Butorphanol and Buprenorphine have been used as adjuvant along with Levobupivacaine for prolonging the duration of peripheral nerve block and found to be effective. Buprenorphine is a thebaine derivative and semi synthetic opioid having strong agonist activity at mu receptors and having antagonist properties at k receptors. Butorphanol is a synthetic opioid with partial agonist partial agonist action at mu receptors and full agonist activity at k receptors, with increased duration of analgesia. Both the drugs are readily available and cost effective [10, 11, 12].

In several different trials, Buprenorphine & Butorphanol have been tried separately. But there is no study of Buprenorphine and Butorphanol comparison with Levobupivacaine in ultrasound guided Transversus Abdominis Plane block [10, 11, 12]. That's why present study was conducted to contrast the efficiency of these two drugs in combination with Levobupivacaine in USG guided TAP Block in terms of enhanced duration of the post-operative analgesia and reduced systemic analgesic/opioid consumption in first 24 hours after lower abdominal surgeries.

MATERIALS AND METHODS

This was a randomized triple-blind controlled study which was carried out in 84 patients divided among 2 groups each comprising of 42 patients which was statistically calculated by using the software Power and sample size program and was done in department of Anaesthesiology, Rohilkhand Medical College & Hospital, Bareilly in the duration of 1st November 2022 to 31st October 2023.. After obtaining the approval from board of institutional Ethical Committee [File No. EC/NEW/INST/2020/1091, NECRBHR, DHR, MOHFW, New Delhi] and registration of this study with clinical trial registry of india (CTRI/2023/08/056741); dated 22/08/2023; this study was conducted. Informed and written consent was taken from the patients or next of the kin.

Total 100 patients were recruited for this study. Among all these patients 12 were excluded and 4 were dropout or lost to follow leaving total 84 patients (42 in each group) as shown in the figure 1.

Sample Size: In our study a total of 84 patients were taken,

Alpha = 0.05

Power = 0.7

$P_0 = 0.90$

$P_1 = 0.68$

M = 1

Where,

ALPHA- Type 1 error

P_0 – Proportion of outcome in group 1

P_1 - Proportion of outcome in group 2

M- Number of cases in control

The sample size calculated in each group was 42.

The inclusion Criteria for this study are Age group of 18-60 years of both sexes posted for lower abdominal surgery, ASA grade I and II, No other associated cardiovascular/ respiratory disease while the exclusion Criteria are patient with known hypersensitivity to local anaesthetics, patients with opioids addiction, patient with any local infection at site. Patients were randomly divided in two groups, each comprising 42 patients by using a computergenerated random number table. 84 patients who underwent elective lower abdominal surgery were included in this trial. Patient was evaluated on the basis of proper history, clinical examination and routine laboratory investigation. Every patient was informed about the procedure Ultrasound guided (USG) Transversus Abdominis Plane Block and was trained to use the visual analogue scale (VAS). They were kept nil per oral for 6 hours before surgery. All patients were given premedication, tablet ranitidine 150mg and tablet alprazolam 0.25mg orally on previous night and on the morning of surgery. A multichannel monitor was connected to every patient to get continuous ECG monitoring for heart rate, non-invasive arterial blood pressure and

peripheral oxygen saturation. Baseline monitoring data was taken. In the operation theatre, two large bore cannula were established. All vitals were monitored and recorded. In sitting position, spinal anaesthesia was given under all aseptic precaution, with 3ml of 0.5% injection heavy bupivacaine intrathecally at intervertebral space L3-L4 or L4-L5 with 25-G Quincke's spinal needle. Failed or partial spinal effect was eliminated from the study. During intraoperative period, all vitals were monitored, and Non-invasive blood pressure was recorded every 5 minutes. Postoperatively, after completion of surgery a US guided transversus abdominis plane block was performed under all aseptic precautions. The abdominal wall was scanned in the multibeam mode using a linear array transducer probe (6-13 MHz). The probe was positioned between lower costal margin and iliac crest in the midaxillary line. After identifying the abdominal layers, the transversus abdominis plane was reached by using 22-gauge short bevel needle and applying a sterile gel on the skin. The needle was advanced from an antero-lateral direction to the medial direction via ultrasound guided real time assessment with in-plane insertion. The needle was visible on the portable ultrasound monitor screen as a hyperechoic line. After negative aspiration, drugs were given once it was accurately located in the intended plane. When the local anesthetic solution expanded and a hypoechoic shadow appeared between the transverse abdominis and internal oblique muscles, it was determined that the needle had been positioned correctly. Group A received 20ml of 0.25% levobupivacaine + 0.3mg (1ml) buprenorphine and Group B received 20ml of 0.25% levo-bupivacaine + 1mg (1ml) Butorphanol, totalling to a 21ml volume in each group. The individuals who prepared the drug, administered the blocks and made the assessments were all different in our study and all were blinded to the study group[11, 13].

In Postoperative ward, the patients were assessed for the presence and severity of pain at rest and on movement (by VAS), nausea, vomiting and any other side effects at intervals of 30 minutes, 2 hours, 4, 6, 8, 12, 24 hours.

The primary outcome of our study was to compare the duration of analgesia while the secondary outcome was to calculate the time of first request for analgesia and any side effects or systemic effects of drugs.

These assessments were performed in the Post anaesthetic care unit. The vitals heart rate, NIBP & SpO₂ was recorded for 30 minutes and at 2, 4, 6, 8, 12, 24 hours postoperatively. The time taken was noted for the first requirement of analgesic and duration of analgesia in the first twenty four hours. Injection Tramadol 2mg/kg was administered intravenously as a rescue analgesic when VAS >4 on rest or on patient's demand and it was not repeated within six hours. If pain persists or VAS >4, injection Paracetamol 15mg/kg was given additionally. [We didn't calculate the total dose of opioids. As we have also mentioned it in the discussion].The patient was assessed for the pain rating and if the VAS score >7 despite of administration of analgesic postoperatively, implies TAP block has failed. Patients were also monitored for any complications like hematoma, infection related to Transversus Abdominis Plane block.

STATISTICAL ANALYSIS: The data were entered on a Microsoft Excel spreadsheet and imported into Statistical Package for Social Sciences (SPSS) version 23 for statistical analysis. Qualitative data was present in frequency and percentage and quantitative data was presented in mean & standard deviation. A chi-square test was performed to find associations in different variables between the 02 groups and student independent t-test was performed to find significant differences in mean in different variables between the two groups. A *P*-value less than 0.05 were observed statistically significant and A *P*-value less than 0.001 was considered statistically highly significant.

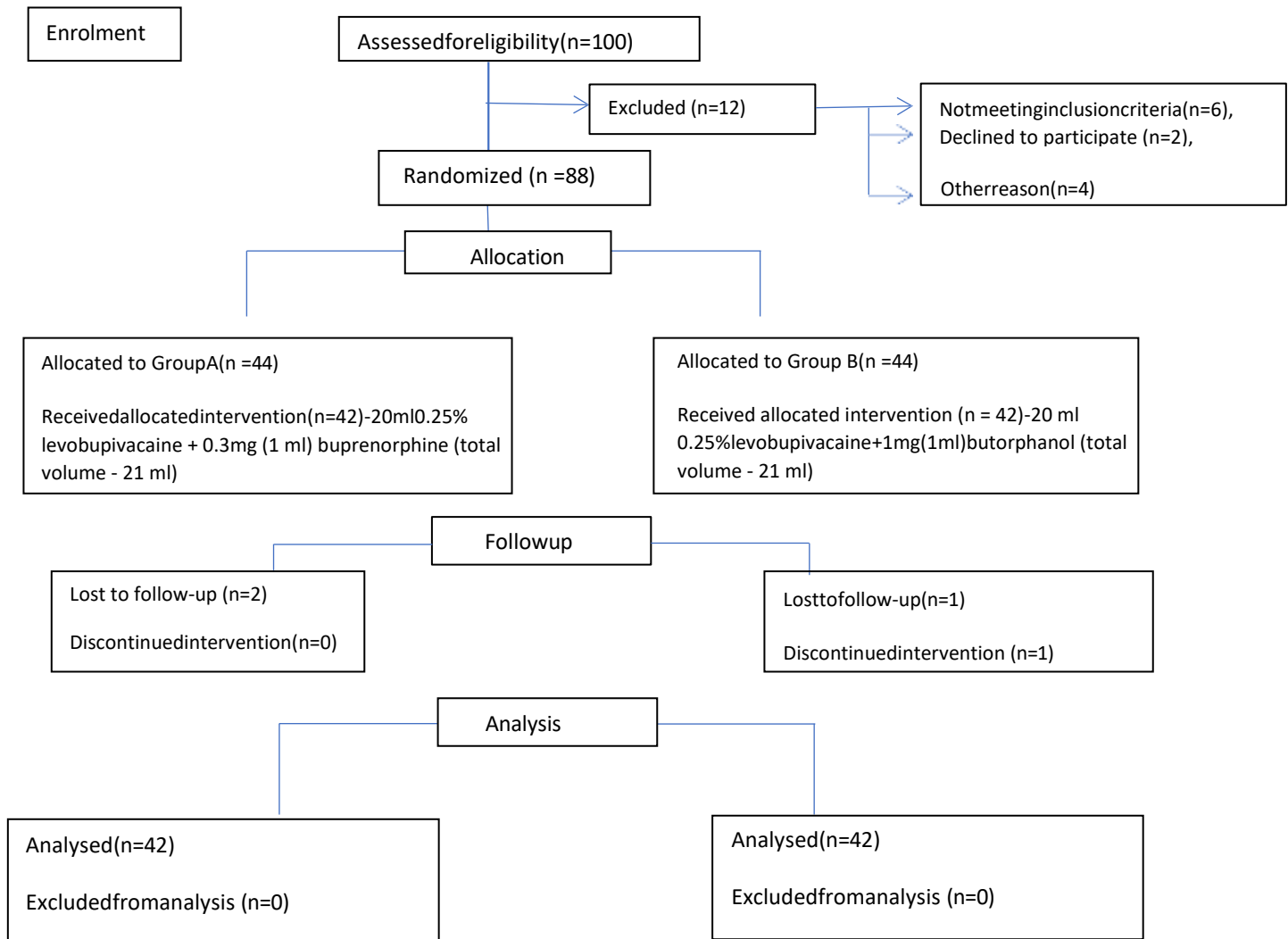


Figure 1-CONSORT flow diagram

RESULT

Total 100 patients were recruited for this study. Among all these patients 12 were excluded and 4 were dropout or lost to follow leaving total 84 patients (42 in each group) as shown in the figure 1.

The study groups were comparable in demographic data such as age, sex, weight and ASA grades as shown in the figure 2. There was no significant difference among the two groups in hemodynamic (HR, SBP, DBP and MAP) and respiratory parameters (SpO₂.

There was no significant difference in age among the groups showing comparability of the groups in terms of age ($p=0.356$) as shown in the figure 2.

There were 36 males and 6 female in GROUP A (BUPRENORPHINE) and 35 males and 7 female in GROUP B (BUTORPHANOL). There was no significant difference noted in the gender of patients among group A & group B ($p=0.416$) as shown in the figure 2.

There were 32 in ASA Grade 1 & 10 ASA Grade 2 in GROUP A (BUPRENORPHINE) and 33 in ASA Grade 1 & 9 ASA Grade 2 in GROUP B (BUTORPHANOL). There was no significant difference noticed in the ASA Grade of patients in between group A & group B ($p=0.154$) as shown in figure 2. There was no significant differentiation spotted in the mean weight and mean heart rate of patients in between group A & group B. ($p=0.406$) as shown in figure 2 and 3.

There was no significant difference observed in Mean SBP, mean DBP, mean MAP of patients in between group A and group B at different time intervals as shown in figure 4, 5, 6.

The comparison of SPO_2 among the groups across the different time periods. SPO_2 was similar among all the groups at all the time periods.

The mean time of the first request of analgesia (in minutes) in the GROUP A (BUPRENORPHINE) was 725.33 ± 40.68 and in the GROUP B (BUTORPHANOL) was 448.2 ± 30.75 as shown in the figure 7. In GROUP A (BUPRENORPHINE), the mean Duration of analgesia was 718.3 ± 41.44 minutes, while in GROUP B (BUTORPHANOL), it was 442.6 ± 38.77 minutes. In comparison to GROUP B (BUTORPHANOL), GROUP A (BUPRENORPHINE) had a higher mean time for the initial request for analgesia and a longer mean duration of analgesia (measured in minutes), and this difference was statistically significant ($P < 0.05$) as shown in the figure 7.

The VAS scores at 8, 12, and 24 hours showed a substantial ($P < 0.001$) difference between the groups. The table and figure illustrate that Group A's VAS score was lower than Group B's as shown in the figure 8.

For all time periods, there was no statistically significant difference in PONV between GROUP A and GROUP B. Patients were also monitored for any complications like hematoma, infection related to Transversus Abdominis Plane block but no complications other than post-operative nausea and vomiting occurred in patients.

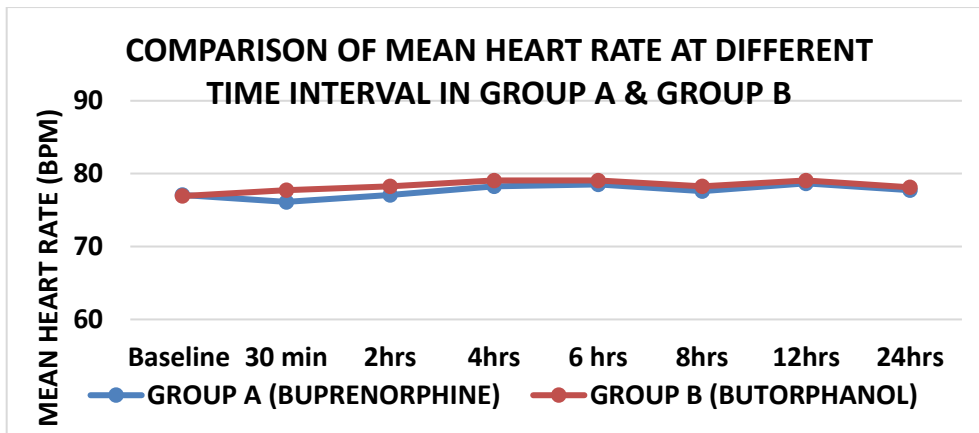
3 out of 42 patients who received buprenorphine with levo-bupivacaine and 4 out of 42 patients who received butorphanol with levo-bupivacaine in tap block have complained of post-operative nausea and vomiting. By the end of 8, 12 and 24 hours, Group A had significantly lower number of patients who needed rescue analgesia than the ones in Group B. 07 patients out of 42 patients needed rescue analgesia in Group A (Buprenorphine) while 10 out of 42 patients in Group B (Butorphanol). This result shows that TAP block with Levobupivacaine and Buprenorphine reduces pain for approximately 8-12 hours but TAP block with Levobupivacaine and Butorphanol prolongs analgesia for around 4-8 hours only. This signifies superiority of Buprenorphine over Butorphanol as an adjunct to local anaesthetic in TAP block.

FIGURE 2- DEMOGRAPHIC CHARACTERISTIC OF PATIENTS

Parameter	GROUP A (BUPRENORPHINE)	GROUP B (BUTORPHANOL)	P-VALUE
	Mean±SD	Mean±SD	
AGE(in years)	42.45 ±9.74	44.24 ±7.78	0.356#
Sex(Male/Female)	36/6	35/7	0.146#
ASA Grade(I/II)	32/10	33/9	0.154#
Weight(inKg)	50.98 ±7.31	49.62 ±7.58	0.406#

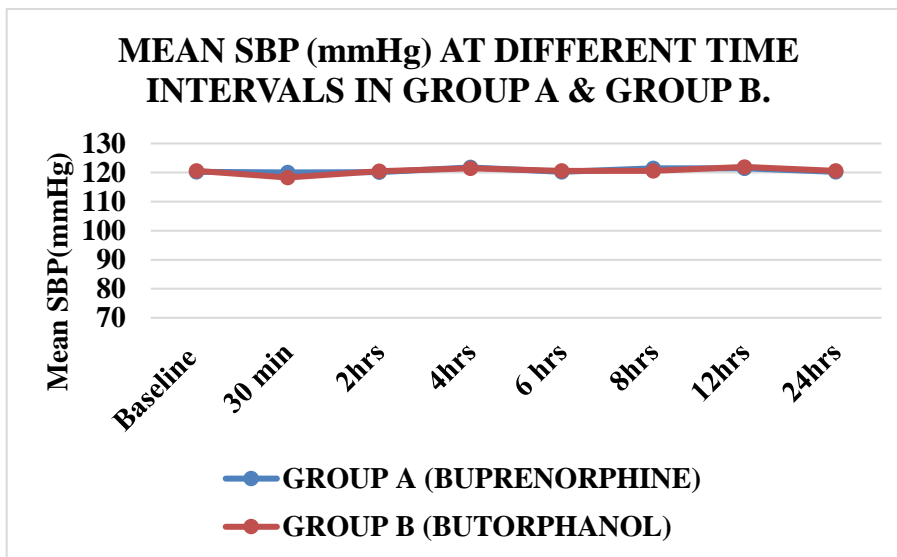
#p>0.05 statistically not significant. [STUDENT INDEPENDENT T- TEST IS USED IN ABOVE FIGURE]

FIGURE-3: COMPARISON OF MEAN HEART RATE AT DIFFERENT TIME INTERVALS IN GROUP A AND B



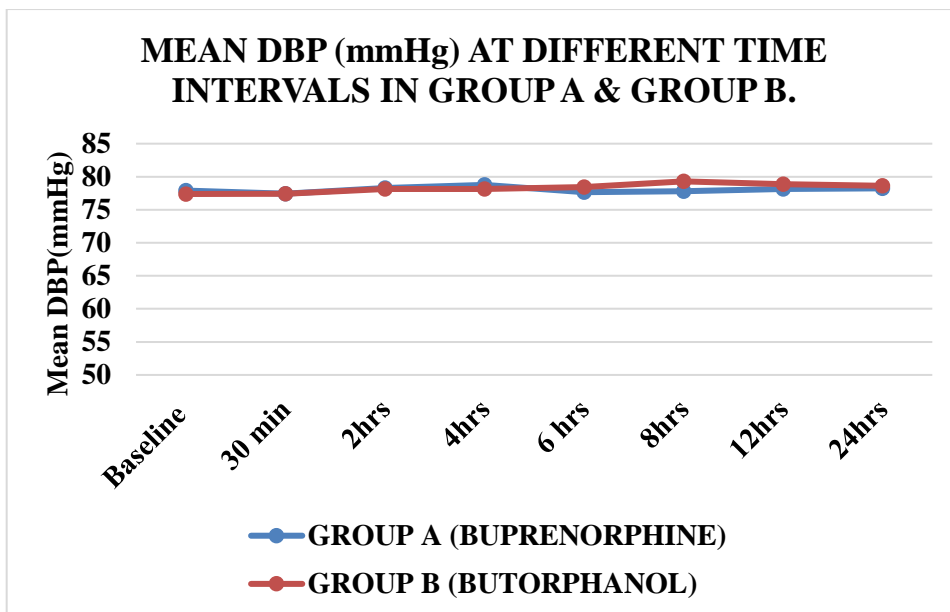
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FIGURE 4: COMPARISON OF MEAN SBP AT DIFFERENT TIME INTERVALS IN GROUP A AND B



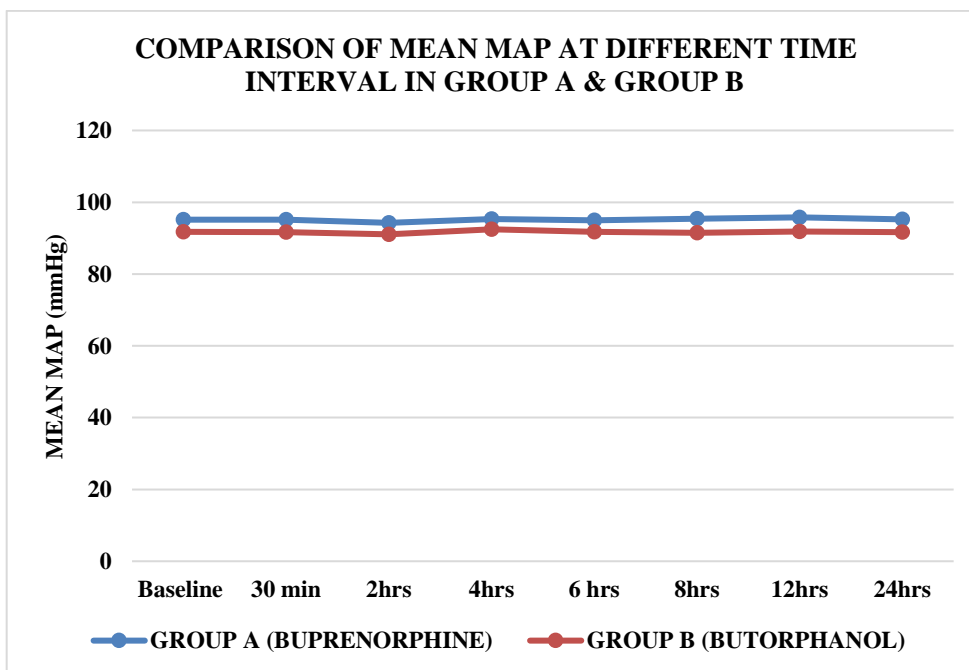
[STUDENT INDEPENDENT T- TEST IS USED IN ABOVE FIGURE]

FIGURE 5: COMPARISON OF MEAN DBP AT DIFFERENT TIME INTERVALS IN GROUP A AND B



[STUDENT INDEPENDENT T- TEST IS USED IN ABOVE FIGURE]

FIGURE 6: COMPARISON OF MEAN MAP AT DIFFERENT TIME INTERVALS IN GROUP A AND B



[STUDENT INDEPENDENT T- TEST IS USED IN ABOVE FIGURE]

Figure7 Comparisonoffirstrequestofanalgesia(inminutes)andduration ofanalgesia(in minutes).

Parameter	GROUPA (BUPRENORPHINE)	GROUPB (BUTORPHANOL)	P-VALUE
	Mean±SD	Mean±SD	
Durationofanalgesia(in minutes)	718.3 ±41.44	442.6 ±38.77	<0.001*
Firstrequestofanalgesia (inminutes)	725.33 ±40.68	448.2 ±30.75	<0.001*

*p<0.05statisticallysignificant. [STUDENT INDEPENDENT T- TEST IS USED IN ABOVE FIGURE]

Figure- 8COMPARISONOF THEMEANVASATDIFFERENTTIMEINTERVALSIN GROUP A & GROUP B.

VAS	GROUP A (BUPRENORPHINE)	GROUPB (BUTORPHANOL)	P-Value
Baseline	0	0	-
30 min	0 ±0	0 ±0	-
2hrs	0 ±0	0 ±0	-
4hrs	0 ±0	0.05 ±0.22	0.156#
6 hrs	0.1 ±0.37	1.14 ±1.7	0.209#
8hrs	0.17 ±0.49	4.1 ±0.82	<0.001*
12hrs	3.76 ±1.16	4.74 ±0.66	<0.001*
24hrs	5.21 ±0.81	5.43 ±0.74	<0.001*

[STUDENT INDEPENDENT T- TEST IS USED IN ABOVE FIGURE]

DISCUSSION

TAP block is an efficient and safe part of multi modal analgesia in lower abdominal surgeries [14, 15, 16, 17, 18]. Various studies including systemic reviews and meta-analysis have proven TAP blocks efficaciousness in reducing post-operative pain, decreased necessity of administrating opioid after surgery, extending the period until an analgesic is first requested, increase analgesia and decreased side effect related to opioid use [5, 13, 19, 20].

Usually large volume of local anaesthetics is needed in TAP Block. Large volumes can cause cardiac and CNS toxicity and So nowadays safer local anaesthetics like

Levobupivacaine and Ropivacaine are being used in TAP Block and other peripheral blocks, but they have limited duration of action. Various adjuvants are being given along with local anaesthetics for prolonging their action. Opioids are increasingly being used as an accessory in various regional blocks for their efficacy in extending the blocks duration and this also reduces the frequency of complications/side effects associated with their systemic use [5, 13, 15]. Buprenorphine and Butorphanol were chosen for this trial as adjuvants in TAP Block due to their accessibility, affordability, absence of notable side effects (respiratory depression and over sedation), extended duration of action and strong affinity towards mu receptors. Fuh et al conducted study on single incision laparoscopic cholecystectomy with ultrasound guided bilateral rectal sheath block [22]. They concluded that Butorphanol group outperforms the Sufentanyl group in terms of occurrence of post-operative nausea and vomiting, NRS score and the necessity for a post-operative rescue analgesic. Although both Buprenorphine and Butorphanol are widely used in various peripheral nerve blocks but their use in TAP Block as an adjuvant to Levobupivacaine is limited, moreover their comparative efficacy in TAP block has not been studied [13, 23, 24].

According to tulsyan study, the total pain-free period was significantly more in groups of buprenorphine than in control groups ($p = 0.001$). In our study the patients who received TAP block with Levobupivacaine and Buprenorphine (Group A) had prolonged analgesia in post-operative period (718.3 \pm 41.44 minutes) than the patients who received TAP block with Levobupivacaine and Butorphanol (Group B) (442.6 \pm 38.77 minutes). Group A Patients first request for analgesia (725.33 \pm 40.68 minutes) was much later than Group B patients (448.2 \pm 30.75 minutes). In previous studies, the authors have observed first request for analgesia but did not calculate the duration of analgesia. They have taken first request of analgesia as duration of analgesia [13, 16, 21]. As per our understanding, duration of analgesia is different than first request for analgesia because duration is calculated once VAS score becomes ≥ 1 , whereas patient may request for analgesia later on once VAS score reaches 3 or more. By the end of 8, 12 and 24 hours, Group A had significantly lower number of patients who needed rescue analgesia than the ones in Group B. This result shows that TAP block with Levobupivacaine and Buprenorphine reduces pain for approximately 8-12 hours but TAP block with Levobupivacaine and Butorphanol prolongs analgesia for around 4-8 hours only. This signifies superiority of Buprenorphine over Butorphanol as an adjunct to local anaesthetic in TAP block. The VAS score of 0, 2 and 6 hours didn't differ statistically. This may be because

during initial period there is sufficient analgesic effect of spinal block anaesthesia. Although we didn't calculate the total dose of rescue analgesia given, but because of better VAS score and late demand for first rescue analgesia in Buprenorphine group, we assumed that their post-operative opioid/analgesia requirement would be less than Butorphanol group.

Similarly Seervi et al used Buprenorphine in TAP block and Tulsyan V et al used Buprenorphine in lumbar plexus block and they concluded that Buprenorphine prolongs duration of analgesia and first request of analgesia, decreases opioid requirement without any significant side effect [13, 23]. Anita K et al in their study on supraclavicular block with Levobupivacaine and Butorphanol revealed significant increase in duration of analgesia (828 ± 87.6 minutes). The supraclavicular block (with limited potential space) and two fold dosage of Butorphanol (2 mg) may have contributed to their analgesia lasting almost twice as long as it did in our trial GROUP A (BUPRENORPHINE), the mean Duration of analgesia was 718.3 ± 41.44 minutes, while in GROUP B (BUTORPHANOL), it was 442.6 ± 38.77 minutes [25]. In comparison to GROUP B (BUTORPHANOL), GROUP A (BUPRENORPHINE) had a longer mean duration of analgesia.

Other advantage after block is reduction in post-operative nausea and vomiting. This reduction in post-operative nausea and vomiting maybe contributed to decreased intensity of pain and limitation of amount of opioid use for control of post-operative pain. Seervi study concluded that the post-operative NRS pain score was reduced in the adjuvant-administered TAP block groups compared to control. Mean NRS scores was found to be significantly better in group LB (levobupivacaine with buprenorphine) than in groups L (levobupivacaine) and LD (levobupivacaine with dexamethasone) from 2 to 12 h and at 24 h postoperatively ($P < 0.05$) while in our study for all time periods, there was no statistically significant difference in PONV between GROUP A and GROUP B [13, 14, 21]. Previous studies have proved that addition of opioid in TAP block doesn't increase incidence of side effects especially nausea and vomiting which is associated with their systemic use [17, 19]. In our study, there was no significant difference in incidence of post-operative nausea, vomiting, sedation and other adverse effect.

The limitation of the current study is that success and extent of TAP block under spinal anaesthesia cannot be determined. Also Systemic effect of study drugs couldn't be ruled out as we have not measured plasma level of these drugs. Furthermore, as our study has involved a small group, more extensive research may

be required to determine the extent and effectiveness of TAP Block when used in conjunction with buprenorphine and butorphanol in addition to levobupivacaine.

CONCLUSION

We came to the conclusion that adding a small dose of buprenorphine as an adjuvant to levobupivacaine in the TAP block for the lower abdominal procedures significantly improves the duration and quality of analgesia postoperatively in comparison to butorphanol and reduced the need for analgesics without causing any significant side effects.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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