Analgesic Effect of Nalbuphine-Bupivacaine Combination in Ultrasound-Guided Transversus Abdominis Plane Block in Patients Undergoing Major Abdominal Cancer Surgeries

Shereen Mamdouh Kamal, Hany Ahmed Ibrahim Elmorabaa, Amira Muhammed Othman[*], Rania Mohammed Abdelemam

Anesthesia, Intensive Care and Pain Management Department, Faculty of Medicine, Assiut University, Assiut, Egypt.

[*]**Corresponding Author:** Amira Muhammed Othman.

E-mail: Amiramothman8@gmail.com

Abstract

Background:

TAP block is considered a modality of pain management following major abdominal cancer surgeries. In this study, we are trying to determine whether adding nalbuphine in two different doses as bupivacaine adjunct in bilateral subcostal transversus abdominis plane block confers better post-major abdominal cancer surgery pain management.

Methods:

A total of ninety patients undergoing major abdominal cancer surgeries were haphazardly categorized into three groups. Group (B) obtained a TAP block with bupivacaine only, group (N10) obtained a TAP block with bupivacaine and 10 mg nalbuphine, and group (N20) obtained a TAP block with bupivacaine and 20 mg nalbuphine. The main outcome of our study was the duration until the initial request for analgesic intervention. The secondary outcomes were the quantity of morphine administered within 24 hours after the surgery, postoperative VAS scores, spirometric lung functions FEVI, FVC, and FEVI/FVC), and postoperative side effects.

Results:

Significant differences were observed among the three groups (B, N10, and N20) regarding the initial request for analgesia, total morphine consumption, VAS score, and respiratory function. However, no meaningful distinctions were observed between the groups regarding hemodynamics and side effects.

Conclusion:

Nalbuphine added to bupivacaine in TAP block has advantages over bupivacaine, only more pain relief, less analgesic request, and less total amount of morphine in patients undergoing cancer abdominal surgeries in a dose-dependent manner.

Keywords: Post-operative, Pain, Opioids.

Introduction

Enhancing post-surgical recovery necessitates the utilization of perioperative analgesia methods that are both safe and effective. The primary objective of optimal pain management protocols is to improve comfort and mobility for the patient while reducing the risk of complications that may impede the after-surgery recovery process. Respiratory function

derangement following abdominal cancer surgery can largely be attributed to postoperative pain [1]. It's imperative for handling postoperative pain to ensure patient ease, early mobilization, and accelerated restoration.

One of these modalities is the Transversus abdominis plane (TAP) block, a comparatively new procedure for administering local anesthetics into the plane among the Transversus abdominis muscle and internal oblique, thereby relieving pain. Including a TAP block in the multimodal anesthetic process is recommended to improve postoperative recuperate following cancer abdominal surgeries with upper abdominal incisions such as gastrectomy, pancreatectomy, nephrectomy, cholecystectomy, liver resection, colonectomy, splenectomy…etc. [2- 4]

Various adjuvants, such as a2 agonists (dexmedetomidine), midazolam, dexamethasone, or nalbuphine, have been utilized to enhance the effectiveness and prolong the period of local anesthetic action in regional block methods and diverse peripheral nerves [5]. Nalbuphine, an opioid agonist-antagonist, is frequently employed as an associate with local anesthetics to prolong the duration period of analgesia for diverse regional anesthetic blocks. This can be attributed to its strong attraction to the κ-opioid receptors.

A powerful analgesic with a combination of k and E antagonist properties, nalbuphine is derived from 14-hydroxymorphine. Nalbuphine provides equivalent analgesic effects to morphine; nevertheless, in contrast to morphine, it displays a ceiling impact on respiration. Nalbuphine can sustain or possibly amplify the analgesic effect on μ-opioid receptors while concurrently alleviating the adverse effects associated with n-opioid receptors. [6, 7]

Based on our research findings, we anticipate that including nalbuphine alongside bupivacaine in TAP block for abdominal surgery will lead to an enhanced analgesic effect and a prolonged duration of pain relief. The patients' postoperative respiratory functions are expected to improve with this analgesic enhancement. Our objective was to evaluate the pain-relieving effectiveness of the nalbuphine with two varying doses (10 mg and 20 mg) when combined with bupivacaine in a bilateral subcostal single-injection ultrasound-guided TAP (transversus abdominis plane) block among patients undergoing upper cancer abdominal surgery.

2. Methods

2.1. Enrollment and Eligibility:

A randomized, prospective, assessor-blinded clinical trial was performed on patients at the South Egypt Cancer Institute (SECI), Assiut University, Egypt. The study was carried out after obtaining approval (IRB: 1710 I 558) from the medical ethics committee and institutional review board. The current research is recorded at "www.clinicaltrial.gov" and has a registration number (NCT05090579). Written informed consent from ninety ASA (1-11) patients aged> 18 years, weighted about 50- 85 Kg and slated for abdominal cancer surgery, were accepted. Patients who have documented allergies to the medications being investigated in the study, significant organ dysfunction, skin infections at the site of needle puncture, epilepsy, sepsis, coagulopathy, and drug or alcohol abuse. Also, the study excluded individuals with psychiatric conditions that could potentially impact pain perception and evaluation.

2.2. Randomization and Blindness:

82

Utilizing an online research randomizer (www.randomizer.org), 30 patients were assigned to one of three groups in a random manner.

Group (B): Patients underwent a TAP block procedure, receiving a volume of 25 mL (bupivacaine represents 20 mL with 0.25% and normal saline represents 5 mL) on each side of the abdominal wall. The subcostal transverse abdominis plane (SCTAP) block was administered to the patients using ultrasound guidance, precisely in the transverse abdominis plane inferior and parallel to the costal margin.

Group (N10): Patients underwent a TAP block procedure with ultrasound guidance. The block involved the administration of bupivacaine (20 mL of 0.25%), nalbuphine (1 mL of 10 mg), and normal saline (4 mL) on the abdominal wall on each side, resulting in a total volume of 25 mL. The subcostal transverse abdominis plane (SCTAP) block was administered to the patients using ultrasound guidance, precisely in the transverse abdominis plane inferior and parallel to the costal margin.

Group (N20): The patients in the study underwent a US-guided TAP block, receiving a volume of 25 mL on both sides of the abdominal wall. The block included bupivacaine (20 mL of 0.25%), nalbuphine (2 mL of 20 mg), and normal saline (3 mL). The subcostal transverse abdominis plane (SCTAP) block was administered to the patients using ultrasound guidance, precisely in the transverse abdominis plane inferior and parallel to the costal margin. The drugs of the study were equipped in the hospital pharmacy, and the consultant anesthetist who performed the block was unaware of the drug composition. A blinded observer will collect the postoperative data to ensure unbiased data collection.

2.3. Preoperative Protocol:

Before the surgery, all patients received guidance on how to assess their personal pain levels utilizing the VAS score, which starts at zero and ends at ten. In this scale, non-pain is represented by zero, while the worst pain is represented by ten. Baseline parameters for respiratory function, including FEVI, FVC, and FEVI/FVC ratio, were recorded preoperatively on the day before the surgery.

2.4. Anesthetic Technique:

The anesthesia plan was standardized across the three groups. Upon the patient's entrance into the operating theatre, standard monitoring techniques were implemented after an appropriate fasting period, including pulse oximetry, temperature monitoring, noninvasive blood pressure measurement, capnography, and ECG. Subsequently, 18-gauge intravenous cannulas were inserted and secured. Anesthesia was carried out using isoflurane at an alveolar concentration of 1.5-2.5% in an air/oxygen mixture of 40%. The patients undergoing mechanical ventilation adjusted their settings to ensure the end-tidal CO_2 (ETCO2) level remained within the 33 to 36 mmHg range. Following the induction of general anesthesia, a TAP block was carried out.

To induce general anesthesia, an intravenous injection of propofol (2 mg/kg), lidocaine (1.5 mg/kg), and fentanyl (1 μg/kg) was given. Cis-atracurium was administered to aid the endotracheal intubation, with a dose of 0.3 mg/kg given at induction and 0.15 mg/kg administered based on the anesthetist's judgment.

The patient's oxygen saturation, mean blood pressure, diastolic, heart rate, systolic, and ETCO2 were documented and computed. The high-

frequency linear ultrasound probe is situated transversely on the abdomen in the mid-axillary line among the iliac crest and costal margin. After identifying the three abdominal muscle layers, the needle was placed in a sagittal orientation, roughly 3-4 cm inward from the ultrasound probe, with insertion occurring in a sagittal plane. The needle insertion point will be located closer to the probe. It was inserted using the in-plane technique to ensure clear needle visibility.

The needle tip was introduced into the plane situated among the transversus abdominis muscles and internal oblique. Initially, a small amount of local anesthetic (2 mL) was administered to verify the correct positioning of the needle tip within the space between the two muscles. Subsequently, the complete dosage of the local anesthetic was injected. If the 2 mL dosage seems to be inside the muscle instead of among them, the adjustment of the needle was necessary. On the ultrasound image, the injected local anesthetic appeared hypoechoic, meaning it seemed black in contrast to the surrounding muscle layers. Neostigmine 50 µg/kg and atropine 10 µg/kg were administered to reverse muscle relaxation at the end of the surgery. After the patients exhibited a response to verbal commands, they were extubated and subsequently transferred to the PACU.

2.5. Postoperative Monitoring:

Vital signs of patients in the PACU were monitored following surgery, including respiratory rate, oxygen saturation, heart rate, and noninvasive blood pressure. This monitoring occurred immediately after the operation and on 2nd, 4th, 6th, 12th, 18th, and 24th hours after surgery. Respiratory function: FVC, FEV1 and FVC/FEV1 ratios were recorded postoperatively at the 6th, 12th, and 24th hours and were contrasted with preoperative values of the same patient a night before the day of surgery. The presence of vomiting, nausea, respiratory depression, and the severity of pain were evaluated after surgery at the 2nd, 4th, 6th, 12th, 18th, and 24th hours.

Pain intensity was evaluated using VAS, a scale of 10 centimeters, with 0 indicating the absence of pain and 10 referring to the worst imaginable pain. It was conducted both when the patient was at rest and during movement. When the Visual Analog Scale (VAS) score reaches 3, the patient is administered postoperative rescue analgesia in the form of morphine. This is done through Patient-controlled Analgesia (PCA) using the B.Braun Mclsungen AG type '8713030' PCA device. The first dose of morphine given when the patient indicates pain is 0.1 mg per kilogram, followed by a subsequent dose of 1 mg after 15 minutes. The initial appeal for pain relief and the overall amount of pain medication used within 24 hours were observed and documented. The administration of morphine was discontinued when the assessment indicated that the VAS score was around 3, both at rest and while moving. Sedation was evaluated using the Ramsay Sedation Scale (RSS), which divides a patient's level of sedation into six categories, ranging from severe agitation to deep coma. When patients experienced nausea or vomiting, they were administered ondansetron 4 mg intravenously as a rescue antiemetic. Intravenous boluses of ephedrine 0.1 mg/kg were administered as needed to treat hypotension. Intravenous atropine 0.01 mg/kg was administered to treat bradycardia.

2.6. Outcome Assessment:

Our study's main focus was determining the duration until the initial request for rescue analgesia. The secondary findings included aggregate morphine usage within the initial 24 hours after surgery hours, postoperative VAS scores, spirometric lung functions (FEV1, FVC, and FEV1/FVC), sedation score (RSS), and postoperative side effects.

2.7. Statistical Analysis:

The data analysis was performed utilizing SPSS (Statistical Package for Social Science), specifically version 26.0, designed for the Windows operating system. Frequency and percentage were used to represent the qualitative data, whereas the quantitative data underwent normality testing employing the Shapiro-Wilk test. The mean ± standard deviation (SD) was used to present the quantitative data. The Chi-square test was employed to compare the proportions between Group (B), Group (N10), and Group (N20). The one-way ANOVA test was utilized in comparison of the mean differences among Group (B), Group (N10), and Group (N20). One Way repeated measures ANOVA compares mean differences within each studied group over time.

Two-way repeated measures ANOVA compares the impact of duration between Group (B), Group (N10), and Group (N20). The Post hoc test was used for Pairwise comparison with Bonferroni correction to compare the significance between each two groups. A P-value of less than 0.05 was used as the significance level.

2.7.1. Sample Size Calculation:

To determine the required sample size for this study using the "EBI" program, considering a power of 80%, confidence level of 95.0%, and an alpha value of 0.5, a minimum of 81 patients, or more, should be divided into three groups (27 patients' group). To account for potential dropouts, 90 patients will be chosen for the study. These patients will be equally distributed among the three groups.

3. Result

3.1. Demographic Data and Patient Characteristics:

Among ninety-eight patients assessed for qualification, five did not satisfy the inclusion standards, three refused to participate, and ninety were scheduled for the research, as shown in (Figure 2). No statistically meaningful distinction among group (B), group (N10), and group (N20) regarding ASA division, gender, age, weight, height, and time of anesthesia, P-value>0.05, as shown in **(Table 1).**

3.2. The Primary Outcome:

The first request time for rescue analgesia was significant (p-value < 0.001). Both the (N10) and (N20) groups had longer analgesic times, with medians (range) of 12 hours (9-14) and 17 hours (15-18), respectively. In contrast, the (B) group had a shorter analgesic time, with a median (range) of 6 hours (4-7).

3.3 The Secondary Outcome:

There was a statistically meaningful distinction in the mean amount of morphine among the groups (B), (NI0), and (N20), as shown in (Table 2). Group (B) had the highest mean total amount of morphine, followed by group (NI0) and group (N20).

Regarding the VAS score (R and M), there was a statistically meaningful higher mean VAS score between (B), (N10), and (N20) groups over time from immediate postoperative to 24 hours. However, there was no statistically meaningful distinction in the mean VAS

score between Group (N10) and Group (N20) within 24 hours after surgery. However, there was a statistically meaningful distinction in mean VAS within Group (B) within 24 hours after surgery (p-value=0.028, as shown in (Figure 3).

For respiratory function, there was no improvement in postoperative FVC, FEV1, and FVC/FEV1 in the (N10) and (N20) groups in comparison to the (B) group. Nevertheless, the mean FVC, FEV1, and FVC/FEV1 were higher statistically significantly in the (N10) and (N20) groups at 6 hours, 12 hours,

and 24 hours postoperative compared to the (B) group (p-value<0.05).

There was no statistically significant change in sedation score (RSS) within group (B), group (N10), and group (N20). However, there was a statistically significant change in the mean sedation score within group (B) from immediate postoperative to 24 hours.

Also, there was no statistically significant change in sedation score within group (B), group (N10), and group (N20) over time from immediate postoperative to 24 hours, as shown in **(Table 3).**

Table Legends

Table (1): characteristics of the patients in the studied groups show no statistically significant difference between group B, group N10, and group N20 regarding age, gender, ASA classification, anthropometric measures, duration of anesthesia and diagnosis, P-value > 0.05

Variables	Group (B) (n=30)	Group (N10) (n=30)	Group (N20) (n=30)	P-value
Age (years)	49.70±5.28	49.37±8.15	49.53±10.06	0.987 [a]
Gender				
- Male	14 (46.7%)	13 (43.3%)	17 (56.7%)	0.561[b]
- Female	16 (53.3%)	17 (56.7%)	13 (43.3%)	
ASA				
- I	21 (70.0%)	23 (76.7%)	24 (80.0%)	0.656 [b]
- II	9 (30.0%)	7 (23.3%)	6 (20.0%)	
Weight/kg	73.67±8.86	73.53±8.50	73.73±8.38	0.996 [a]
Height/cm^2	167.10±5.02	167.67±4.90	167.27±5.30	0.906 [a]
BMI	26.18±3.64	26.06±4.07	26.31±3.26	0.967 [a]
Duration of anesthesia (minutes)	249.50±12.88	248.47±9.96	248.93±23.88	0.972 [a]
Diagnosis				
- Renal tumor	3 (10.0%)	2 (6.7%)	2 (6.7%)	
- GIT tumor	11 (36.7%)	12 (40.0%)	13 (43.3%)	
- Splenic tumor	2 (6.7%)	3 (10.0%)	1 (3.3%)	
- Hepatobiliary tumor	4 (13.3%)	3 (10.0%)	5 (16.7%)	0.995 b
- Pancreatic tumor	6 (20.0%)	6 (20.0%)	6 (20.0%)	
- Other types of tumors (lipoma-retroperitoneal sarcoma …etc.)	4 (13.3%)	4 (13.3%)	3 (10.0%)	

Table 2 shows the need for analgesia among the studied groups

There was a statistically significantly lower mean time of first request of analgesia among group B followed by group N10 and group N20 (5.37±0.89 hrs. vs. 11.97±1.37 hrs. vs. 16.43±0.97 hrs. respectively), P-value < 0.001 and on pairwise comparison there was a statistically significant difference between each two groups.

Also, there was a statistically significantly higher mean of the total amount of morphine among group B followed by group N10 and group N20 (7.30±1.51 mg vs. 5.40±1.99 mg vs. 3.80±1.34 mg respectively), P-value < 0.001 and on pairwise comparison there was a statistically significant difference between each two groups.

Table (2): Comparison of needs for analgesia among studied groups

	Group (B) (n=30)	Group (N10) (n=30)	Group (N20) (n=30)	P-value*
Time of first request of analgesia (hrs.)	5.37±0.89	11.97±1.37	16.43±0.97	<0.001
*P-Value**	Gr B vs Gr N10 <0.001	Gr N10 vs Gr N20 <0.001	Gr B vs Gr N20 <0.001	
Total amount of morphine (mg)	7.30±1.51	5.40±1.99	3.80±1.34	<0.001

Table (3): sedation score (RSS) follow-up among studied groups:

I. There was a statistically significant lower mean sedation score **between** group B, group N10, and group N20 at 4 hrs. and 6 hrs. postoperative, p-value < 0.05.
II. There was no statistically significant change in mean sedation score **within** group **N10 and group N20** from immediate postoperative to 24 hrs. postoperative, P-value=0.089, 0.326 respectively. However, there was a statistically significant change in the mean sedation score **within group B** from immediate postoperative to 24 hrs. postoperative, P-value=0.019.
III. Also, there was a statistically significant change in sedation score R between group B, group N10, and group N20 over time from immediate postoperative to 24 hrs. postoperative, P-value =0.006 (Group B changed over time and significantly differed from the other two groups).

Table (3): Comparison of the patient's sedation score by (RSS) among studied groups.

| Sedation score	Group (B) (n=30)	Group (N10) (n=30)	Group (N20) (n=30)	P-value *
Immediate post-op	2.0±0.0	2.0±0.0	2.0±0.0	NA
2 hrs. post-op	2.0±0.0	2.0±0.0	2.0±0.0	NA
4 hrs. post-op	1.87±0.34	2.0±0.0	2.0±0.0	0.014
6 hrs. post-op	1.77±0.43	2.0±0.0	2.0±0.0	<0.001
12 hrs. post-op	1.87±0.34	1.87±0.34	2.0±0.0	0.114
18 hrs. post-op	1.93±0.25	1.93± 0.25	1.97±0.18	0.814
24 hrs. post-op	1.93±0.25	1.93±0.25	2.0±0.0	0.359

Figure Legends
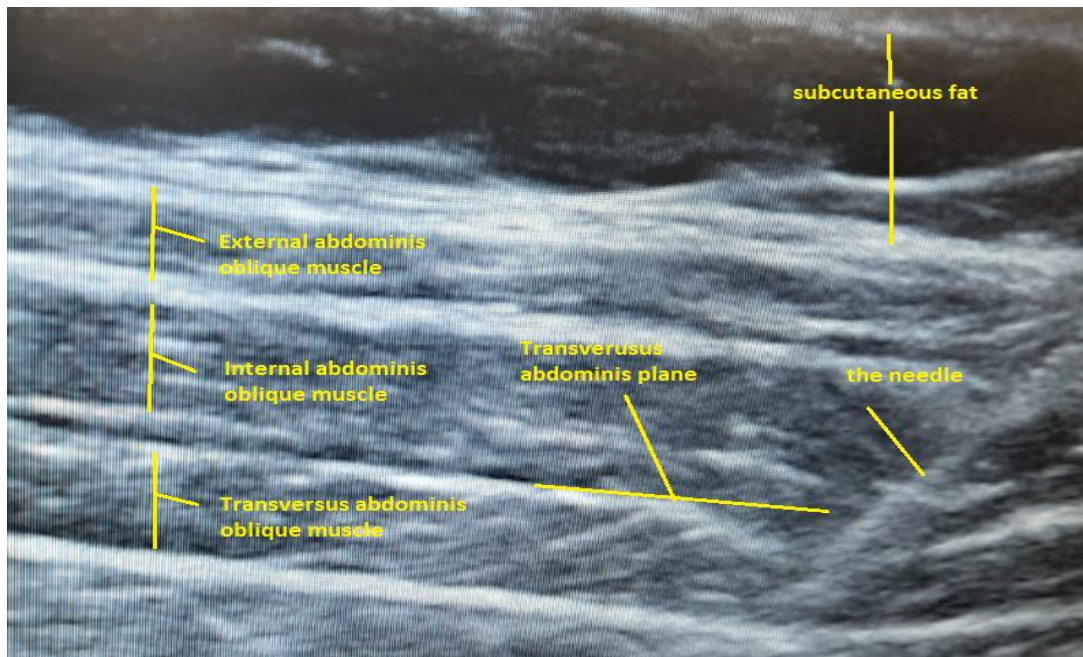
Figure (1): ultrasound view of the three abdominal muscle layers with the needle inserted into the transversus abdominis plane, with the local anaesthetic dissecting the plane.
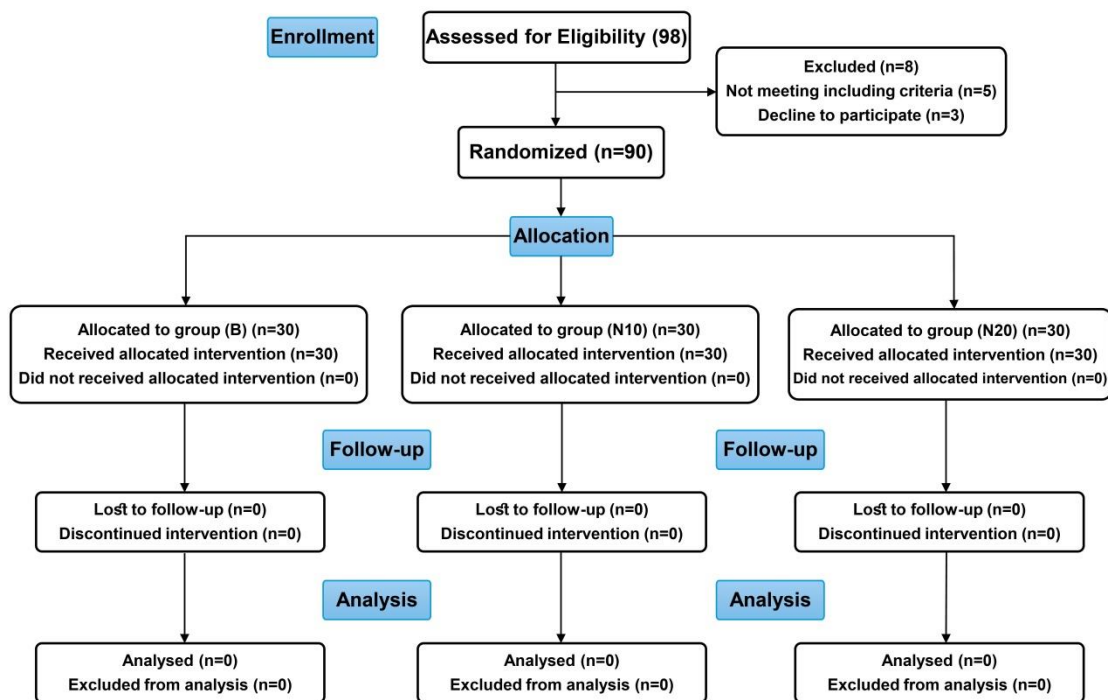
Figure (2): Flow chart of the current study. (B) bupovacaine,(N10)10mg Nalbuphine and (N20) Nalbuphine 20mg.
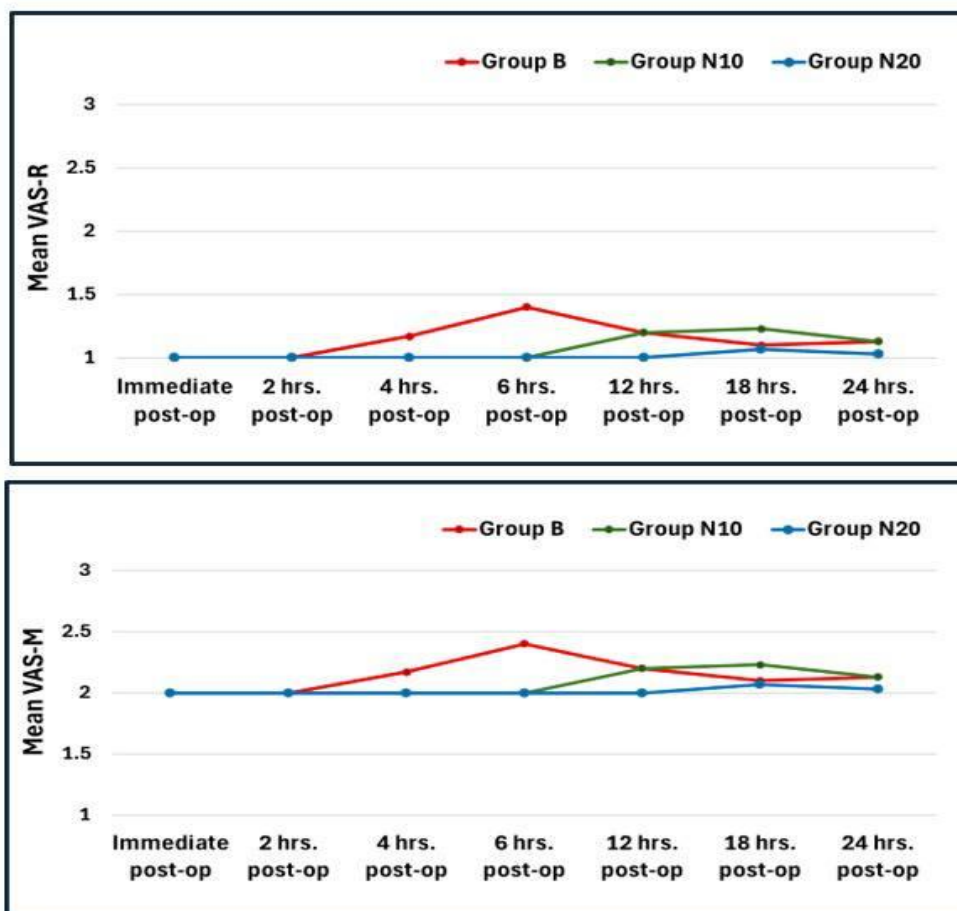
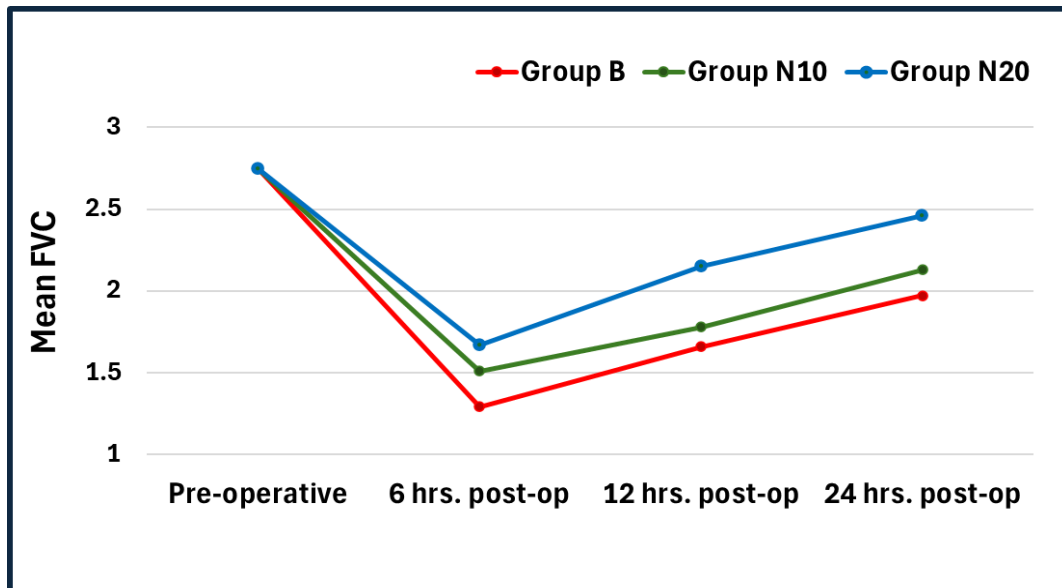**Figure (3):** VAS (R-M) follows up between studied groups.

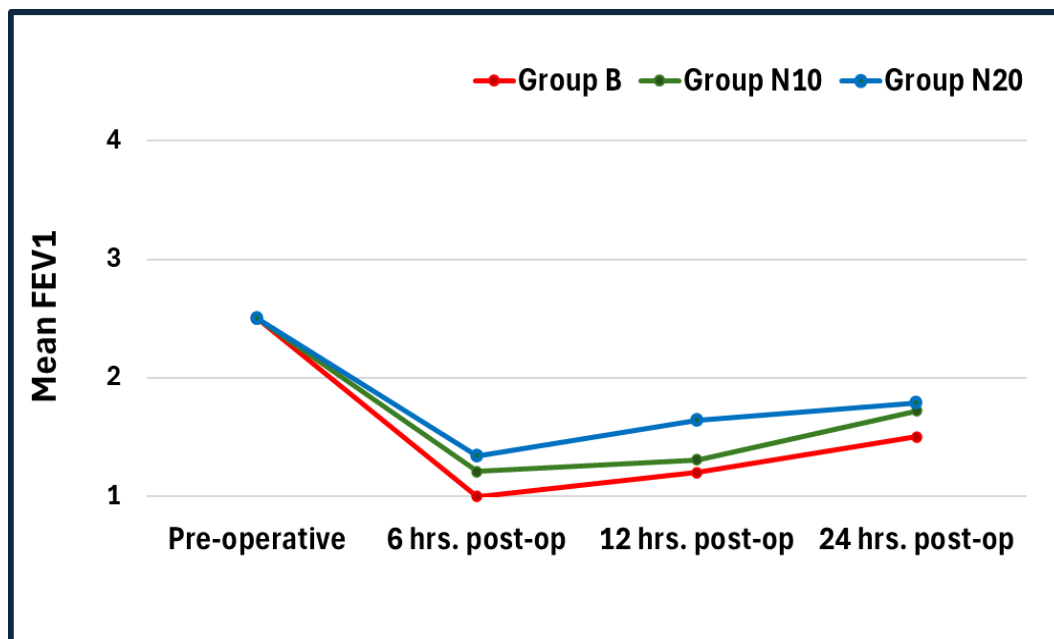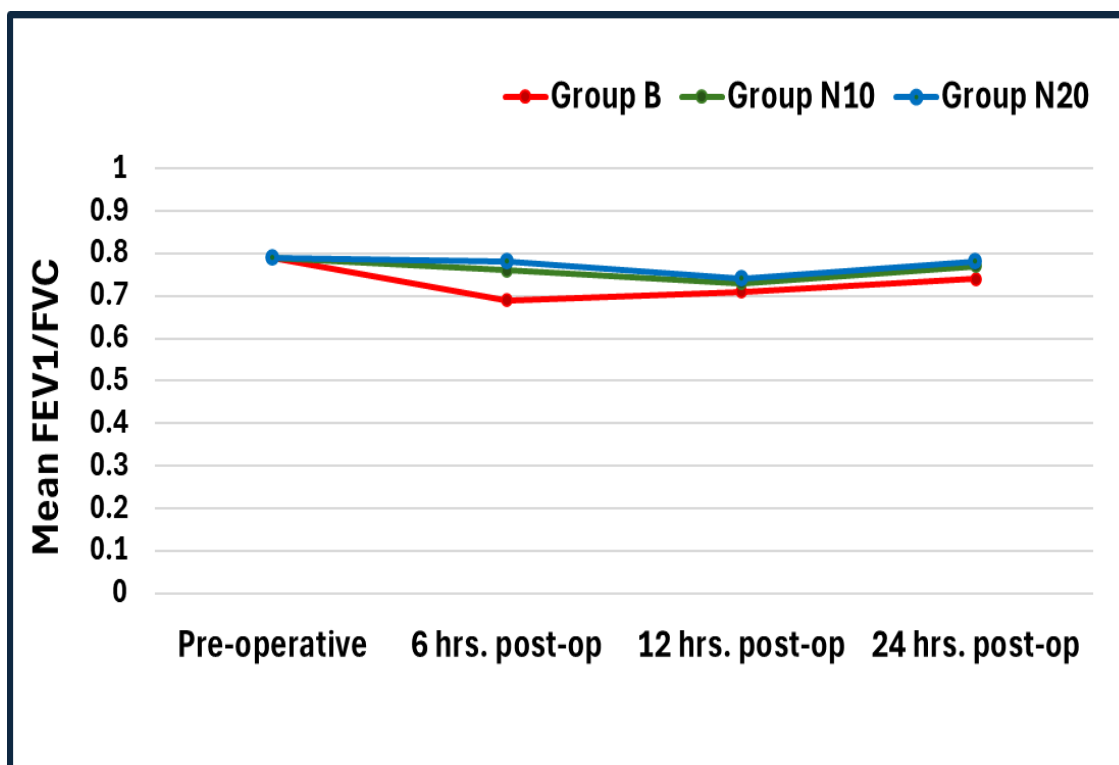**Figure** (**4**): FVC follows up between studied groups.

Figure (**5**): FEV1 follows up between studied groups.

Figure (6): FVC/FEV1 follows up between studied groups

4. Discussion

This research involves a randomized, double-blind study aimed at comparing the pain-relieving effects of two doses of nalbuphine (10 mg and 20 mg) when combined with bupivacaine in bilateral subcostal single injection in ultrasound-guided TAP block for abdominal surgeries. In the nalbuphine groups, we observed reduced pain scores at rest and during movement, as well as better maintenance of lung volumes in the early postoperative period. In the first twenty-four hours following surgery, the nalbuphine groups consumed less morphine in a dose-dependent way. Nalbuphine, in comparison to morphine, exhibits a moderate analgesic effect and functions as a mixed agonist-antagonist opioid. Minimal respiratory depression is observed due to its strong binding affinity to x-opioid receptors, leading to analgesic effects, sedation, and cardiovascular stability. (8). ln our study, the time of the initial inquiry of rescue analgesia was showed with a high significance (p-values: S 0.00 I) that both (NI0) and (N20) groups had more analgesic time.

There was a significant distinction among the three studied groups in the first request for analgesia, with a p-value of < 0.00 I, and in the total amount of morphine (mg) consumption, with a p-value of < 0.00 I. A significant distinction was observed among group (B) and group (N10) with a p-value of less than 0.001. There was a meaningful distinction among groups (B), (N10), and

(N20) with a p-value of <0.00 I. The quantity of morphine taken within the initial 24 hours after surgery should be that both group (N20) and group (NI0) required less amount than group (B) with means ± SD of 7.30± 1.51, 5.40±1.99, and 3.80± 1.34, respectively. Ankit Shanna (2022) discovered that patients who received intrathecal fentanyl (287.05 ± 78.87 minutes) and intrathecal nalbuphine (323.18 ± 57.39 minutes) experienced a notable prolongation in the time to the initial rescue analgesia, in comparison to the control group. However, the duration of spinal analgesia was comparable among patients who received nalbuphine [9].

The VAS score, widely utilized in clinical settings, is a straightforward and pragmatic assessment scale employed to gauge pain level. Our study observed that increasing the nalbuphine dose from 10 to 20 mg prolonged the duration of postoperative analgesia. At the 12th hour, Group (N10) had a VAS score of 5.0 (0-7.0), which was higher than Group (N20), which recorded a VAS score of 4.0 (1.0-6.0) with a p-value of O.O I. The VAS score was higher in Group (B) compared to Group (N20) at the 6th hour with a p-value of 0.581. Shah et al. (2022) demonstrated the potential utility of Nalbuphine as an adjunct in spinal anesthesia for abdominal hysterectomy procedures in a sample of seven patients. It extended the duration of pain relief considerably without causing any negative effects or lengthening the period of motor block.

This can also prove beneficial in daycare surgeries, as it allows patients to start walking soon after the procedure without encountering pain or side effects. The study findings indicated that adding 1.6 mg of intrathecal Nalbuphine to 0.5% hyperbaric bupivacaine in SAB for total abdominal hysterectomies is a successful supplementary treatment. It increased the SAB characteristics, prolonging the analgesic effect without impacting respiration. Administering Nalbuphine at a dosage of 2.4 mg did not provide any additional benefits [10]. Regarding respiratory function, in the current study, there was a significant distinction in respiratory function among the three groups postoperatively at the 6th hour, with a p-value of less than 0.001. A significance was found between Group (B) and Group (N10), with p-values greater than 0.001. There were significant differences between Group (B) and Group (N20) postoperatively at the 6th, 12th, and 24th hour, with p-values of less than 0.001 and 0.035, respectively. In this double-blind, randomized study conducted by Basaran et al. in 2015, 76 patients undergoing laparoscopic cholecystectomy were segregated into two groups: the oblique subcostal TAP (OSTAP) group with (20 ml 0.25% bupivacaine) and the control group. Patients belonging to the (OSTAP) group exhibited notably higher values of postoperative FEVI at 2 (p=0.002) and 24 hours (p=0.008) in comparison to the control group. The OSTAP group exhibited improved FVC values at 2 (p=0.029) and 24 hours (p=0.019) compared to the control group. Nonetheless, no meaningful distinctions were recorded among the groups regarding FRV1 /FVC and PEFR values [11].

In the present study, regarding side impacts, there was no meaningful distinction regarding the incidence of itching, vomiting, and nausea between the three groups. No notable side effects, such as respiratory depression or pruritus, were observed in any of the patients in either group during our study.

In the group (N10), only one patient experienced each of the following side effects: vomiting, urinary retention, and nausea. Two patients in group (B) experienced symptoms of urinary retention and nausea. Also, similar results were documented by Singh et al. (2017) (11).

5. Study Limitation

The results were not corrected for the socioeconomic and educational levels of the patients, which might have confounded the interpretation of the same pain level due to the presence of different socioeconomic statuses and educational levels. Additionally, the study had a short follow-up duration and only measured the serum level of nalbuphine.

6. Conclusion

After abdominal cancer surgery, the administration of nalbuphine added to bupivacaine in a single-injection subcostal TAP block effectively manages pain and reduces opioid usage in a manner that is dependent on the dosage. Also, it shows improvement in postoperative respiratory parameters without serious side effects.

Reference

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49.

2. Joshi GP, Ogunnaike BO. Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain. Anesthesiol Clin North Am. 2005;23(1):21-36.

3. Macrae WA. Chronic pain after surgery. Br J Anaesth. 2001; 87:88-98.

4. Kehlet H, Jensen TS, Woolf CJ. Persistent post-surgical pain: risk factors and prevention. Lancet. 2006;367(9522):1618-25.

5. Singleton PA, Moss J, Karp DD, Atkins JT, Janku F. The mu-opioid receptor: a new target for cancer therapy? Cancer. 2015;121(16):2681-8.

6. Nimmo SM, Foo ITH, Paterson HM. Enhanced recovery after surgery: pain management. J Surg Oncol. 2017;116(5):583-91.

7. Abdelhaq MM, Elramely MA. Effect of nalbuphine as adjuvant to bupivacaine for ultrasound-guided supraclavicular brachial plexus block. Open J Anesthesiol. 2016;6(3):20-6.

8. Xue M, Guo C, Han K, Bai R, An R, Shen X. Analgesia effect of ultrasound-guided transversus abdominis plane block combined with intravenous analgesia after cesarean section: a double-blind controlled trial. Pain Ther. 2022;11(4):1287-98.

9. Chawda PM, Pareek MK, Mehta KD. Effect of nalbuphine on haemodynamic response to orotracheal intubation. Indian J Anaesth. 2010;26(4):458-60.

10. Sharma RK, Chaudhary S, Kumar M. Comparison of nalbuphine versus fentanyl as intrathecal adjuvant to bupivacaine for orthopedic surgeries: a randomized controlled, double-blind trial. J Anaesthesiol Clin Pharmacol. 2022;34(3):329-46.

11. Chen JW, Tian L, Zhang L, Hu JY, Huang SQ, Jiao J. Nalbuphine on postoperative gastrointestinal tract

dysfunction after laparoscopic surgery for gynecological malignancies: a randomized controlled trial. Clin Exp Pharmacol Physiol. 2021;48(2):170-6.

12. Basaran B, Basaran A, Kozanhan B, et al. Analgesia and respiratory function after laparoscopic cholecystectomy in patients receiving ultrasound-guided bilateral oblique subcostal transversus abdominis plane block: a randomized, double-blind study. Pain Res Manag. 2015;20(3):1304-12.