Intrapleural Nebulization of Bupivacaine to Reduce the Postoperative Pain and Improve the Pulmonary Function After Video-Assisted Thoracic Surgery: A Randomized Prospective Double-Blinded Controlled Clinical Trial

Running title: Intrapleural Bupivacaine Nebulization to Reduce Pain

Essam-Eldin Moubarak Mohammed Hussien[1*], Fatma Nabil Ahmed[1], Essam-Eldin Mohammed Abdallah[1], Mahmoud Mohammed Atef [2], Abd-Raouf Mohammed Sayed[1]
[1-]Anesthesia and Intensive Care Department, Faculty of Medicine, Assiut University.
[2-] Department Cardiothoracic Surgery, Faculty of Medicine, Assiut University.
Corresponding Author: Essam-Eldin Moubarak Mohammed.
E-mail: Emobarak94@gmail.com

Abstract

Significant pain can occur after video-assisted thoracic surgery (VATS), which affects recovery and optimization of pulmonary function at discharge. Different pain control regimens have been used. Here, we try intrapleural nebulization of Bupivacaine.

Patients and Methods: The study recruited 50 patients scheduled for lobectomy of either sex and of ASA class I-III. Participants were gathered into two groups: The Bupivacaine group (Group B), in which patients had intrapleural nebulization of Bupivacaine 0.5% (10ml) in a syringe labeled for nebulization via Aero-neb device (aregeon) before skin closure. The control group (Group C) in which patients received intravenous analgesia in the form of paracetamol 1 gram and ketorolac 30mg. Postoperative pain was measured using the NRS score at rest and during cough at the following time (2, 4, 8, 12, and 24 hours after surgery). Rescue analgesia was given whenever the NRS score was ≥ 4 at rest with nalbuphine (0.1 mg/kg).frequency and total nalbuphine consumption during the first 24 hours postoperatively were recorded. A Volumetric incentive spirometer was used to record patients' maximal inspired volume generated (Vmiv). Postoperative complications during the first 24 hours were reported.

Results: The duration needed to require pain medications was significantly longer in the bupivacaine group versus control group[485.76 (414.3 – 557.23) min] versus [129.6 (110.59 – 148,61) min] respectively ($P < 0.001$). Also, patients who had opioid analgesia as rescue analgesia in the first 24 hours were significantly fewer in the bupivacaine group($P < 0.001$).

Conclusion: Intrapleural Bupivacaine nebulization is effective in controlling pain following uniportal video-assisted thoracic surgery.

Keywords: VATS lobectomy, Pain, Intra-pleural nebulization, Bupivacaine.

Introduction:

Video-assisted thoracoscopic surgery (VATS) became the choice in many thoracic procedures because of the many advantages it offers, such as better pain control and hastened recovery (1).

Video-assisted thoracoscopic surgery (VATS) offers better postoperative pulmonary functions (2) and reduced LOS (3). The pathophysiology of pain following such a procedure is due to the surgical incision (4). Inflammatory response and noxious stimuli were shown to have less effect in VATS(5). However, postoperative pain following major operations, such as lobectomies, was found to be moderate to severe(6).

Pain following surgery originates from different mechanisms, such as nociceptive and neuropathic.

Nociceptive somatic nerve impulses are conducted on intercostal nerves to the dorsal horn of the spinal cord. Nerve signals are then delivered to higher pain centers through the spinal cord. Visceral pain is conducted through the vagus and phrenic nerves.

Due to these surgical traumas, various inflammatory pain mediators, such as prostaglandins, stimulate pain receptors. The pain increases significantly when coughing, which halts pulmonary exercise performance.

Continuous stimulation of nociceptors after the procedure leads to increased excitability of pain centers due to the release of various mediators, such as glutamate, leading to central sensitization. Also, neuropathic pain develops, which leads to chronic pain, which may still be present along the incision site at least 2 months postoperative. (7)

Aim of the Study:

To test the efficacy of intrapleural nebulization of Bupivacaine by 0.5% and its effects on ventilatory function in patients undergoing uniportal VATS.

Patients and Methods:

This randomized prospective clinical trial was conducted in Assiut University cardiothoracic hospital through May 2024 and August 2024. It was approved by Assiut University, Egypt's medical institutional review board (IRB no: 17101515). Written informed consent was explained and signed by the patients involved. This study is consistent with the Declaration of Helsinki (Revised DOH 2013) and is registered at ClinicalTrials.gov (NCT05282251).

The sample size was calculated based on a previous study(10). At least 25 patients were included in each group, with a power of 80% and an error of 0.05. Fifty patients will be randomly allocated (using computer-generated random numbers) into the Bupivacaine and the control groups.

Study Participants and Exclusion Criteria

For the study, 50 participants of either sex (aged 18–65 years) and of ASA class I-III were to have uniportal VATS lobectomy. Exclusion criteria were: patient refusal, pleural inflammation due to recent pneumonia, allergy to local anaesthetics, history of bronchial asthma, coagulopathy, previous thoracic surgery, morbid obesity (BMA > 30), renal failure, hepatic dysfunction, history of addiction or psychiatric disorders.

Randomization, Masking, and Grouping:

Randomization was done using computer-generated random numbers and sealed opaque envelopes opened on the morning of the surgeries. Participants were divided into two groups:

The Bupivacaine Group (Group B):

Patients received intrapleural nebulization with Bupivacaine 0.5%(10ml - 50 mg) in a syringe labeled for nebulization via Aero-neb device (aregeon) at the end of surgery.

The Control Group (Group C):

Patients received intravenous analgesia in paracetamol 1 gram (100 ml prepared in Burette set) and ketorolac 30 mg (2 ml diluted in 10 ml normal saline).

To keep blindness towards the group allocation, the patient in group B received intravenous normal saline prepared as 100 ml in a burette set and 10 ml in a syringe labeled for intravenous injection, while the control group patients received intrapleural nebulization of 10 ml normal saline in a syringe labeled for nebulization via Aero-neb device at the end of surgery. An anesthesiologist with no other role prepared the drugs, while the main anesthesiologist (observer) and the surgeon were blinded to the groups. Postoperative pain was also assessed by nurses who were blinded to groups. The same thoracic surgeon and anesthesia team operated on both groups. Pain measurement by numerical rating scale (NRS) was explained to patients

preoperatively. Also, how to use a spirometer was learned.

Intraoperative Management:

In the operative room (OR), the patient was monitored according to the American Society of Anesthesia (ASA) standard monitoring by pulse-oximetry, ECG, non-invasive blood pressure, and temperature. An intravenous line was inserted. Anesthesia induction was done with fentanyl (2 μg/kg), propofol (1.5–2 mg/kg), and cisatracurium (0.15 mg/kg). The patient was intubated by a double-lumen tube. Then, capnography was attached. Anesthesia was continued by isoflurane.

At the end of the surgery, the surgeon did intrapleural nebulization by connecting the thoracoscope to the Aero-neb device and oxygen flow source (10 L/min) from the anesthesia machine. A good seal around the surgical incision was made with a plastic sheath to prevent the leakage of the nebulization vapor.

By the end of the nebulization process and after inserting the intercostal tube, double-lung ventilation was restored, Valsalva maneuver at a pressure of 35 mmHg was done. The port incision was infiltrated with 0.5% bupivacaine (10 ml).

Finally, reversal of neuromuscular blockade with neostigmine was given, and then the patient was extubated and delivered to the postoperative care unit (PACU).

Postoperative Management:

Postoperatively, pain was measured using the NRS score at rest and during cough at the following time (2, 4, 8, 12, and 24 hours after surgery). Rescue analgesia was given whenever the NRS score was ≥ 4 at rest with Nalbuphine (0.1 mg/kg). The frequency and nalbuphine doses were recorded during the first 24 hours after operation.

A volumetric incentive spirometer was used to record the patients' maximal inspired volume (Vmiv) at the following time (2, 4, 8, 12, and 24 hours after surgery). The patients were asked to perform three trials during the test, and the best one was recorded.

Postoperative complications (bleeding, atelectasis, respiratory distress, and complications related to the used medication) during the first 24 hours were reported.

Study Outcomes:

The primary outcome is the time to first analgesic requirement (in minutes), while the secondary outcomes were postoperative pain assessed by NRS, the total consumption of Nalbuphine as a rescue analgesic dose during the first 24 hours following operation, Maximal inspired volume generated (Vmiv), and any reported side effects.

Statistical Analysis:

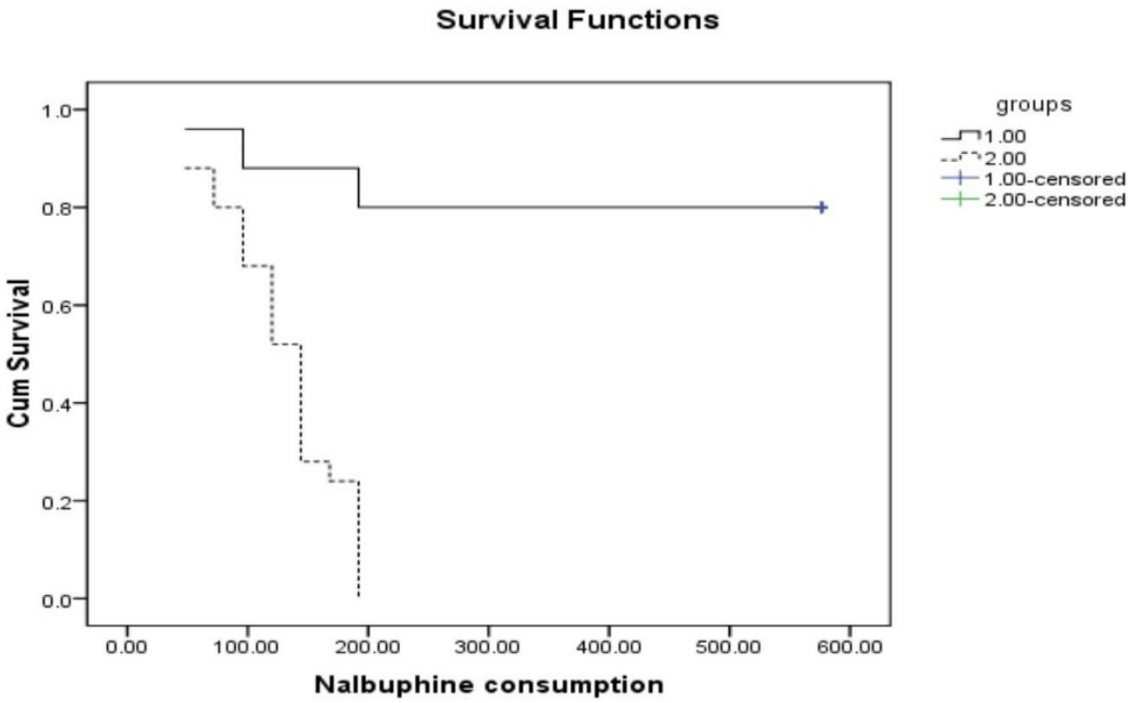
Results:

Of the 87 patients who were scheduled for lobectomy via video-assisted thoracoscopic, 50 patients fulfilled the inclusion criteria and were randomly gathered into two equal groups (bupivacaine group and control group).

Table (1) Describes Patients' and Surgical Data.

	Bupivacaine group (n=25)	Control group (n=25)	P-value
Age (years)	43.28±14.3	42.08±17.2	0.789
Sex	16 / 9	13 / 12	0.284
Weight (Kg)	75.04±11	73.84±10	0.689
Height (cm)	171.84±7.47	173.72±7.2	0.369
BNI (kg/m2)	25.5±3.9	24.6±3.8	0.408
Duration of Surgery (min)	110.16±8.8	112.16±9.1	0.432
Duration of Anesthesia (min)	149.2±9.5	152.76±11.3	0.233
Operation Side	15 / 10	13 / 12	0.388

Significant P-value < 0.05
Non-significant P-value > 0.05
There were no significant differences between both groups in terms of patient factors and surgical factors **(Table 1).**



Significant P-value < 0.05
Non-significant P-value > 0.05

Figure (1)
Kaplan-Meier survival analysis showed that the duration needed first to rescue analgesia was significantly longer in the bupivacaine group versus the control group [485.76 (414.3 – 557.23) min] versus [129.6 (110.59 – 148,61) min] respectively (P < 0.001) (Figure 1).

Table (2) Comparison of the number of patients requiring Nalbuphine as rescue analgesia, ambulation time, and intercostal tube removal time between both groups:

	Bupivacaine group (n=25)	Control group (n=25)	P-value
Estimated time to first analgesic request (min; mean (Cl))	485.76 (414.3-557.23)	129.6 (110.59-148.61)	< 0.001)
Number of patients required Nalbuphine N (%)	5 (20 %)	25 (100%)	< 0.001
Amputation time	24.96 ±4.8	26.4±9.8	0.512
Time to remove lCT	61.44±12.16	63.36±13.65	0.602

Significant P-value < 0.05
Non-significant P-value > 0.05

The number of participants who received Nalbuphine as rescue analgesia during 24 hours was significantly lower in the bupivacaine group (P < 0.001). Also, there were no significant differences in ambulation and intercostal tube removal time (Table 2).

Table(3) Comparison of volumetric incentive spirometer measurements between both groups:

Columetric incentive spirometer	Bupivacaine group (n=25)	Control group (n=25)	P-value
Baseline	720 ± 165.83	724 ± 176.26	0.934
After 4 hours	744 ± 175.78	788 ± 150.89	0.347
After 12 hours	680 ± 152.75	700 ± 202.07	0.695
After 25 hours	732 ± 184.21	844 ± 129.36	0.016

Significant P-value < 0.05
Non-significant P-value > 0.05

Also, both groups had no significant difference in baseline volumetric incentive spirometer results. Similarly, the results did not significantly differ at 4, 12, or 24 hours postoperatively **(Table 3).**

Table (4) Comparison of heart rate data between both groups:

Columetric incentive spirometer	Bupivacaine group (n=25)	Control group (n=25)	P-value
Baseline	89.48 ± 15.09	87.48 ± 15.74	0.649
After 2 hours	85.6 ± 15.59	81.84 ± 15.02	0.389
After 4 hours	84.76 ± 13.95	86.32 ± 15.92	0.714
After 8 hours	87.6 ± 11.15	85.08 ± 15.25	0.508
After 12 hours	80 ± 13.82	86.56 ± 14.13	0.103
After 24 hours	82.2 ± 16.59	80.48 ± 13.38	0.688

Significant P-value < 0.05
Non-significant P-value > 0.05

Table (5) Comparison of Mean arterial blood pressure data between both groups:

Columetric incentive Spirometer	Bupivacaine group (n=25)	Control group (n=25)	P-value
Baseline	90.6 ± 6.78	89.52 ± 6.42	0.566
After 2 hours	89.84 ± 6.26	88.56 ± 7.15	0.504
After 4 hours	89.72 ± 5.83	90.24 ± 6.08	0.759
After 8 hours	88.92 ± 6.44	89.72 ± 5.86	0.648
After 12 hours	91.96 ± 5.84	91.48 ± 5.64	0.769
After 24 hours	89.28 ± 6.21	90.12 ± 5.88	0.625

Significant P-value < 0.05
Non-significant P-value > 0.05

Table (4) and **Table (5)** compare mean arterial blood pressure and heart rate changes between the two groups during the first 24 hours.
The baseline mean arterial blood pressure was compared between both groups and did not differ significantly at 2, 4, 8, 12, or 24 hours postoperatively. (Table 4). Also, both groups' baseline heart rate was comparable and did not differ significantly at 2, 4, 8, 12, or 24 hours postoperatively. (Table 5).
There were no reported incidences of significant hypotension, arrhythmia, or respiratory depression.

Discussion

This clinical trial had 50 participants undergoing VATs who were gathered into two equal groups: Group B had 10 ml of Bupivacaine 0.5% (50mg) in nebulization, while Group C had 0.9 NaCl normal saline (10ml) nebulization just before skin closure as a placebo.

In this study, we found that group B had a significantly lower time regarding first rescue analgesia and total consumed Nalbuphine than the control group (p-value: < 0.001, < 0.05; respectively).

However, the two groups had no significant differences regarding MAP and heart rate at different times.

Our study is the first to demonstrate the effect of local anesthetic nebulization in thoracic surgery, as most of the studies were done in abdominal surgeries. Nebulization produces small-sized particles (<5 μm), which allows better distribution to the peritoneal surface(8). We used nebulization over instillation as Catenacci et al. found that nebulization is better than instillation in abdominal procedures (9). Nebulization has been studied extensively in abdominal procedures. Here are a few studies evaluating the efficacy of nebulization: Allegri et al. found that ropivacaine nebulization effectively controls postoperative pain after cholecystectomy(10).

Alkhamesi et al. showed better outcomes of nebulization after laparoscopic surgeries. Ingelmo et al demonstrated the same(8, 11).Somaini et al. found that ropivacaine nebulization provided better pain control following gynecologic surgery, donor nephrectomy, and Kumar et al. (12,13). Das et al. demonstrated that ropivacaine nebulization is associated with good analgesia following laparoscopic cholecystectomy (14).

On the other hand, other studies, like

Zimmer et al. found that bupivacaine nebulization is ineffective in controlling pain after laparoscopic procedures (15). Also, nebulization was found to obtain any advantage in a study done by Kaufman et al. (16). Baird et al. demonstrated that ropivacaine nebulization hasn't decreased opioid consumption following abdominal procedures. (17). The failure of these studies was attributed to factors such as surgical washing after nebulization, the use of an insuflow device that can evaporate water but not solutes, or the loss of local anaesthetic due to high-flow currents inside the abdomen carrying the anaesthetic out during the removal of trocars.

Aeronob Pro, which we used in our study, is a reusable nebulizer that produces tiny particles and can be sterilized by plasma sterilization (18).

In this study, we used Bupivacaine as ropivacaine was not available. However, a study done by Porika et al. found that both Bupivacaine and ropivacaine had the same efficacy in pain control(19).

However, no complications were associated with the study, and local anaesthetic toxicity did not occur.

Study Limitations:

- We only followed the patients for a short follow-up, 24 hours.
- The use of Bupivacaine as ropivacaine was not available.
- Small sample size.

Study Recommendations:

- Longer prospective studies with larger sample sizes are warranted.
- Investigating the role of Intrapleural nebulization of ropivacaine in thoracic surgery.

Conclusion:

Intrapleural Bupivacaine nebulization is effective in controlling pain following uniportal video-assisted thoracic surgery.

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