A Randomized Study Comparing the Incidence of Postoperative Pain After Phrenic Nerve Infiltration Vs Nonphrenic Nerve Infiltration During Thoracotomy

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Thoracotomy is a common surgical procedure performed worldwide for lung disease. Despite major advances in analgesia, patients still experience severe shoulder, central back and surgical incision site pain in the postoperative period. This study aimed to assess whether intraoperative phrenic nerve infiltration reduces the incidence of postoperative pain and improves peak flow volume measurements during incentive spirometry. 90 patients undergoing open lobectomy were randomly assigned to have phrenic nerve infiltration ($n = 46$) or not ($n = 44$). The phrenic nerve infiltration group received 10 mL of 0.25% bupivacaine into the periphrenic fat pad. Preoperative assessments of spirometry and pain scores were recorded (at rest and with movement). Postoperative assessments included peak flow and pain measurements at intervals up to 72 hours. Less shoulder pain was experienced with phrenic nerve infiltration up to 6 hours postsurgery at rest ($P = 0.005$) and up to 12 hours with movement ($P < 0.001$). Reduced back pain was reported in the phrenic nerve infiltration group up to 6 hours after surgery both at rest ($P = 0.001$) and with movement ($P = 0.00$). Phrenic nerve infiltration reduced pain at the incision site for up to 3 hours both at rest ($P < 0.001$) and with movement ($P = 0.001$). Spirometry readings dropped in both groups with consistently lower readings at baseline and follow-up in the PNI group ($P = 0.007$). Lower analgesic usage of patient controlled analgesia morphine ($P < 0.0001$), epipleural bupivacaine ($P = 0.001$), and oramorph/zomorph ($P = 0.0002$) were recorded. Our findings indicate that the use of phrenic nerve infiltration significantly reduced patient pain scores during the early postoperative period, particularly during movement. We believe that each technique has advantages and disadvantages; however, further studies with large sample size are warranted.

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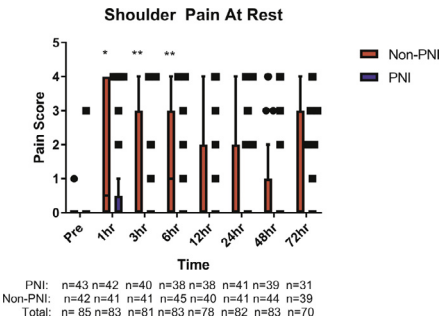

Shoulder pain is significantly reduced by phrenic nerve infiltration.

Central Message

Intraoperative phrenic nerve infiltration following open thoracotomy significantly reduces the postoperative pain during movement.

Perspective Statement

The use of phrenic nerve infiltration can reduce the intensity of the postoperative shoulder, back and surgical site incision pain during movement following lobectomy. Our data support the use of phrenic nerve infiltration as this significantly reduces the incidence of pain for up to 72 hours. This could allow the patient to mobilize more quickly after surgery.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; NHS, National Health Service; NPNI, nonphrenic nerve infiltration; NYHA, New York Heart Association; PCA, patient-controlled analgesia; PNI, phrenic nerve infiltration; VRS, verbal ranking score

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INTRODUCTION

Thoracotomy is one of the most commonly performed surgical procedures required for lung resections. Despite recent advances in anesthesia for controlling postoperative pain, many patients report severe pain in their shoulder, back and their surgical incision site. The use of thoracic epidural analgesia has proven efficacious in pain control,[1] however the failure rate and the incidence of catheter malfunction after proper insertion has been reported in the literature to be as high as 12%.[2] As such, alternative treatment strategies have received significant attention, including suprascapular nerve block and intrapleural and phrenic nerve infiltration.[3] Intercostal and intrapleural analgesic strategies have proven useful, although their efficacy has recently been questioned.[4]

Consequently, there is a lack of consensus regarding the optimal analgesic procedure for abating postoperative pain. The thoracotomy procedure is also associated with the frequent development of postoperative pulmonary complications, which can lead to increased comorbidities following surgery.[5] In addition, perioperative factors (such as reduced functional residual capacity and pulmonary gas exchange, retention of mucous secretions and postoperative pain with breathing) contribute to delayed mobilization, postoperative complications, and increase the length of hospital stay.[6] The use of physiotherapy and incentive spirometry aids in reducing pulmonary complications but is associated with significant postoperative pain, which prevents the patient from taking deep breaths, limiting the ultimate benefit of the procedure.[5,6]

There is currently a paucity of data within the literature regarding the use of bupivacaine for phrenic nerve infiltration following open thoracotomy in regards to outcome measures and the associated benefit in reducing postoperative pain. We therefore aimed to perform a randomized controlled study to assess whether the intraoperative use of phrenic nerve infiltration affects the postoperative pain score and peak flow volume measurements during incentive spirometry.

METHODS

This study was a single center, randomized controlled trial performed between July 2014 and March 2015. The study was approved by the Greater Manchester South Ethics Committee and sponsored by the University Hospital of South Manchester NHS Foundation Trust. Written informed consent was obtained from all the study participants. We enrolled 100 patients but only 90 patients' data were analyzed (see Consort diagram in Fig. 1). The inclusion criteria were: all patients undergoing routine open thoracotomy with lobectomy surgical procedure with patient-controlled analgesia (PCA) and epipleural insertion. Patients were excluded if they had epidural anesthesia, emergency surgery, hypersensitivity to local anesthetic agents, intravenous regional anesthesia, and known liver disease. Ten patients were removed because different surgical procedures were carried out (pneumonectomy or wedge resections). Patients were randomized to 1 of the 2 groups with a 1:1 allocation ratio. Computerized simple block randomization using random block sizes was performed by an independent statistician. Patient allocation was concealed in a sealed envelope by an independent team member and was revealed to the surgeon just before closing the open thoracotomy to avoid any bias. The independent theater team member was not involved in any part of the data collection or data analysis.

Surgical Technique

All patients underwent standard open thoracotomy with lobectomy surgery. The surgery was performed through a fifth intercostal space with latissimus muscle divided along the line of the skin incision. However, the serratus anterior muscle was spared and no intercostal neurovascular bundle was mobilized. There were no ribs notched or surgically removed in all our patients. All the patients' lobes were dissected and resected using Echelon flex 60 vascular and tissue Endopath stapler (Ethicon Endosurgery, Putero Rico). After completion of the lobectomy, the surgeon washed the cavity with warm saline and inserted the epipleural cannula. The epipleural catheter from the standard Portex epidural set (Smith Medical, Czech Republic) was inserted with a use of a Touhy needle under direct vision by the surgeon. The tip of the catheter was positioned in intrapleural space. The other end of the catheter was taken outside the chest wall through the skin and sutured with 4/0 prolene (Ethicon, Diegem, Belgium) to be in situ. A size 28Fg chest tube (Rocket Medical, Washington, England) was placed as an apical drain according to our local surgeon's practice. A standard thoracotomy closure was performed with either pericostal or intercostal method using No. 1 and No. 2 Vicryl plus braided sutures (Ethicon, Diegem, Belgium) and careful attention was taken not to trap the intercostal vessels or nerves. The latissimus muscle was reapproximated with No. 1 Vicryl suture. A subcuticular skin was closed with 3/0 monocryl (Ethicon, Diegem, Belgium).

Anesthetic Techniques

All patients underwent standardized anesthetic techniques which consisted of intravenous induction of anesthesia. Propofol (2−3 mg/kg) was provided to each patient and muscle relaxation was achieved with either Atracurium (0.5 mg/kg) or Fentanyl (2−3 mcg/kg) bolus. After muscle relaxation, the patients were intubated with a single lumen tube. A bronchoscopy was carried out and subsequently the endotracheal tube was changed to a double lumen tube. A paravertebral block was performed with 0.25% bupivacaine with adrenaline 1 in 200,000 (1 mL/kg) divided into 2 injection points (T5 and T8

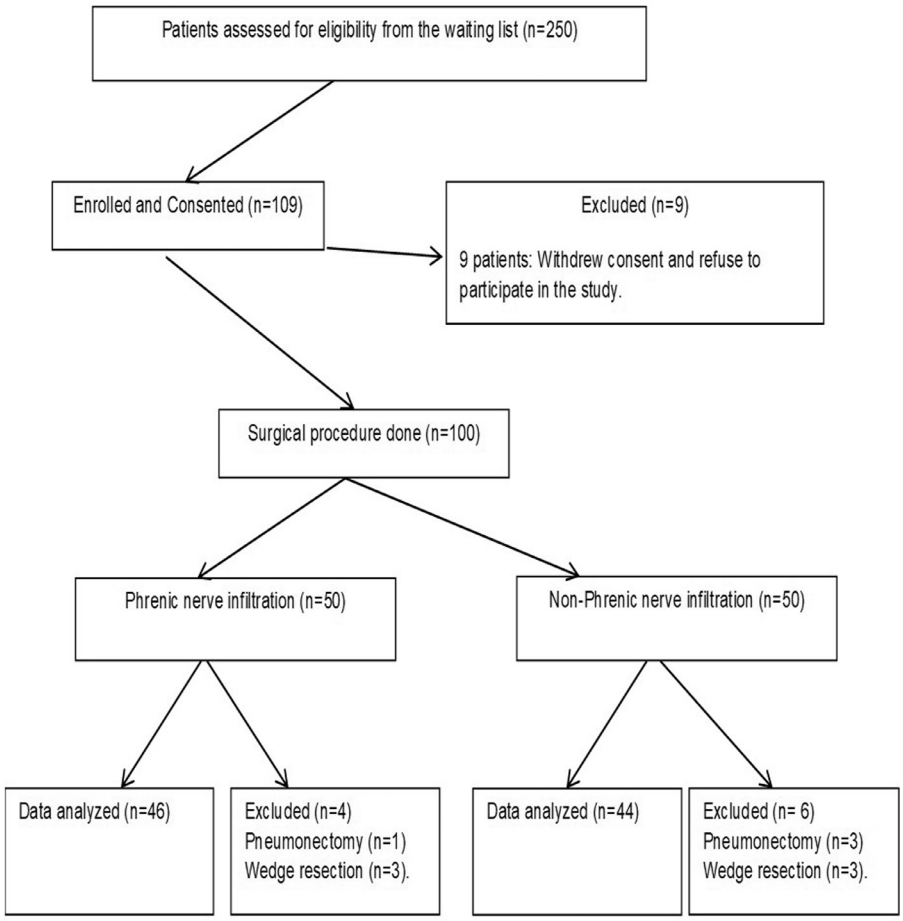


Figure 1. Consort diagram indicating the number of patients in each group and reasons for drop out.

levels). Maintenance of anesthesia during surgery was achieved with a combination of inhalational agents (Sevoflurane) and intravenous opioids (morphine 0.1 mg/kg). After emergence from anesthesia, the patients were able to use a morphine PCA self-administered pump. The concentration of morphine was 1 mg/mL; the bolus was 1 mL with 5 minutes lock-out time. Our routine practice is to stop the PCA and epipleural infusion within 48 hours following surgery and continue pain relief with oral +/— IV pain relief.

The use of epipleural analgesia is a standard practice in our institution. Epipleural analgesia catheter was inserted by the surgeon under direct vision. A bolus of 10 mL of local anesthetic (0.25% bupivacaine with adrenaline 1 in 200,000) was injected by the anesthetist through the epipleural catheter before closure of the thoracotomy wound. A continuous infusion of between 5 mL and 10 mL/h of bupivacaine 0.25% was started immediately after closure of the surgical wound. The infusion was adjusted manually by the nursing staff according to the patients pain score.

Standardization and Group Variation

The surgical methods, size of surgical incision (10 cm), diathermy settings (fulcrate), and use of double retractors was standardized throughout the study to ensure consistency between the groups. All patients in Group 1 received standard anesthetic drugs, PCA and epipleural infusion. Group 2 patients received the same anesthetic procedures but additionally had infiltration of 10 mL of 0.25% bupivacaine into the periphrenic fat[1] above (5 cc) and below (5 cc) hilum level just before the expansion of the lung after lobectomy and closure of the thoracotomy. The phrenic nerve infiltration was performed using a 22G spinal needle (Becton-Dickinson) inserted into the fat pad near the phrenic nerve at the level of the diaphragm. We injected in this fat pad as a site for infiltration because it will act as a reservoir for the local anesthetic and reduce the risk of intraneural injection and nerve damage.[3] More detailed injection of the phrenic nerve infiltration (PNI) has been videoed and attached as an appendix.

Data Collection

All patient data collection sheets were numerically coded and anonymized. During the preoperative visit, patients were familiarized with the incentive spirometry and pain scoring measurement (Likert scale at rest and movement) system. We also obtained baseline spirometer readings with preoperative pain scores for the shoulder and central back. Standard

preoperative and intraoperative variables were recorded prospectively for all patients. The peak flow measurement was taken using a portable spirometer. Both groups of patients were asked to take a slow, deep breath using the 3-ball incentive spirometer for as long as they could. Pain scores were subsequently recorded.

Group allocation was revealed to the surgical team just prior to lung expansion and closure of the thoracotomy so that PNI could be performed for the intervention group. The postoperative data collecting research team were blinded to the study group and they assessed patients at 1, 3, 6, 12, 24, 48, and 72 hours after surgery. The overall pain score was assessed with a 5-point verbal ranking score[7] as follows (0—no pain, 1—mild, 2—moderate, 3—severe, and 4—unbearable pain) during rest and movement.

Power Calculation

The study compared 2 randomized groups, assessing postoperative pain and peak flow at different time points. With 50 patients in each group, the study was prospectively calculated to have 80% power to detect a change in the proportion of the study population without pain of at least 26.7% at a single time point at the conventional 5% significance level. A total of 100 patients were determined to be robust enough to allow for regression analysis methods adjusting for up to 10 total independent variables, such as time effect and group factor.

Statistical Analysis

Pain at rest and pain with movement were assessed with longitudinal mixed effects ordinal models, taking group and time as fixed effects and a random intercept for each individual. Spirometry measurements were examined with a longitudinal mixed effects model with a random intercept. Analyses were conducted in R v3.2.4 (R Foundation for Statistical Computing, Vienna, Austria)[8] (libraries "mixor"[9] and "nlme").[10] The remaining tests were performed with Prism v7 software (GraphPad, La Jolla). Post hoc analyses of pain scores were performed as chi-squared tests only up to 24 hours due to the duration of biological activity of bupivacaine. Data is shown beyond 24 hours but not assessed. Timing of chest drain removal was analyzed by the chi-squared test. Analgesic usage was assessed by 2 way repeated measures analysis of variance (ANOVA) followed by post hoc multiple comparisons Sidak's test. After adjusting for the number of analyses, statistical significance was accepted when $P \leq 0.002$.

RESULTS

Demographics

A total of 90 patients' data were analyzed whilst 10 patients were excluded from this study. These patients were excluded due to complicated surgical procedures such as pneumonectomy ($n = 4$) and simple wedge resections were required for $n = 6$ patients. Demographic variables were similar between groups, with no statistically significant differences observed. Complete demographic data are provided in Table 1.

Shoulder Pain

Shoulder pain at rest was similar between the groups prior to surgery. The non-NPI group experienced greater

Table 1. Preoperative Demographic Data for Patients in the PNI and Non-PNI Groups

Variable	Non-PNI Group	PNI Group	P value
Age	70.00 [13.00]	74.00 [15.00]	
Sex (M/F)	23/21 (52.3%/47.7%)	20/28 (41.7%/58.3%)	
BMI	25.34 [5.98]	23.08 [3.38]	
NYHA class			
I	18 (40.9%)	17 (39.5%)	
II	1 (2.3%)	2 (4.7%)	
III	12 (27.3%)	12 (27.9%)	
IV	13 (29.5%)	12 (27.9%)	
Hypertension	5 (21.7%)	10 (20.8%)	
Hypercholesterolemia	5 (11.4%)	3 (6.5%)	
Smoking status			
Never smoked	29 (65.9%)	32 (68.1%)	
Previous smoker	11 (25.0%)	12 (25.5%)	
Current smoker	4 (9.1%)	3 (6.4%)	
Perioperative details			
Pericostal sutures	36 (81.8%)	37 (80.4%)	0.87
Intercostal sutures	8 (18.2%)	9 (19.6%)	
Right thoracotomy	27 (61.4%)	28 (60.9%)	0.96
Left thoracotomy	17 (38.6%)	18 (39.1%)	
Surgical rib fractures	0 (0.0%)	0 (0.0%)	N/A
Accidental rib fractures	6 (13.6%)	4 (8.7%)	0.46
Chest drain inserted	44 (100.0%)	46 (100.0%)	N/A

Table 2. Shoulder Pain Scores at Rest. Note: No Assessment Was Made Beyond 24 Hours Due to the Efficacy Period of Bupivacaine

Time		Shoulder Pain Score at Rest					*P* Value
		No Pain	Mild	Moderate	Severe	Unbearable	
Pre	Non-PNI ($n = 43$)	42 (97.7%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	—
	PNI ($n = 42$)	41 (97.7%)	0 (0.0%)	0 (0.0%)	1 (2.3%)	0 (0.0%)	
1 h	Non-PNI ($n = 42$)	21 (50.0%)	2 (4.8%)	5 (11.9%)	0 (0.0%)	14 (33.3%)	0.07
	PNI ($n = 41$)	31 (75.6%)	2 (4.9%)	1 (2.4%)	1 (2.4%)	6 (14.6%)	
3 h	Non-PNI ($n = 40$)	21 (52.5%)	5 (12.5%)	0 (0.0%)	6 (15.0%)	8 (20.0%)	0.0009
	PNI ($n = 41$)	35 (85.4%)	1 (2.4%)	3 (7.3%)	0 (0.0%)	2 (4.9%)	
6 h	Non-PNI ($n = 38$)	18 (47.4%)	6 (15.8%)	2 (5.3%)	5 (13.2%)	7 (18.4%)	0.0017
	PNI ($n = 45$)	40 (88.9%)	1 (2.2%)	1 (2.2%)	1 (2.2%)	2 (4.4%)	
12 h	Non-PNI ($n = 37$)	22 (59.5%)	3 (8.1%)	4 (10.8%)	2 (5.4%)	6 (16.2%)	0.29
	PNI ($n = 40$)	32 (80.0%)	1 (2.5%)	1 (2.5%)	1 (2.5%)	5 (12.5%)	
24 h	Non-PNI ($n = 41$)	27 (65.9%)	1 (2.4%)	5 (12.2%)	2 (4.9%)	6 (14.6%)	0.26
	PNI ($n = 41$)	34 (82.9%)	0 (0.0%)	2 (4.9%)	3 (7.3%)	2 (4.9%)	
48 h	Non-PNI ($n = 39$)	29 (74.4%)	3 (7.7%)	2 (5.1%)	2 (5.1%)	3 (7.7%)	
	PNI ($n = 44$)	39 (88.6%)	0 (0.0%)	1 (2.3%)	1 (2.3%)	3 (6.8%)	
72 h	Non-PNI ($n = 31$)	21 (67.6%)	0 (0.0%)	2 (6.5%)	4 (12.9%)	4 (12.9%)	
	PNI ($n = 39$)	31 (79.5%)	1 (2.6%)	2 (5.1%)	2 (5.1%)	3 (7.7%)	

postoperative shoulder pain at rest compared to the PNI group (coefficient = −1.77, $P = 0.005$). The difference was noted to decrease over time after 6 hours, (Table 2) although overall no significant effect of time or interaction of group and time was found.

Shoulder pain was also similar between the 2 groups upon movement prior to surgery. Pain was recorded as greater in the non-PNI group compared to the PNI group following surgery (coefficient = −2.00, $P < 0.001$). The difference was noted to decrease over time after 12 hours (Table 3), although overall no significant effect of time or interaction of group and time was found.

Back Pain

Preoperative back pain level was consistent between groups at rest. However, postsurgery pain was significantly greater in the non-PNI group compared with the PNI group (coefficient = −2.20, $P = 0.001$). The difference was noted to decrease over time (Table 4), but overall no significant effect of time or interaction of group and time was found.

Again, back pain was similar between the groups with movement prior to surgery. The level of back pain was significantly greater in the non-PNI group (coefficient = −1.40, $P = 0.001$). The difference was noted to decrease over time (Table 5), but

Table 3. Shoulder Pain Scores With Movement. Note: No Assessment Was Made Beyond 24 Hours Due to the Efficacy Period of Bupivacaine

Time		Shoulder Pain Score With Movement					*P* Value
		No Pain	Mild	Moderate	Severe	Unbearable	
Pre	Non-PNI ($n = 43$)	39 (90.7%)	1 (2.3%)	1 (2.3%)	0 (0.0%)	2 (4.7%)	0.36
	PNI ($n = 42$)	39 (92.9%)	2 (4.8%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	
1 h	Non-PNI ($n = 33$)	10 (30.3%)	1 (3.0%)	2 (6.0%)	4 (12.1%)	16 (48.5%)	0.06
	PNI ($n = 29$)	18 (62.0%)	2 (6.9%)	0 (0.0%)	3 (10.3%)	6 (20.7%)	
3 h	Non-PNI ($n = 40$)	10 (25.0%)	4 (10.0%)	3 (7.5%)	8 (20.0%)	15 (37.5%)	<0.0001
	PNI ($n = 42$)	33 (78.6%)	3 (7.1%)	2 (4.8%)	1 (2.4%)	3 (7.1%)	
6 h	Non-PNI ($n = 38$)	7 (18.4%)	8 (21.1%)	3 (7.9%)	5 (13.2%)	15 (39.5%)	<0.0001
	PNI ($n = 45$)	34 (75.6%)	5 (11.1%)	1 (2.2%)	1 (2.2%)	4 (8.9%)	
12 h	Non-PNI ($n = 37$)	9 (24.3%)	9 (24.3%)	6 (16.2%)	3 (8.1%)	10 (27.0%)	0.0002
	PNI ($n = 40$)	29 (72.5%)	2 (5.0%)	1 (2.5%)	0 (0.0%)	8 (20.0%)	
24 h	Non-PNI ($n = 41$)	20 (48.8%)	5 (12.2%)	4 (9.8%)	3 (7.3%)	9 (22.0%)	0.29
	PNI ($n = 42$)	30 (71.4%)	2 (4.8%)	3 (7.1%)	1 (2.4%)	6 (14.3%)	
48 h	Non-PNI ($n = 39$)	20 (51.3%)	3 (7.7%)	2 (5.1%)	6 (15.4%)	8 (20.5%)	
	PNI ($n = 44$)	35 (79.6%)	2 (4.5%)	1 (2.3%)	0 (0.0%)	6 (13.6%)	
72 h	Non-PNI ($n = 30$)	14 (46.7%)	1 (3.3%)	5 (16.7%)	3 (10.0%)	7 (23.3%)	
	PNI ($n = 39$)	29 (74.4%)	1 (2.6%)	1 (2.6%)	2 (5.1%)	6 (15.4%)	

Table 4. Back Pain Scores at Rest. Note: No Assessment Was Made Beyond 24 Hours Due to the Efficacy Period of Bupivacaine

Time		Back Pain Score at Rest					*P* Value
		No Pain	Mild	Moderate	Severe	Unbearable	
Pre	Non-PNI ($n = 43$)	41 (95.3%)	2 (4.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	—
	PNI ($n = 42$)	40 (95.2%)	0 (0.0%)	1 (2.4%)	1 (2.4%)	0 (0.0%)	
1 h	Non-PNI ($n = 34$)	15 (44.1%)	3 (8.8%)	4 (11.8%)	1 (2.9%)	11 (32.4%)	0.13
	PNI ($n = 29$)	22 (75.9%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	4 (13.8%)	
3 h	Non-PNI ($n = 39$)	20 (51.3%)	4 (10.3%)	4 (10.3%)	1 (2.6%)	10 (25.6%)	0.008
	PNI ($n = 42$)	37 (88.1%)	1 (2.4%)	1 (2.4%)	1 (2.4%)	2 (4.8%)	
6 h	Non-PNI ($n = 38$)	19 (50.0%)	4 (10.5%)	3 (7.9%)	4 (10.5%)	8 (21.1%)	0.01
	PNI ($n = 45$)	39 (86.7%)	1 (2.2%)	1 (2.2%)	1 (2.2%)	3 (6.7%)	
12 h	Non-PNI ($n = 37$)	23 (62.2%)	2 (5.4%)	4 (10.8%)	4 (10.8%)	4 (10.8%)	0.11
	PNI ($n = 40$)	33 (82.5%)	0 (0.0%)	1 (2.5%)	1 (2.5%)	5 (12.5%)	
24 h	Non-PNI ($n = 41$)	25 (61.0%)	2 (4.9%)	5 (12.2%)	4 (9.8%)	5 (12.2%)	0.04
	PNI ($n = 42$)	37 (88.1%)	1 (2.4%)	0 (0.0%)	1 (2.4%)	3 (7.1%)	
48 h	Non-PNI ($n = 39$)	25 (64.1%)	0 (0.0%)	4 (10.3%)	5 (12.8%)	5 (12.8%)	
	PNI ($n = 45$)	41 (91.1%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	3 (6.7%)	
72 h	Non-PNI ($n = 30$)	17 (56.7%)	2 (6.7%)	5 (16.7%)	2 (6.7%)	4 (13.3%)	
	PNI ($n = 39$)	34 (87.2%)	1 (2.6%)	2 (5.1%)	1 (2.6%)	1 (2.6%)	

overall no significant effect of time or interaction of group and time was found.

Surgical Incision Site Pain

At rest, the level of pain at the surgical incision site was significantly greater in the non-PNI compared with the PNI group (coefficient = −1.59, $P < 0.001$). A significant decrease in pain over time was also noted (coeff = −0.01, $P < 0.001$), but there was no significant interaction of group and time (Table 6).

Significantly greater incision site pain with movement was observed in the non-PNI group compared with the PNI group (coefficient = −1.31, $P = 0.001$), but no significant differences with time were seen (Table 7).

Spirometry Readings

Spirometry readings were taken at each time point up to 72 hours. The PNI group displayed a lower volume prior to surgery compared to the non-PNI group (non-PNI vs PNI: 1875.00 ± 633.73 vs 1581.71 ± 669.77). A large drop was observed in the volume recorded by patients in both groups following surgery. Spirometry results in the PNI group were found to be significantly lower compared to the non-PNI

Table 5. Back Pain Scores With Movement. Note: No Assessment Was Made Beyond 24 Hours Due to the Efficacy Period of Bupivacaine

Time		Back Pain Score With Movement					*P* Value
		No Pain	Mild	Moderate	Severe	Unbearable	
Pre	Non-PNI ($n = 43$)	40 (93.0%)	3 (7.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.40
	PNI ($n = 42$)	38 (90.5%)	1 (2.4%)	1 (2.4%)	1 (2.4%)	1 (2.4%)	
1 h	Non-PNI ($n = 34$)	15 (44.1%)	0 (0.0%)	4 (11.8%)	3 (8.8%)	12 (35.3%)	0.08
	PNI ($n = 29$)	21 (72.4%)	1 (3.4%)	1 (3.4%)	0 (0.0%)	6 (20.7%)	
3 h	Non-PNI ($n = 39$)	16 (41.0%)	5 (12.8%)	4 (10.3%)	3 (7.7%)	11 (28.2%)	0.01
	PNI ($n = 42$)	33 (78.6%)	4 (9.5%)	1 (2.4%)	1 (2.4%)	3 (7.1%)	
6 h	Non-PNI ($n = 38$)	15 (39.5%)	4 (10.5%)	5 (13.2%)	3 (7.9%)	11 (28.9%)	0.04
	PNI ($n = 44$)	32 (72.7%)	3 (6.8%)	3 (6.8%)	2 (4.5%)	4 (9.0%)	
12 h	Non-PNI ($n = 37$)	17 (45.9%)	6 (16.2%)	4 (10.8%)	2 (5.4%)	8 (21.6%)	0.22
	PNI ($n = 40$)	29 (72.5%)	3 (7.5%)	2 (5.0%)	1 (2.5%)	5 (12.5%)	
24 h	Non-PNI ($n = 41$)	17 (41.4%)	8 (19.5%)	6 (14.6%)	1 (2.4%)	9 (22.0%)	0.06
	PNI ($n = 41$)	26 (63.4%)	7 (17.1%)	0 (0.0%)	2 (4.9%)	6 (14.6%)	
48 h	Non-PNI ($n = 39$)	21 (53.8%)	2 (5.1%)	3 (7.7%)	4 (10.3%)	9 (23.1%)	
	PNI ($n = 45$)	36 (80.0%)	2 (4.4%)	1 (2.2%)	1 (2.2%)	5 (11.1%)	
72 h	Non-PNI ($n = 30$)	14 (46.7%)	3 (10.0%)	8 (26.7%)	3 (10.0%)	2 (6.7%)	
	PNI ($n = 39$)	30 (77.0%)	1 (2.6%)	3 (7.7%)	4 (10.3%)	1 (2.6%)	

Table 6. Incision Pain Scores at Rest. Note: No Assessment Was Made Beyond 24 Hours Due to the Efficacy Period of Bupivacaine

Time		Incision Pain Score at Rest					*P* Value
		No Pain	Mild	Moderate	Severe	Unbearable	
1 h	Non-PNI (*n* = 34)	10 (29.4%)	4 (11.8%)	3 (8.8%)	5 (14.7%)	12 (35.3%)	0.49
	PNI (*n* = 30)	13 (43.3%)	1 (3.3%)	2 (6.7%)	2 (6.7%)	12 (40.0%)	
3 h	Non-PNI (*n* = 39)	13 (33.3%)	5 (12.8%)	3 (7.7%)	5 (12.8%)	13 (33.3%)	0.004
	PNI (*n* = 41)	31 (75.6%)	1 (2.4%)	1 (2.4%)	1 (2.4%)	7 (17.1%)	
6 h	Non-PNI (*n* = 38)	16 (42.1%)	3 (7.9%)	4 (10.5%)	1 (2.6%)	14 (36.8%)	0.03
	PNI (*n* = 45)	34 (75.6%)	2 (4.4%)	2 (4.4%)	1 (2.2%)	6 (13.3%)	
12 h	Non-PNI (*n* = 36)	19 (52.8%)	1 (2.8%)	5 (13.9%)	5 (13.9%)	6 (16.7%)	0.28
	PNI (*n* = 40)	29 (72.5%)	1 (2.5%)	1 (2.5%)	3 (7.5%)	6 (15.0%)	
24 h	Non-PNI (*n* = 41)	18 (43.9%)	4 (9.8%)	5 (12.2%)	4 (9.8%)	10 (24.4%)	0.05
	PNI (*n* = 42)	32 (76.2%)	3 (7.1%)	2 (4.8%)	1 (2.4%)	4 (9.5%)	
48 h	Non-PNI (*n* = 38)	20 (52.6%)	4 (10.5%)	5 (13.2%)	2 (5.3%)	7 (18.4%)	
	PNI (*n* = 44)	35 (79.5%)	1 (2.3%)	2 (4.5%)	2 (4.5%)	4 (9.1%)	
72 h	Non-PNI (*n* = 30)	13 (43.3%)	5 (16.7%)	4 (13.3%)	1 (3.3%)	7 (23.3%)	
	PNI (*n* = 39)	31 (79.5%)	1 (2.6%)	2 (5.1%)	3 (7.7%)	2 (5.1%)	

group (coefficient = −240.99, $P = 0.007$) and there was also an effect of time, as time from surgery increased, readings decreased (coefficient = −2.44, $P = 0.002$; Fig. 2).

Chest Drain Removal

The removal of the chest drain is an important step that strongly influences the level of pain experienced. The proportion of patients having the drain removed on each postoperative day was similar between the groups (non-PNI vs PNI; proportion of drains in place at 24 hours: 100.0% vs 100.0%; at 48 hours: 70.5% vs 71.7%; at 72 hours: 25.0% vs 34.8%; at 96 hours: 2.27% vs 0.0%).

Pain Medication Usage

The types of analgesics provided to each patient were recorded postsurgery and compared between groups. A variety of medications were used by patients as required.

Morphine was provided to patients via PCA (1 mg/mL) with a 5-minute lock out period and maximum 12 mg/h. The amount of morphine requested by the patients was recorded as well as the actual amount delivered. Significantly less morphine was requested via PCA by patients in the PNI group compared with the non-PNI group (2-way repeated measures ANOVA: $P = 0.0001$, Fig. 3a). Post hoc multiple comparisons demonstrate that this significant difference was seen over the first 48 hours

Table 7. Incision Pain Scores With Movement. Note: No Assessment Was Made Beyond 24 Hours Due to the Efficacy Period of Bupivacaine

Time		Incision Pain Score With Movement					*P* Value
		No Pain	Mild	Moderate	Severe	Unbearable	
1 h	Non-PNI (*n* = 34)	10 (29.4%)	1 (2.9%)	2 (5.9%)	4 (11.8%)	17 (50.0%)	0.43
	PNI (*n* = 28)	11 (39.3%)	1 (3.6%)	2 (7.1%)	0 (0.0%)	14 (50.0%)	
3 h	Non-PNI (*n* = 39)	8 (20.5%)	4 (10.3%)	5 (12.8%)	4 (10.3%)	18 (46.2%)	0.002
	PNI (*n* = 41)	26 (63.4%)	3 (7.3%)	4 (9.8%)	0 (0.0%)	8 (19.5%)	
6 h	Non-PNI (*n* = 38)	13 (34.2%)	4 (10.5%)	5 (13.2%)	1 (2.6%)	15 (39.5%)	0.21
	PNI (*n* = 45)	22 (48.9%)	9 (20.0%)	3 (6.7%)	0 (0.0%)	11 (24.4%)	
12 h	Non-PNI (*n* = 36)	8 (22.2%)	9 (25.0%)	3 (8.3%)	4 (11.1%)	12 (33.3%)	0.10
	PNI (*n* = 40)	20 (50.0%)	4 (10.0%)	2 (5.0%)	2 (5.0%)	12 (30.0%)	
24 h	Non-PNI (*n* = 41)	9 (22.0%)	4 (9.8%)	4 (9.8%)	4 (9.8%)	20 (48.8%)	0.11
	PNI (*n* = 42)	20 (47.6%)	4 (9.5%)	5 (11.9%)	2 (4.8%)	11 (26.2%)	
48 h	Non-PNI (*n* = 38)	10 (26.3%)	5 (13.2%)	3 (7.9%)	3 (7.9%)	17 (44.7%)	
	PNI (*n* = 44)	27 (61.4%)	1 (2.3%)	3 (6.8%)	5 (11.4%)	8 (18.2%)	
72 h	Non-PNI (*n* = 29)	5 (17.2%)	4 (13.8%)	5 (17.2%)	4 (13.8%)	11 (37.9%)	
	PNI (*n* = 39)	18 (46.2%)	4 (10.3%)	5 (12.8%)	5 (12.8%)	7 (17.9%)	

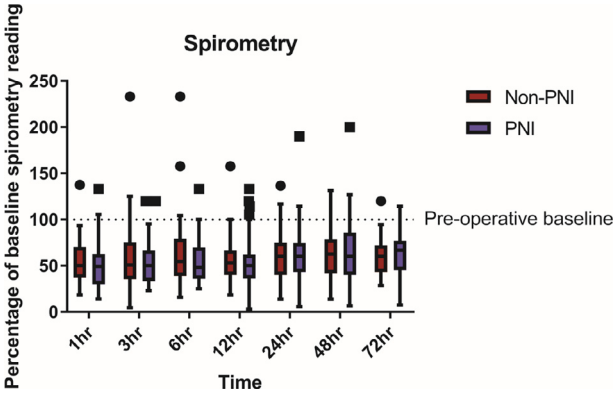


Figure 2. Spirometry readings for each group over the 72-hour period. The drop in lung function is consistent between the groups.

(up to 24 hours: $P < 0.0001$; 24–48 hours: $P = 0.003$; 48–72 hours: $P = 0.24$; 72–96 hours: $P > 0.99$). The lower demand for morphine in the PNI group was also reflected by significantly reduced delivery of morphine to those patients compared to the non-PNI group (2-way repeated measures ANOVA: $P < 0.0001$, Fig. 3b). Again, this significant difference was seen up to 48 hours (up to 24 hours: $P < 0.0001$; 24–48 hours: $P = 0.0004$; 48–72 hours: $P = 0.24$; 72–96 hours: $P = 1.00$).

Epipleural bupivacaine usage was also significantly lower in the PNI group vs the non-PNI group (2-way repeated measures ANOVA: $P = 0.0012$, Fig. 3c). Significantly lower bupivacaine usage was seen over the first 24 hours (up to 24 hours: $P < 0.0001$; 24–48 hours: $P = 0.40$; 48–72 hours: $P = 0.38$).

Based upon the P value adjusted for multiple testing (0.002), paracetamol usage was not significantly different between groups (2-way repeated measures ANOVA: $P = 0.0027$, Fig. 3d).

The amount of oramorph/zomorph received was significantly lower in the PNI group compared to the non-PNI group (2-way repeated measures ANOVA: $P = 0.0002$, Fig. 3e). Post hoc multiple comparisons suggest that less oramorph/zomorph was received in the later postoperative days with no significant differences seen up to 48 hours (up to 24 hours: $P = 1.000$; 24–48 hours: $P = 0.12$; 48–72 hours: $P < 0.0001$; 72–96 hours: $P = 0.0015$; 96–120 hours: $P = 0.07$).

Codeine use was not statistically different between the groups (2-way repeated measures ANOVA: $P = 0.0024$, Fig. 3f). Finally, no statistically significant difference in the amount of gabapentin required was observed (2-way repeated measures ANOVA: $P = 0.33$, Fig. 3g).

Diazepam was provided to only 2.7% of the non-PNI and none of the PNI group. Lidocaine patches were not used in the non-PNI and in 2.7% of patients in the PNI group. Naproxen was received in 5.4% of patients without PNI whereas none of those in the PNI group used this medication. Oxycontin was given to 40.5% and 34.1% of patients in the non-PNI and PNI groups respectively ($P = 0.65$). Tramadol usage was also not significantly different between groups at 8.1% and 9.1% for non-PNI and PNI respectively. No voltarol was given to either group.

DISCUSSION

This is the first study to directly assess the impact of phrenic nerve infiltration on the intensity of postoperative shoulder, back and surgical site pain following incentive spirometry after lobectomy. Many studies have published findings on postoperative pain after thoracic surgery, yet these are not contextualized to account for functional activity. It is vital to understand

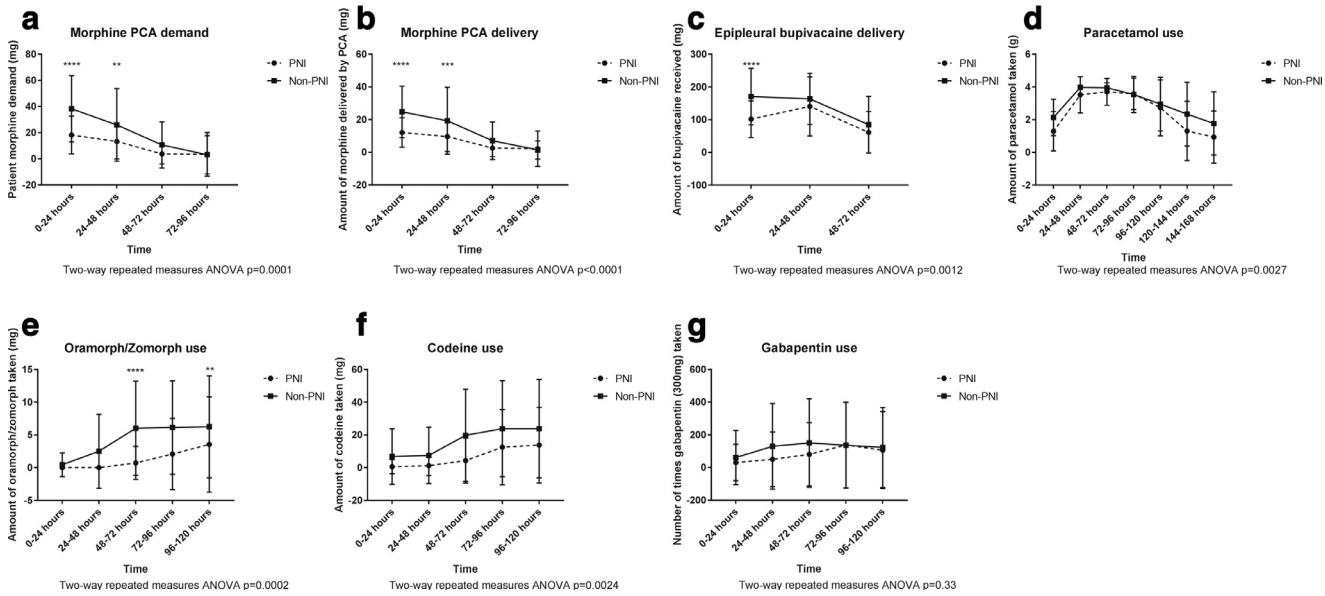


Figure 3. Pain medication usage for patients in each group. Greater requirement for pain medication was observed in the non-phrenic nerve infiltration group. Data is presented as mean ± standard deviation.

the patient's experience of postoperative pain while taking deep breaths both at rest and with movement. Most patients who experience pain during coughing or deep breathing avoid these activities postsurgery. Postsurgical pain after thoracotomy directly affects the postoperative recovery of the patient and promotes atelectasis, retention of sputum,[11] and lung infection.[12,13]

The gold standard method to reduce postoperative pain in thoracic surgery is epidural analgesia but associated risks are higher.[14,15] Scawn and colleagues studied the use of 1% lidocaine for phrenic nerve block in 48 patients undergoing thoracic surgery and demonstrated a reduced incidence of shoulder pain for up to 2 hours compared to saline infiltration.[1] Our study results also demonstrate that phrenic nerve infiltration markedly reduces shoulder pain up to 6 hours at rest and improves pain with movement for up to 12 hours. Similar results of reduced shoulder pain have also been reported by other colleagues, thus validating our findings.[1,16]

When we designed this study, we were aware that previous studies had already explored the use of lidocaine or ropivacaine to block the phrenic nerve to avoid any ventilator-related adverse events such as reduced vital capacity and forced vital capacity.[17,18] However, we wanted to explore the use of the longer acting local anesthetic bupivacaine. No adverse events were observed in any patients throughout the study. In addition to the shoulder pain, we have also explored the incidence of back pain and surgical site incision pain. Similar patterns were observed for both back and incision site pain, with reported pain levels consistently lower both at rest and with movement until 6 hours postsurgery. While the use of several analgesics following surgery was relatively common, their use was significantly greater in the non-PNI group and as such this is not thought to have altered the findings. In fact, this further emphasizes the extent of benefit of the PNI as less pain is experienced meaning less of the other analgesics are required. It is therefore clear from our findings that bupivacaine demonstrates significant benefit to the patient in the early postoperative setting associated with marked and relatively sustained pain reduction. This is important to enable the patient to breathe as normally as possible and as such attempt to prevent the development of adverse respiratory events.

To our knowledge, this is the first study to evaluate pain outcomes in association with measurement of peak flow pressure. Monitoring peak flow volume as well as postoperative pain is vital to increase the early mobilization and ambulation of thoracic surgery patients as a part of rehabilitation program to improve postoperative recovery.[19]

The phrenic nerve group patients demonstrated consistently lower peak flow measurements, both prior to surgery and throughout the postoperative period, and as such it is clear that PNI does not increase the respiratory capacity of the patient. However, many of these patients had low peak flow volume at baseline due to chronic lung conditions such as chronic obstructive pulmonary disease, asthma and fibrosis, which could have contributed to their lower values. Importantly, both groups demonstrated markedly lower peak flow postsurgery. It remains unclear therefore whether the difference between the groups is related to pre-existing conditions or is driven by the PNI delivery. In theory, patients receiving phrenic nerve block through the periphrenic nerve fat could also experience temporary paralysis of the diaphragm although this has not yet been proven. Our findings do not provide any further elucidation of this but further studies are necessary to clarify whether this is the case.

LIMITATIONS

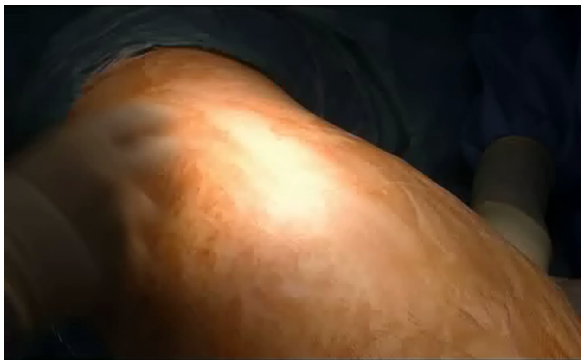
The current study aimed to avoid any possible bias; however, we were unable to standardize the use of anesthetic drugs and postoperative drugs due to variety of practice in our unit. Postoperative drug usage and chest drains were also removed at times determined by the clinician and were not standardized for the study. However, greater pain medication was required in the non-PNI group, strongly suggesting benefit of PNI. The second limitation of this study was that some of the patients felt drowsy and refused to perform incentive spirometry, particularly at the 1-hour postoperative time point. As such our follow-up data are incomplete, although the pattern of effect appears to be consistent and therefore should be reliable. Some of the patients from the phrenic nerve infiltration group had low peak flow volume at baseline before surgery because of chronic lung conditions. We therefore cannot be certain whether the postoperative peak flow volume was reduced because of chronic lung diseases or whether the use of phrenic nerve infiltration caused a temporary cessation of diaphragm function. We would also like to highlight that the perception of pain by every patient is different and it is impossible to control this factor. We ensured that all pain scores were obtained at the correct timings and before the patient received oral pain medications. However, it was not possible to control timings of pain measurements around PCA use as this is used as necessary by the patients themselves and timings are not recorded.

CONCLUSION

Our study demonstrated that the use of phrenic nerve infiltration reduces the intensity of postoperative shoulder, back and surgical incision pain in the early postoperative period. The phrenic nerve infiltration at the level of the diaphragm significantly reduced the incidence of pain for between 3 and 12 hours compared to the non-PNI group. This could allow greater patient mobilization and a more active recovery period, which could potentially help to minimize the incidence of postoperative respiratory complications. Furthermore, this significantly reduces the necessity for the use of other pain medication.

SUPPLEMENTARY MATERIAL

The following is the supplementary data to this article:



Video 1. Video of phrenic nerve infiltration to relieve the postoperative pain on patients undergoing thoracotomy.

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