Long-term Pain and Activity during Recovery from Major Thoracotomy Using Thoracic Epidural Analgesia

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Background: Pain following thoracotomy can persist for years with an undetermined impact on quality of life. Factors hypothesized to modulate this painful experience include analgesic regimen, gender, and type of incision.

Methods: A total of 157 generally healthy patients of both genders scheduled for segmentectomy, lobectomy, or bilobectomy through a posterolateral or muscle-sparing incision were randomly assigned to receive thoracic epidural analgesia initiated prior to incision or at the time of rib approximation. Pain and activity scores were obtained 4, 8, 12, 24, 36, and 48 weeks after surgery.

Results: Overall, there were no differences in pain scores between the control and intervention groups during hospitalization ($P \geq 0.165$) or after discharge ($P \geq 0.098$). The number of patients reporting pain 1 yr following surgery (18 of 85; 21.2%) was not significantly different ($P = 0.122$) from the number reporting preoperative pain (15 of 120; 12.5%). During hospitalization, women reported greater pain than men (worst pain, $P = 0.007$; average pain, $P = 0.016$). Women experienced fewer supraventricular tachydysrhythmias ($P = 0.013$) and were thus discharged earlier ($P = 0.002$). After discharge women continued to report greater discomfort than men ($P \leq 0.016$), but did not differ from men in their level of physical activity ($P = 0.241$).

Conclusions: Initiation of thoracic epidural analgesia prior to incision or the use of a muscle-sparing incision did not significantly impact pain or physical activity. Although women reported significantly greater pain during hospitalization and after discharge, they experienced fewer complications, were more likely to be discharged from the hospital sooner, and were just as active after discharge as men.

PAINFUL sequelae of major thoracotomy can persist long after surgery and limit normal function.[1] Prospective and retrospective studies demonstrate residual pain in about one half of patients 1 yr after surgery and as long as 4 yr in about one third of patients.[1-6] Female gender,[5] chest wall resection,[4] a more intense acute painful experience,[6] and greater acute analgesic use[1] have each been associated with the development of longer-term pain. Modifiable factors that are thought to decrease the impact of major thoracotomy include the analgesic regimen[7,8] and the incision type.[9]

Initiation of an analgesic regimen capable of preventing pain-induced sensitization of the nervous system before the onset of the noxious stimulus may limit the extent of the painful experience,[10-12] an approach often referred to as preemptive analgesia.[13,14] Benefits of preemptive analgesia for major thoracotomy have been demonstrated with lumbar[15] and thoracic epidural catheters[8,16] and intercostal nerve blocks.[17] Other studies,[18] but not all,[19,20] have indicated that aggressive perioperative analgesia can lead to reductions in pain following thoracotomy.

As recently emphasized,[21] gender may be an important factor leading to a more intense pain experience for women.[22-24] This may be compounded by decreased efficacy of commonly used analgesic drugs in women.[25] Female animals appear to be more susceptible to the development of painful syndromes following nerve damage,[26] and this is more likely to occur in intact than in ovariectomized animals.[27] Given these factors, female patients may be at higher risk for the development of painful conditions following thoracotomy, which is often associated with some sensory nerve damage.[28] Overall, the relation of gender to pain and recovery of function after major surgery is not well established for thoracotomy or other surgical procedures.

A classic posterolateral thoracotomy involves division of the latissimus dorsi at its midportion after a posterolateral incision at the fifth intercostal space. Division of the latissimus dorsi can be avoided with a muscle-sparing approach, which can be conducted with a less-disfiguring vertical incision made at the midaxillary line.[29] In addition to their cosmetic benefits, muscle-sparing incisions have been shown to decrease pain in some,[9] but not all,[30] settings, but have not been associated with long-term decrements in morbidity.[30] Some degree of pain reduction might be anticipated because muscle-sparing incisions are associated with less intercostal nerve disruption than classic thoracotomy incisions.[28]

Our primary hypothesis was that intraoperative thoracic epidural blockade would decrease short- and long-term postoperative pain following major thoracotomy in

patients who would all receive aggressive postoperative thoracic epidural analgesia. Because of their potential importance as effect modifiers, the role of gender and incision type were also explored. To allow the impact of pain and surgery on physical activity to be explored, inclusion criteria selected for patients whose preoperative level of function and extent of surgery were such that postoperative physical activity should not be substantially affected by previous limitations or the quantity of lung parenchyma removed.

Methods

Patients

According to a protocol approved by the Committee on Studies Involving Human Beings at the University of Pennsylvania Medical Center, and outlined in figure 1, all patients scheduled for elective major open thoracotomy through either a classic or a muscle-sparing incision, including segmentectomy, lobectomy, and bilobectomy, but excluding pneumonectomy and chest wall resection, were considered for inclusion in the study. When study personnel were available, all patients who had consented to an anesthetic plan consisting of general anesthesia with an epidural catheter to be placed prior to induction of general anesthesia were invited to participate if they were without neurologic impairment, any type of chronic painful condition, chronic analgesic use, except for aspirin or nonsteroidal antiinflammatory drugs or analgesics associated with the condition for which they were receiving surgery, significant cardiovascular disease (severe valvular heart disease or congestive failure [New York Heart Association class III–IV] or severe coronary artery disease [Canadian Cardiovascular Society class III–IV]), or significant decreases in pulmonary reserve (forced expiratory volume or forced expiratory volume in 1 s < 50% of predicted value, arterial oxygen saturation while breathing room air < 95%, or an arterial carbon dioxide partial pressure > 44 mmHg). Patients with specific contraindications to epidural catheter placement such as coagulopathy, systemic infection, or spinal stenosis were also excluded.

Study Protocol

Written informed consent was obtained by one of the physician investigators on the day of surgery. Patients and physicians were unaware of the assignment of subjects to specific treatment arms.

Baseline Measures

A research assistant who was blinded with respect to eventual treatment assignment obtained demographic data, administered a health survey, and assessed baseline pain and analgesic use. Baseline pain was assessed by determining current pain on a 100-mm visual analog scale (VAS),[31] and use of the Brief Pain Inventory Short Form (BPI),[32] which assesses least, current, average, and worst pain on a discrete 0–10 scale. The health survey is a 10-question subset of the Quality-of-Life Short Form Health Survey (SF-36),[33-35] where each question assesses one of 10 physical activities, each on a discrete three-point scale. After obtaining this information, the patient was randomized to one of the two treatment groups with a 1:1 allocation ratio using fixed blocking, where 120 patients were to complete the hospital-based portion of the study.

Epidural Catheter Placement

After obtaining intravenous access, intravenous midazolam (0–2 mg) and fentanyl citrate (0–3 μg/kg) were titrated in to make epidural catheter placement tolerable. Prior to the induction of general anesthesia, a thoracic epidural catheter was placed at the level of the T6–T8 interspaces in all patients, and a 3-ml test dose of 1.5% lidocaine with epinephrine 1:200,000 was administered through the epidural catheter. If there was tachycardia or hypertension suggesting intravascular delivery of the epinephrine, rapid onset of neuroaxial blockade suggesting subarachnoid delivery of the local anesthetic, or if blood or cerebrospinal fluid was aspirated from the epidural catheter, it was replaced at another interspace. Patients were dropped from the study if an epidural catheter could not be placed above the T12 interspace.

Course of Anesthesia

After placement of an arterial catheter, a standardized general anesthetic induction was conducted with propofol (1.5–2.5 mg/kg), cisatracurium (0.1–0.2 mg/kg), and fentanyl citrate (3 μg/kg, including the fentanyl citrate administered during epidural catheter placement). General anesthesia was maintained with isoflurane in oxygen titrated to blood pressure, and cisatracurium titrated to achieve an adequate level of muscle relaxation. Following bronchoscopically assisted placement of a double-lumen endotracheal tube to enable selective lung ventilation, medication was administered through the epidural catheter. Patients in the control group received 6 ml of saline followed by an infusion of saline at 8 ml/h. Patients in the intervention group received 6 ml of a mixture of 0.375% bupivacaine and 3 μg/ml of fentanyl citrate followed by an infusion at 8 ml/h of the same mixture. Drugs administered intraoperatively through the epidural catheter were prepared by a pharmacist and provided to the anesthesiologist who, along with all other personnel, remained blinded as to their content. The type of incision was determined at the time of surgery by the surgeon, who balanced the need for exposure against the desire for a more limited incision. Patients in whom the surgery proved to be less (no lung resection) or more (pneumonectomy or chest wall resection) extensive than the inclusion criteria were

Patients Presenting for Elective Open Thoracotomy
(N=428)

Eligible Procedure
(open segmentectomy, lobectomy or bilobectomy,
via posterolateral or muscle sparing incision and not pneumonectomy, chest wall resection, volume reduction or
metastatic disease,)
N=216

Not Randomized (N=59)
Personnel Not Available for Study (n=13)
Preexisting Pain/Opioid Use (n=25)
Refused Epidural Catheter (n=0)
Declined (n=3)
Angina with Minimal Exertion or Rest (n=18)

Randomized
N=157

Control Group
Postoperative Epidural Analgesia Only
N=79

Intervention Group
Intraoperative *and* Postoperative Epidural Use
N=78

Did Not Complete Hospital Protocol (N=16)
Epidural Catheter Not Functioning (n=4)
Surgery More/Less Extensive Than Scheduled (n=9)
Underwent Repeated Thoracotomy (n=2)
Protocol Deviation (n=1)
Withdrew (n=0)
Death (n=0)

Did Not Complete Hospital Protocol (N=21)
Epidural Catheter Not Functioning (n=7)
Surgery More/Less Extensive Than Scheduled (n=9)
Underwent Repeated Thoracotomy (n=2)
Protocol Deviation (n=0)
Withdrew (n=1)
Death (n=2)

Completed Hospital Protocol (N=63)

*Telephone Follow-up
4 Weeks (n=57, M/F=33/24, PL/MS=18/39)
8 Weeks (n=54, M/F=31/23, PL/MS=18/36)
12 Weeks (n=58, M/F=32/26, PL/MS=18/40)
24 Weeks (n=56, M/F=31/25, PL/MS=18/38)
36 Weeks (n=57, M/F=32/25, PL/MS=18/39)
48 Weeks (n=44, M/F=26/18, PL/MS=16/28)
**None (n=0)

Completed Hospital Protocol (N=57)

*Telephone Follow-up
4 Weeks (n=51, M/F=20/31, PL/MS=17/34)
8 Weeks (n=49, M/F=20/29, PL/MS=14/35)
12 Weeks (n=54, M/F=21/33, PL/MS=16/38)
24 Weeks (n=47, M/F=20/27, PL/MS=13/34)
36 Weeks (n=42, M/F=14/28 PL/MS=12/30)
48 Weeks (n=41, M/F=16/25, PL/MS=13/28)
**None (n=0)

*Indicates total participating in follow-up in each group as well as number in group who are male or female (M/F) and received posterolateral or muscle sparing incisions (PL/MS)
**Completely lost to follow-up after discharge.

Fig. 1. Flowchart for the clinical trial. Ineligible subjects included those scheduled for lung volume reduction (n = 28), pneumonectomy (n = 33), or photodynamic therapy (n = 16), those with known metastatic disease of the lung (n = 15) or metastatic disease from sources outside of the lung (n = 23), those undergoing repeat thoracotomy (n = 40), and those who would receive other than a posterolateral or muscle sparing incision (n = 57). Of these 212 ineligible subjects, 19 underwent chest wall resection. Five eligible subjects underwent chest wall resection, four at the time of the initial surgery and one on repeat thoracotomy, and did not complete the hospital protocol.

dropped from the study. Fluid therapy consisted of physiologic saline, and blood pressure was supported by intravenous ephedrine sulfate or phenylephrine.

Postoperative Pain Management

At the time of rib approximation, all patients received an epidural bolus dose of a mixture of 5 ml of 0.5% bupivacaine and 50 μg fentanyl citrate in a total volume of 6 ml. On completion of the surgery, the isoflurane was discontinued, neuromuscular relaxation was reversed, and, on the return of adequate levels of muscle strength and consciousness, the patient was extubated and transported to the postanesthesia care unit. On arrival in the postanesthesia care unit, all patients were assessed by

pinprick for a band of thoracic anesthesia, and patients who failed to demonstrate an anesthetic band received 6 ml of 1.5% lidocaine with epinephrine 1:200,000. At this point, patients who still failed to demonstrate a band of thoracic anesthesia were dropped from the study since both intraoperative and postoperative catheter function would have been unlikely. Patient-controlled epidural analgesia (PCEA) was initiated in the postanesthesia care unit by a member of the acute pain service. This consisted of a mixture of 0.05% bupivacaine and fentanyl citrate 0.001% at an infusion rate of 4 ml/h and 3-ml bolus doses permitted every 10 min. Patients who complained of shoulder pain in the postanesthesia care unit received a single intravenous dose of 30 mg ketorolac. Opioids other than those administered through the epidural catheter were not administered routinely while the epidural catheter was in place, although they were permitted if epidural analgesia was judged to be inadequate. As per institutional routine, the epidural catheter was maintained until thoracostomy tube removal, or longer if pain control was still a problem. After removal of the epidural catheter, pain control was achieved with oral analgesics under the supervision of the surgical team. This oral analgesic regimen typically included 600 mg ibuprofen three to four times per day and a combination of 5–10 mg oxycodone hydrochloride and 325–650 mg acetaminophen every 4–6 h as needed.

Outcome Measures

Each postoperative morning epidural and other analgesic use was recorded, the presence of significant complications was assessed, and pain scores were obtained. Epidural analgesic use was determined by downloading the entire history of epidural analgesic demand and use from the patient-controlled epidural infusion pump. Significant complications included angina, myocardial infarction, cardiac dysrhythmias, pneumonia, respiratory failure, renal dysfunction, stroke, and death. Pain, the primary outcome variable, was determined using a 100-mm VAS while the patient was at rest and the BPI. All data were obtained by a research assistant or anesthesiologist who was blinded with respect to treatment group. An attempt was made to contact by telephone all patients who had completed the hospital-based portion of the study 4, 8, 12, 24, 36, and 48 weeks after surgery. At that time pain, the primary outcome variable and related variables were assessed with the BPI, and activity was assessed with the 10-question subset of the SF-36 specific for physical activity. The telephone survey was always performed by a research assistant who was blinded with respect to treatment group.

Statistical Analysis

The number of patients required for each analgesic group when pain is the primary outcome variable was determined from a power analysis of data taken from a previous study of epidural analgesia for major thoracotomy.[15] This analysis indicated that a total of 120 patients would be required to observe a decrement of 10 mm on a VAS pain score (a medium effect size) with a power of 0.8 and a type I error rate of 0.05. This number of subjects would permit the observation of a reduction in the rate of patients reporting pain 1 yr following thoracotomy from 50% to 25% with a power of 0.8 and a type I error rate of 0.05.

Demographic data were analyzed using one-way analysis of variance, the Mann–Whitney U test, and the Fisher exact test (two-tailed) for continuous, ordinal, and proportional data, respectively. The pain scores and other data from the BPI were treated as continuous variables and analyzed using a multifactorial (treatment, gender, incision, and time) repeated-measures analysis of variance ($2 \times 2 \times 2$ for single measurement, $2 \times 2 \times 2 \times 5$ for data obtained at multiple time points during hospitalization, and $2 \times 2 \times 2 \times 6$ for data obtained at multiple time points after discharge). This analysis was repeated where average preoperative pain was controlled for by including it as a covariate. Total drug use was transformed using $\log(1 + x)$, and significance was determined with multifactorial analysis of variance. Time in the hospital and time with an epidural catheter in place were analyzed with the log-rank test. The effects of gender and the occurrence of complications on the duration of hospitalization were investigated with the Cox proportional hazards model. Logistic regression was used to investigate the likelihood of experiencing persistent pain after discharge if pain levels during hospitalization were elevated. Because deviation from the intended surgical plan or a nonfunctioning epidural catheter could bias the study in either direction, data were analyzed only with respect to the 120 patients completing the hospital-based portion of the protocol. However, complications were analyzed for both this group of 120 patients and on an intention-to-treat basis for all patients who were randomized. Throughout, differences were considered significant at $P \leq 0.05$.

Results

Over a period of 16 months, from March 1998 to July 1999, 157 patients were randomized to one of two treatment groups (fig. 1). Patient characteristics and perioperative parameters are summarized in tables 1 and 2. These are notable for a greater number of women reporting preoperative pain ($P = 0.026$) and the greater number of women in the intervention group ($P = 0.046$). Although larger absolute doses of intravenous fentanyl citrate were administered intraoperatively to men, there was no gender difference when these doses were normalized with respect to body weight ($P = $

Table 1. Demographic Data for Patients Completing Hospital-based Portion of Study

Characteristic	Overall (n = 120)	Treatment Group			Gender			Incision Type		
		Control (n = 63)	Intervention (n = 57)	P	Male (n = 58)	Female (n = 62)	P	Classic (n = 38)	MS (n = 82)	P
Age (yr)	61.2 (13.0)	61.9 (13.5)	60.4 (12.4)	0.519	63.8 (11.7)	58.7 (13.7)	0.031	60.2 (12.2)	61.2 (13.3)	0.581
Gender (male/female)	58/62	36/27	22/35	0.047	N/A	N/A	N/A	19/19	39/43	0.846
Height (cm)	166 (13.8)	166 (16.5)	165 (10.1)	0.810	172 (15.9)	160 (8.1)	<0.001	166 (9.7)	166 (15.4)	0.832
Weight (kg)	76.7 (19.8)	76.9 (19.4)	76.5 (20.5)	0.910	85.7 (20.2)	68.3 (15.4)	<0.001	78.8 (22.5)	75.7 (18.6)	0.423
ASA physical status (I–IV)	3 (2–3)	3 (2–3)	2.5 (2–3)	0.927	3 (2–3)	2 (2–3)	0.181	3 (2–3)	2.5 (2–3)	0.691
Goldman score[36] (0–49)	5 (5–10)	5 (5–10)	5 (5–10)	0.968	5 (5–10)	5 (5–10)	0.441	5 (5–5)	5 (5–10)	0.140
FVC (% predicted)	87.7 (21.5)	87.7 (17.5)	87.6 (25.4)	0.973	86.2 (20.6)	88.9 (22.3)	0.505	80.4 (22.2)	90.8 (20.5)	0.016
FEV_1 (% predicted)	78.8 (23.5)	78.4 (21.3)	79.2 (26.0)	0.857	79.6 (21.5)	78.1 (25.4)	0.748	75.5 (23.3)	80.2 (23.6)	0.322
FEV_1/FVC (% predicted)	71.6 (16.5)	71.8 (14.7)	71.4 (18.6)	0.892	72.6 (15.4)	70.7 (17.6)	0.551	74.9 (18.5)	70.2 (15.5)	0.166
Room air SpO_2 (%)	97.2 (2.4)	97.3 (2.1)	97.1 (2.6)	0.711	97.1 (2.6)	97.3 (2.1)	0.645	96.8 (2.8)	97.4 (2.1)	0.208
Number with pain (n)*	15 (12.5)	8 (12.7)	7 (12.3)	1.00	3 (5.2)	12 (19.4)	0.026	5 (13.1)	10 (12.2)	1.00
Preoperative nonopioid analgesics (n)	20 (16.7)	12 (19.0)	8 (14.0)	0.625	10 (17.2)	10 (16.1)	1.00	6 (15.8)	14 (17.1)	1.00
Preoperative opioid analgesics (n)	6 (5.0)	4 (6.3)	2 (3.5)	.682	4 (6.9)	2 (3.2)	0.428	1 (2.6)	5 (6.1)	0.663

Continuous data are reported as mean (SD), ordinal data (ASA physical status and Goldman score) are reported as median (lower quartile-upper quartile), and frequency data are reported as the number of events n (%). *P* values are reported as determined by one-way analysis of variance, Mann–Whitney U test, and Fisher exact test for the continuous, ordinal, and frequency data, respectively.

*Nonzero average pain from Brief Pain Inventory Short form.

ASA = American Society of Anesthesiologists; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; MS = muscle-sparing incision.

0.579). Although fluid use did not differ between the control and intervention groups ($P = 0.303$), the quantities of ephedrine ($P < 0.001$) and phenylephrine ($P = 0.030$) used for blood pressure control were significantly different between the control and intervention groups. The time from incision until rib approximation was significantly shorter for women ($P = 0.001$).

Overall, postoperative pain control during hospitalization was excellent[37] for both the control and the intervention groups (fig. 2) but without significant decline in any of the pain measures during hospitalization ($P \geq 0.197$). As described in figure 2, pain did not differ between the control and the intervention groups. However, an analgesic-sparing effect was noted for the intervention group (table 2, $P = 0.035$) which used 499 ± 32 ml (mean $\pm$ SEM) of epidural analgesic solution compared with 622 ± 38 ml by the control group. As shown in table 2, there was a trend toward a greater number of demands for epidural analgesic boluses by the control group ($P = 0.066$), which was locked out by the PCEA pump significantly more times than the intervention group ($P = 0.040$). Total nonepidural analgesic use, where all nonepidural opioid analgesics were converted to equivalent doses of intravenous morphine sulfate,[38,39] did not differ for opioids ($P = 0.311$) or ketorolac ($P = 0.588$).

As seen in figure 3, the pain reported by women during hospitalization differed significantly from that of men with respect to worst pain ($P = 0.007$) and average pain ($P = 0.016$), and these differences remained significant even when average preoperative pain was controlled for. As shown in table 2, analgesic use (epidural, $P = 0.588$; nonepidural opioids, $P = 0.402$; ketorolac, $P = 0.961$) did not significantly differ between men and women, even when normalized for height and weight, and total number of PCEA demands ($P = 0.415$) and lockouts ($P = 0.318$) were also similar between men and women. Despite the increased pain, women were discharged from the hospital earlier than men ($P = 0.002$), primarily because they experienced fewer supraventricular tachydysrhythmias, as discussed below. Differences in pain and patterns of analgesic use were not associated with the type of incision.

Pain and physical activity following discharge are shown in figures 4 and 5. All subjects participated to some extent in follow-up after discharge (fig. 1) and, at each point in time, those responding could not be distinguished from those who did not on the basis of their pain during hospitalization ($P \geq 0.314$). After discharge from the hospital, analgesic group or incision type was not associated with significant differences in any of the pain measures or activity. However, throughout the period of study following discharge, women reported significantly greater discomfort than men (fig. 4) for all pain categories (worst pain, $P = 0.011$; average pain, $P = 0.015$; current pain, $P = 0.006$; least pain, $P = 0.016$). Despite these differences, physical activity of women was not significantly different from men ($P = 0.241$). At the conclusion of the study period, but not prior to this, pain scores were not significantly different from preoperative pain scores for any pain category ($P \geq 0.081$). At this time, the number of patients reporting nonzero

Table 2. Perioperative Data for Patients Completing Hospital-based Portion of Study

Characteristic	Overall (n = 120)	Control (n = 63)	Intervention (n = 57)	P	Male (n = 58)	Female (n = 62)	P	Classic (n = 38)	MS (n = 82)	P
		Treatment Group			Gender			Incision Type		
Intravenous fentanyl (μg)*	151 (62)	161 (69)	140 (52)	0.068	173 (64)	131 (53)	<0.001	152 (71)	151 (58)	0.902
Intravenous midazolam (mg)*	2.1 (0.9)	2.0 (0.9)	2.1 (0.9)	0.784	2.2 (1.1)	2.0 (0.7)	0.220	2.0 (0.8)	2.1 (0.9)	0.652
Epidural insertion level (T–n)†	7 (6–7)	7 (6–7)	7 (6–7)	0.411	7 (6–7)	7 (6–7)	0.410	6.5 (6–7)	7 (6–7)	0.270
Incision type (classic/MS)	38/82	20/43	18/39	1.00	19/39	19/43	0.846	N/A	N/A	N/A
Duration of surgery (min)‡	151 (70)	158 (72)	144 (67)	0.821	175 (73)	130 (59)	0.001	162 (72)	146 (69)	0.296
Fluid use (l)‖	1.50 (0.67)	1.44 (0.63)	1.57 (0.71)	0.303	1.69 (0.80)	1.34 (0.49)	0.004	1.68 (0.64)	1.42 (0.67)	0.050
Phenylephrine use (mg)#	0.40 (0.55)	0.29 (0.37)	0.51 (0.68)	0.030	0.49 (0.60)	0.32 (0.50)	0.096	0.37 (0.53)	0.41 (0.56)	0.745
Ephedrine use (mg)#	12.0 (16.9)	6.7 (9.6)	17.8 (20.7)	<0.001	10.8 (15.0)	13.1 (18.4)	0.460	8.1 (13.0)	13.8 (18.1)	0.087
Epidural volume (ml)	563 (281)	622 (303)	499 (242)	0.035	592 (289)	537 (274)	0.588	586 (258)	553 (292)	0.511
PCEA demands (n)	168 (158)	198 (187)	135 (110)	0.067	180 (159)	157 (157)	0.415	193 (167)	156 (153)	0.381
PCEA locked out (n)	93 (118)	118 (143)	65 (76)	0.040	105 (119)	82 (119)	0.318	115 (129)	83 (113)	0.270
Nonepidural opioids (mg)††	18.2 (28.2)	18.1 (32.3)	18.2 (23.2)	0.311	20.8 (34.3)	15.7 (20.9)	0.402	18.3 (23.0)	18.1 (30.4)	0.216
Ketorolac (mg)	13.8 (33.7)	14.8 (37.3)	12.7 (29.4)	0.588	11.9 (28.2)	15.6 (38.2)	0.961	13.9 (30.7)	13.7 (35.1)	0.938
Days with epidural (n)	4 (3–4)	4 (3–5)	4 (3–4)	0.429	4 (3–5)	4 (3–4)	0.596	4 (3–4)	4 (3–5)	0.683
Days hospitalized (n)	5 (4–6)	5 (5–6)	5 (4–6)	0.932	6 (5–6)	5 (4–6)	0.002	5 (4–6)	5 (4–6)	0.758
Complications‡‡										
AFIB or SVT (n/n)	20/33	11/14	9/19	1.00/0.333	15/26	5/7	0.013/<0.001	7/12	13/19	0.794/0.387
Nonlethal events (n/n)	30/45	17/21	13/24	0.675/0.600	19/32	11/13	0.091/0.002	12/20	18/23	0.266/0.018
Death (within 30 d) (n/n)	0/3	0/0	0/3	1.00/0.245	0/2	0/1	1.00/1.00	0/2	0/1	1.00/0.241
Death (within 1 yr) (n/n)	3/10	0/2	0/8	1.00/0.056	2/8	1/2	0.610/0.099	1/3	2/4	1.00/0.680

Continuous data are reported as mean (SD), ordinal data (epidural insertion level, days with epidural, days hospitalized) are reported as median (lower quartile–upper quartile), and frequency data are reported as the number of events n (%). P values are reported as determined by one-way analysis of variance, Mann–Whitney U test, and Fisher exact test for the continuous, ordinal, and frequency data, respectively. For postoperative analgesic use (epidural volume, PCEA demands, PCEA locked out, nonepidural opioids, and ketorolac), significance was determined by 2 × 2 × 2 (treatment, gender, and incision) analysis of variance. For days with epidural and days hospitalized, significance was determined with the log-rank test.

*Medications administered prior to anesthetic induction to make procedures tolerable. †No patient in the study experienced a dural puncture or was treated for a dural puncture headache. ‡Defined from the time of incision until the time of rib approximation. ‖Fluid therapy during surgery (crystalloid, colloid, and packed erythrocytes). #Vasopressors administered during surgery to support blood pressure. ††Equivalent dose of intravenous morphine sulfate. ‡‡Complications are reported for both the 120 patients completing the hospital-based portion of the protocol and on an intention-to-treat basis for the 157 patients initially randomized. In addition to atrial fibrillation and reentrant supraventricular tachycardia (SVT), nonlethal complications included wound infection (2), pneumonia (2), myocardial infarction (1), congestive failure (2), reinstitution of mechanical respiratory support (2) and deep venous thrombosis (1). Multiple complications are included (*e.g.*, congestive failure or pneumonia in a patient with atrial fibrillation). One of the two deaths in randomized patients who did not complete the hospital-based portion of the protocol (fig. 1) occurred in a patient whose epidural catheter was nonfunctional.

MS = muscle-sparing incision; PCEA = patient-controlled epidural analgesia; AFIB = atrial fibrillation; SVT = supraventricular tachydysrhythmia.

average pain (18 of 85; 21.2%) was not significantly different (P = 0.122) than that observed prior to surgery (15 of 120; 12.5%). The number of patients reporting pain scores greater than or equal to 5 (6 of 85; 7.1%) at the conclusion of the study was not significantly different (P = 0.167) than that prior to surgery (3 of 120; 2.5%). At the conclusion of the study there were no differences in the number reporting nonzero average pain with respect to analgesic regimen, gender, or type of incision (P ≥ 0.588). Also at this time, those with preoperative pain did not report nonzero average pain to a greater extent than those without preoperative pain (P = 0.714). At the conclusion of the study, only 11 of 85

(12.9%) reported the use of opioid analgesics. At this time, 8 of the 18 patients (44.4%) reporting nonzero average pain also reported opioid analgesic use. Only one patient reported receiving a nerve block to control pain.

Pain prior to hospitalization and shortly after surgery was predictive of subsequent pain levels. Nonzero average preoperative pain was associated with greater average pain during hospitalization (P = 0.009) and after discharge (P < 0.001). However, as noted above, nonzero preoperative pain was not significantly associated with nonzero average pain at the conclusion of the study. Current pain scores (VAS) on the first postopera-
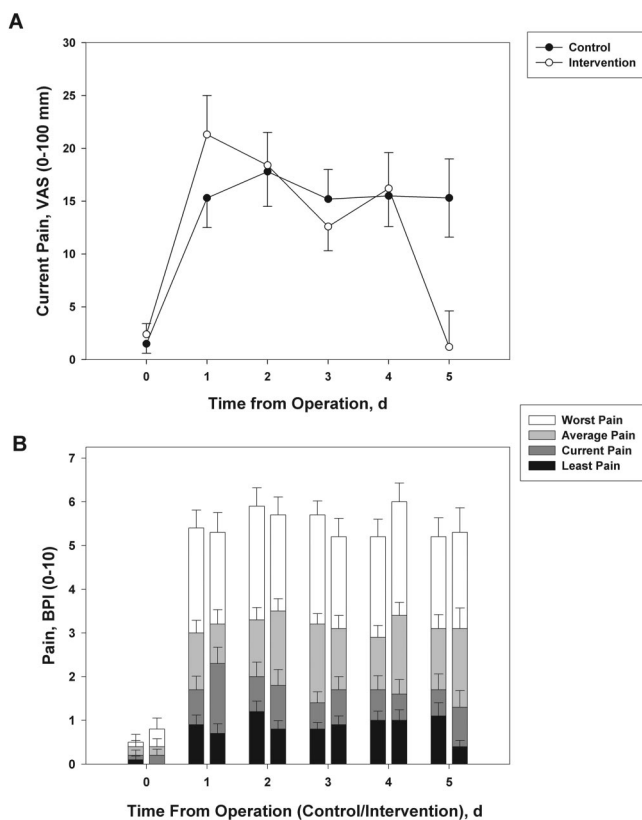
Fig. 2. Postoperative pain while hospitalized (mean ± SEM). Pain was measured at rest on a 100-mm visual analog scale (VAS) or with the 10-point Brief Pain Inventory (BPI), with zero indicating no pain in both cases. Zero time from operation indicates preoperative values. Current pain is assessed with the VAS (*A*), whereas worst, average, current, and least pain is assessed with the BPI (*B*). Differences between the control and intervention groups could not be appreciated for any of these pain measures (VAS, *P* = 0.165; worst pain, *P* = 0.222; average pain, *P* = 0.486; current pain, *P* = 0.350; least pain, *P* = 0.122), even when average preoperative pain was included as a covariate (VAS, *P* = 0.217; worst pain, *P* = 0.273; average pain, *P* = 0.602; current pain, *P* = 0.444; least pain, *P* = 0.157).
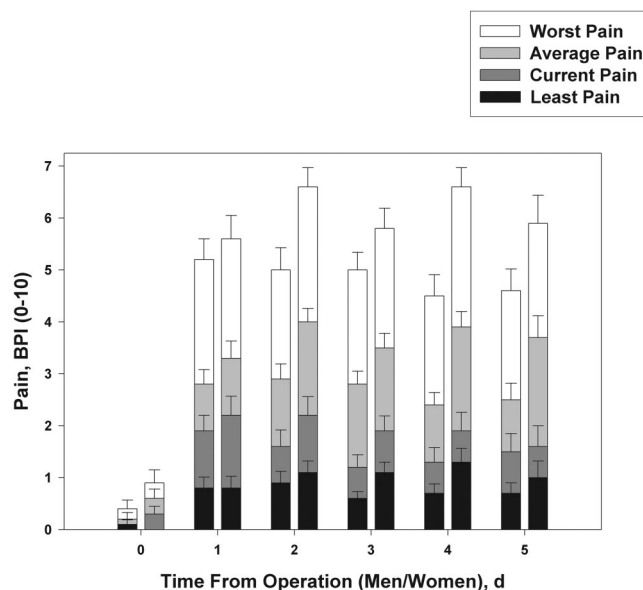

Fig. 3. Gender differences in postoperative pain while hospitalized (mean ± SEM). Pain was measured with the 10-point Brief Pain Inventory (BPI), with zero indicating no pain. Zero time from operation indicates preoperative values. For each day, pain levels for men are shown in the left-hand column and those for women in the right-hand column. Significant differences were observed for worst pain (*P* = 0.007) and average pain (*P* = 0.016) but not for current pain (*P* = 0.168) or least pain (*P* = 0.262). Current pain assessed on a 100-mm visual analog scale (not shown) did not reveal significant gender differences (*P* = 0.182). When average preoperative pain was included as a covariate, significant gender differences remained (worst pain, *P* = 0.012; average pain, *P* = 0.029).

The number of complications experienced over the course of the study is shown in table 2 and is notable for the fewer women experiencing supraventricular tachydysrhythmias (*P* = 0.013). When the effect on discharge from the hospital of both gender and the occurrence of a supraventricular tachydysrhythmia is considered, gender is not significant (*P* = 0.079). By itself, the occurrence of a supraventricular tachydysrhythmia had a significant effect on the length of hospitalization (*P* = 0.007).

Discussion

When thoracic epidural analgesia is used until the time of thoracostomy tube removal, intraoperative use of the epidural catheter was not associated with decreases in short- or long-term pain following major thoracotomy. Despite pain control as good or better than reported in other studies of pain following thoracotomy,[15,18,19,40,41] patients, especially women, still reported periods of substantial discomfort during hospitalization, as indicated by their scores for worst pain, which did not significantly decline during hospitalization. Although some patients, particularly women, reported considerable pain after discharge, this steadily declined so that by the
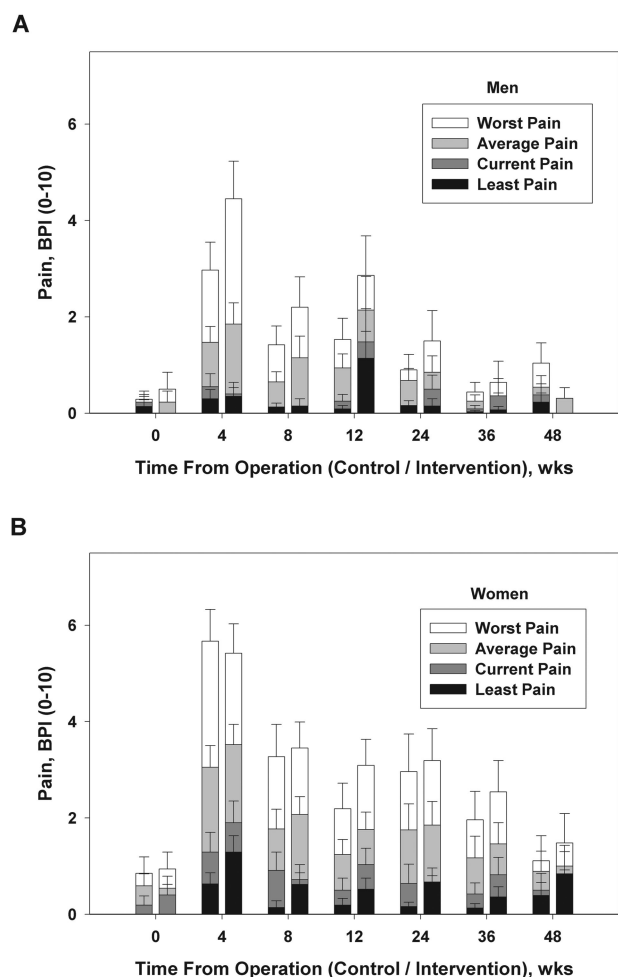
tive day were predictive of nonzero average pain 24 weeks after surgery (*P* = 0.006) but not 36 or 48 weeks after surgery and, as shown in figure 6, those with nonzero average pain 24 weeks after surgery reported significantly greater pain while hospitalized. However, significant differences were not observed for analgesic use (epidural analgesic, *P* = 0.709; nonepidural opioids, *P* = 0.058; ketorolac, *P* = 0.208), PCEA demands (*P* = 0.312), or PCEA lockouts (*P* = 0.333).

Patient activity levels after surgery were significantly less than preoperative levels throughout the entire study period (fig. 5A), and those with nonzero average pain were significantly less active than those with zero average pain for the entire study period (fig. 7). Patients reporting zero average pain also reported physical activity levels not significantly different from preoperative activity 8, 24, 36, and 48 weeks after surgery (*P* ≥ 0.130).

Fig. 4. Postoperative pain after discharge (mean ± SEM) for the control *versus* the intervention group for men (*A*) and women (*B*). Pain was measured with the Brief Pain Inventory (BPI) on a 10-point scale, with zero indicating no pain. Zero time from operation indicates preoperative values. Differences between the control and intervention groups were not significant. However, as detailed in the text, gender differences were present for all pain measures.
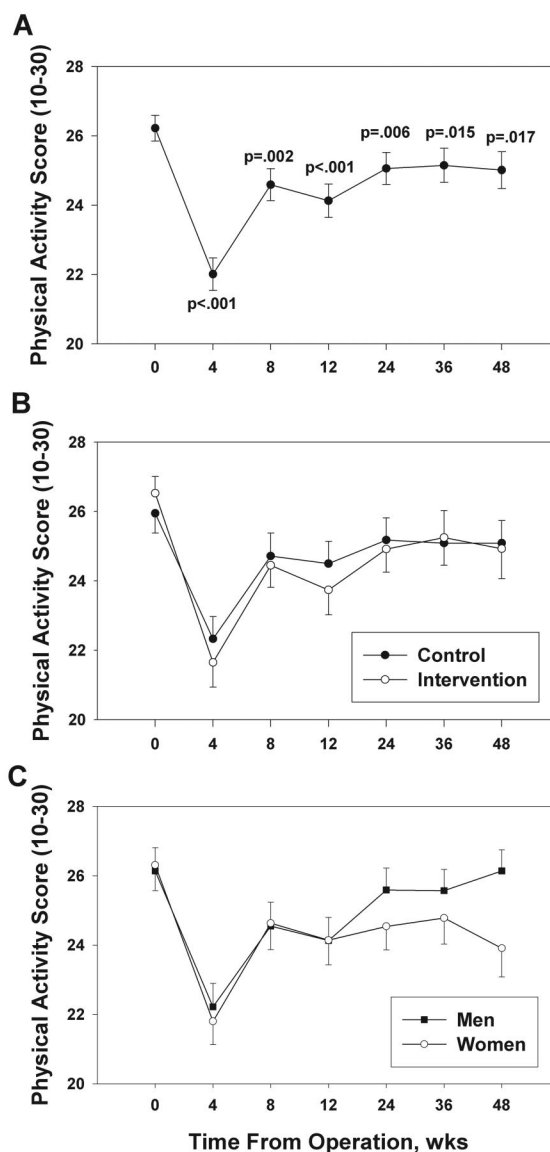

Fig. 5. Physical activity after discharge (mean ± SEM). Physical activity was determined from the sum of the 10 physical activity questions from the Quality-of-Life Short Form Health Survey, which rates each activity on a three-point scale so that the possible activity scores range from 10 to 30. Zero time from operation indicates preoperative values. Physical activity is shown for (*A*) the entire study population, (*B*) the control *versus* the intervention group, and (*C*) for men *versus* women. As indicated in (*A*), activity levels following surgery remained significantly different from preoperative activity levels throughout the entire study period. Differences between the control and intervention groups (*P* = 0.813) or men and women could not be appreciated (*P* = 0.241).

conclusion of the study the pain scores and number of patients reporting pain (21%) were not significantly different than observed prior to surgery. This rate of long-term postthoracotomy pain is less than the rate of at least 50% demonstrated in prior, mostly retrospective, studies.[1–6] Despite this, patients had not returned to their usual level of physical activity at the conclusion of the study.

Although an analgesic-sparing effect of about 20% was observed in the intervention group, patients in the intervention group did not appreciably differ from the control group with respect to outcome. Although benefits have been demonstrated for intraoperative blockade directed at the surgical site,[15,42,43] preemptive analgesia has led to equivocal results for thoracotomy[8,15–20] and other procedures.[44] It is possible that the intraoperative dose of local anesthetic and opioid used in the interven-

tion group was inadequate to prevent sensitization of the nervous system, even though the dose used generally permits surgery to be conducted with minimal levels of volatile anesthetic. However, hemodynamic response to surgery may not indicate nociceptor blockade since thoracic epidural anesthesia can directly blunt the hemodynamic response to surgery.[45] That thoracic epidural blockade could be incomplete is suggested by the inabil-
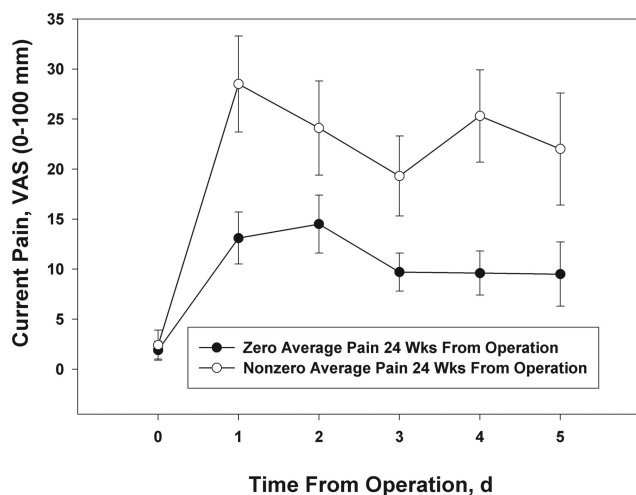
Fig. 6. Relation between postoperative pain after discharge and postoperative pain during hospitalization using the same measure as in figure 2A. Postoperative pain during hospitalization is shown for those reporting zero levels of average pain 24 weeks from operation and is significantly different from those reporting nonzero average pain levels at that time (*P* = 0.026). VAS = visual analog scale.

ity of thoracic epidural blockade to attenuate somatosensory evoked potentials elicited at the level of catheter insertion, even though lumbar epidural blockade with larger volumes of local anesthetic could decrease evoked potentials from the same dermatome.[46,47] Moreover, even complete blockade of the thoracic dermatomes will not prevent noxious signals from the diaphragmatic pleura, mediastinal pleura, and the pericardium transmitted by the phrenic nerve.[48] In addition, since adequate analgesic therapy permitted both groups to experience similar pain levels during hospitalization, it is consistent that their longer-term experience was also similar.
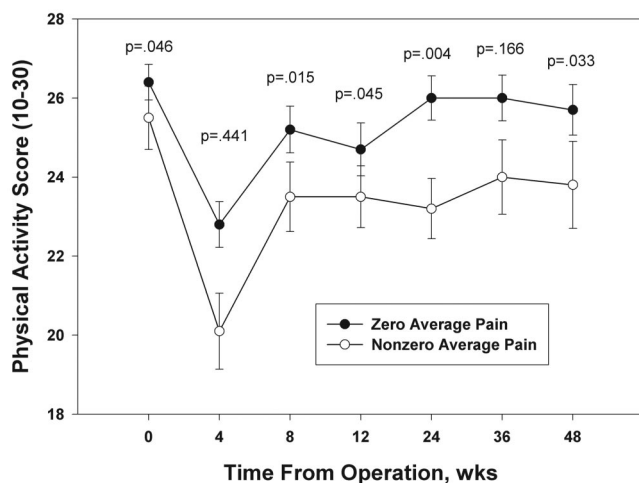
Fig. 7. Impact of postoperative pain after discharge on physical activity, where physical activity was assessed as in figure 5. Physical activity is shown for those reporting zero average pain at the time of assessment and is compared with those reporting nonzero average pain at that time, with the significance of these differences noted on the figure.

Using thoracic epidural analgesia, this study demonstrated a rate of residual pain 1 yr following thoracotomy of 21%, a rate less than half that reported in many,[1-6] but not all,[18] prior, largely retrospective, studies. Consistent with a prior retrospective study,[6] patients who reported more severe pain while hospitalized were more likely to report persistent pain after discharge. However, the current study demonstrated an association only as long as 6 months afterward as opposed to 1.5 yr. Although preoperative pain was predictive of more intense pain while hospitalized and after discharge, it was not associated with reports of pain at the conclusion of the study. It is possible that exclusion of patients who underwent chest wall resection biased the results, since these patients may be more likely to experience long-term pain.[4] However, if it is assumed that all patients undergoing chest wall resection in this study went on to experience residual pain 1 yr following surgery and that the remaining patients experienced pain at the rate of 21%, this would lead to a rate of pain 1 yr after surgery of only 25%.

Women in this study reported more severe pain than men. However, for reasons not completely elucidated, this did not affect their discharge from the hospital or resumption of physical activity after discharge. The interaction of pain and gender is a complex process that has yet to be fully understood and emerges from the interplay of multiple psychologic and physiologic variables over a lifetime.[49] However, experimental evidence of decreased pain thresholds,[22-24] decreased efficacy of some analgesics,[25] and increased sensitization by painful experience[26,27] makes it plausible that women could experience more intense perioperative pain than men. To date, the limited data for acute perioperative pain have been equivocal,[24] although the results from the current study are consistent with recent short-term observations of acute postoperative pain following knee surgery.[50] It may also be that the men in this study were more reluctant to disclose their pain[51] or sought to minimize their discomfort when speaking to the female research assistants[52] who saw them in the hospital and spoke with them by telephone after discharge.

Although the decreased likelihood of intercostal nerve damage during a muscle-sparing thoracotomy as compared with a classic posterolateral incision could theoretically reduce development of postoperative pain,[28] this benefit has not been realized in all studies,[9,30] including the current one. It is possible that the increased dissection involved in a muscle-sparing incision leads to increased perioperative pain levels, or that the level of intercostal nerve damage previously described[28] does not significantly affect development of perioperative pain.

Overall, despite the quality of pain control, patients did not return to their usual level of physical activity, even 1 yr after surgery. However, patients reporting zero average pain had returned to their preoperative activity

levels as soon as 8 weeks following surgery. It is doubtful that loss of lung parenchyma during surgery was responsible for decreases in activity levels since patients were selected on the basis of the adequacy of their pulmonary reserve, which would not be expected to be substantially compromised with the loss of no more than two lobes. Although pain may be a marker of ongoing disease capable of limiting physical activity, it may also be the primary reason for decreased activity since even relatively modest pain levels have previously been associated with limitation of physical activity.[53]

Supraventricular tachydysrhythmia was the most common complication observed in this study, with rates similar to those reported previously.[54–57] Although postoperative thoracic epidural analgesia with bupivacaine has been associated with a decreased rate of supraventricular tachydysrhythmias,[58] these results were obtained with more concentrated local anesthetic solutions than those used in the current study. When compared with earlier studies, the current study is notable for significantly fewer episodes of supraventricular tachydysrhythmia in women as compared with men. This difference appeared to account for the earlier discharge of women from the hospital.

In summary, the intensity of pain and its persistence following major thoracotomy is less than commonly believed and minimally affected by intraoperative epidural catheter use, at least when pain is aggressively managed with a thoracic epidural catheter from the time of rib approximation until after thoracostomy tube removal. Despite this, many patients reported at least brief periods of intense pain after surgery and did not return to their preoperative levels of activity. Women reported greater pain levels throughout the entire study period but experienced fewer complications, were discharged earlier, and were just as active as men. These gender differences suggest greater potential benefits for aggressive pain therapy in women and the importance of controlling for gender in future studies of perioperative pain.

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