Original Investigation

Effect of Opioids vs NSAIDs and Larger vs Smaller Chest Tube Size on Pain Control and Pleurodesis Efficacy Among Patients With Malignant Pleural Effusion

The TIME1 Randomized Clinical Trial

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IMPORTANCE For treatment of malignant pleural effusion, nonsteroidal anti-inflammatory drugs (NSAIDs) are avoided because they may reduce pleurodesis efficacy. Smaller chest tubes may be less painful than larger tubes, but efficacy in pleurodesis has not been proven.

OBJECTIVE To assess the effect of chest tube size and analgesia (NSAIDs vs opiates) on pain and clinical efficacy related to pleurodesis in patients with malignant pleural effusion.

DESIGN, SETTING, AND PARTICIPANTS A 2×2 factorial phase 3 randomized clinical trial among 320 patients requiring pleurodesis in 16 UK hospitals from 2007 to 2013.

INTERVENTIONS Patients undergoing thoracoscopy (n = 206; clinical decision if biopsy was required) received a 24F chest tube and were randomized to receive opiates (n = 103) vs NSAIDs (n = 103), and those not undergoing thoracoscopy (n = 114) were randomized to 1 of 4 groups (24F chest tube and opioids [n = 28]; 24F chest tube and NSAIDs [n = 29]; 12F chest tube and opioids [n = 29]; or 12F chest tube and NSAIDs [n = 28]).

MAIN OUTCOMES AND MEASURES Pain while chest tube was in place (0- to 100-mm visual analog scale [VAS] 4 times/d; superiority comparison) and pleurodesis efficacy at 3 months (failure defined as need for further pleural intervention; noninferiority comparison; margin, 15%).

RESULTS Pain scores in the opiate group (n = 150) vs the NSAID group (n = 144) were not significantly different (mean VAS score, 23.8 mm vs 22.1 mm; adjusted difference, −1.5 mm; 95% CI, −5.0 to 2.0 mm; $P = .40$), but the NSAID group required more rescue analgesia (26.3% vs 38.1%; rate ratio, 2.1; 95% CI, 1.3-3.4; $P = .003$). Pleurodesis failure occurred in 30 patients (20%) in the opiate group and 33 (23%) in the NSAID group, meeting criteria for noninferiority (difference, −3%; 1-sided 95% CI, −10% to ∞; $P = .004$ for noninferiority). Pain scores were lower among patients in the 12F chest tube group (n = 54) vs the 24F group (n = 56) (mean VAS score, 22.0 mm vs 26.8 mm; adjusted difference, −6.0 mm; 95% CI, −11.7 to −0.2 mm; $P = .04$) and 12F chest tubes vs 24F chest tubes were associated with higher pleurodesis failure (30% vs 24%), failing to meet noninferiority criteria (difference, −6%; 1-sided 95% CI, −20% to ∞; $P = .14$ for noninferiority). Complications during chest tube insertion occurred more commonly with 12F tubes (14% vs 24%; odds ratio, 1.91; $P = .20$).

CONCLUSIONS AND RELEVANCE Use of NSAIDs vs opiates resulted in no significant difference in pain scores but was associated with more rescue medication. NSAID use resulted in noninferior rates of pleurodesis efficacy at 3 months. Placement of 12F chest tubes vs 24F chest tubes was associated with a statistically significant but clinically modest reduction in pain but failed to meet noninferiority criteria for pleurodesis efficacy.

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The incidence of malignant pleural effusion is estimated to be 150 000 new cases in the United States each year.[1,2] To prevent symptoms of breathlessness and chest pain, removal of pleural fluid by thoracocentesis and subsequent pleurodesis is advocated in evidence-based national guidelines such as the 2010 British Thoracic Society guideline,[2,3] with talc being most effective in randomized trials.[3,4]

Pleurodesis and chest tube insertion are painful.[5-8] Most physicians use opiates,[8] despite nonsteroidal anti-inflammatory drugs (NSAIDs) being effective in randomized trials of other causes of acute pain,[9] with which pleurodesis pain is probably comparable. Avoidance of NSAIDs in pleurodesis relates to concerns that these drugs may impair long-term fluid control by suppressing acute inflammation caused by pleurodesis agents. An evidence synthesis addressing this question[10] identified only 3 reports, all of which were animal models of pleurodesis. There are no prospective studies of NSAIDs in pleurodesis in humans, with only supportive data available from retrospective analysis of pneumothorax pleurodesis.[11]

The optimal chest tube size for pleurodesis has not been identified. The British Thoracic Society guideline[3] advocates use of smaller tubes and cites an overall success rate for talc pleurodesis of 60% to 90%, with 7 of 15 studies cited using large (20-28 French [F]) tubes. Evidence suggesting that smaller tubes (<16F) are successful in pleurodesis comes from case series[3] and from 3 comparative studies,[12-14] of which only 1 was randomized,[13] and it was not designed to address pleurodesis noninferiority. In addition, smaller tubes may be less safe, with 1 observational study reporting a higher complication rate.[15]

This pragmatic trial was designed to assess (1) the effect of NSAIDs compared with opiates in treatment of pleurodesis pain (superiority) and pleurodesis efficacy (noninferiority), and (2) the effect of small (12F) chest tubes compared with larger (24F) chest tubes on pain (superiority) and pleurodesis success (noninferiority) in a 2×2 factorial, randomized controlled design.

Methods

Study Design

This was a multicenter 2×2 factorial randomized clinical trial with superiority and noninferiority primary end points. The study recruited patients across 16 centers (14 in the United Kingdom, 1 in the United States, and 1 in Canada) from March 2007 to October 2013 (date of last follow-up).

Ethical and regulatory approval for the study was obtained before recruitment commenced, with approval from the local and regional institutional review boards (the Oxfordshire Research Ethics Committee and the Medicines and Healthcare Products Regulatory Agency).

Patients Enrolled

Adults aged 18 years or older were eligible provided they had a diagnosis of a symptomatic malignant pleural effusion that was clinically determined to require pleurodesis. Malignant pleural effusions were defined by meeting any 1 of the following: (1) histocytologically proven pleural malignancy; (2) typical features of pleural malignancy visualized during thoracoscopy; or (3) pleural effusion in the context of histologically proven cancer elsewhere.

Patients were ineligible if they had primary lymphoma or small cell lung carcinoma (due to likely chemosensitivity and therefore no need for pleurodesis); were pregnant or lactating; had a history of gastrointestinal bleeding or of untreated peptic ulceration; had known sensitivity to NSAIDs or opiates, hypercapnic respiratory failure, current intravenous drug misuse, severe renal or liver disease, known bleeding diathesis, or current warfarin therapy; or were expected to survive less than 1 month.

Allocation to Trial Groups

After written informed consent had been obtained, patients were randomized to trial group by minimization[16] with a random component using a central telephone service (United Kingdom Medical Research Council Clinical Trials Unit at University College London). Minimization criteria were histological tissue type (mesothelioma vs nonmesothelioma vs unknown), procedure performed (thoracoscopy vs nonthoracoscopy), and center of recruitment.

The decision to conduct a thoracoscopy was clinical and based on the need for a diagnostic and therapeutic procedure in a single sitting. Patients undergoing thoracoscopy (which requires a 24F tube postprocedure) were randomized to either NSAID or opiate analgesic treatment and were not included in the primary analysis of chest tube size outcomes. Patients not undergoing thoracoscopy were randomized to opiate or NSAID analgesic treatment and to a 24F or 12F chest tube. All patients were aware of treatment allocations, but outcome assessors were blinded to the primary outcome of average pain score and to pleurodesis failure.

All patients received regular background analgesia (acetaminophen, 1 g 4 times daily) from the time of randomization to chest tube withdrawal. Patients allocated to NSAID analgesia were treated with ibuprofen, 800 mg orally 3 times daily to a maximum of 2.4 g per 24 hours, and those allocated to opiate analgesia were treated with oral morphine at a dosage of 10 mg 4 times daily, escalating to 20 mg 4 times daily (if needed) to a maximum of 80 mg per 24 hours for the duration that the tube was in situ. If pain continued to an intolerable degree as judged by the patient despite maximum trial medication, breakthrough analgesia (intravenous morphine) was permitted in both groups. Pleurodesis was performed according to written standard operating procedures (eAppendix 9 in Supplement 1) and was performed using 4 g of sterile high-grade talc. Patients undergoing talc slurry–based pleurodesis received intrapleural anesthetic as per current United Kingdom guidelines.[3]

Trial Outcomes

Primary End Point

The 2 co-primary outcomes were a superiority comparison of pain scores and a noninferiority comparison of the occurrence of pleurodesis failure.

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Pain | The primary outcome for pain was mean pain score while the chest tube was in situ (up to 5 days), measured using a participant-completed 100-mm visual analog scale (VAS)[9] 4 times per day (at 8 AM, 12 PM, 4 PM, and 8 PM), with 0 mm indicating no pain and 100 mm indicating worst pain ever experienced. The published minimum clinically significant threshold for a 100-mm VAS pain score is 13 mm (95% CI, 10-16 mm).[17] A mean pain score was calculated using all VAS measurements from randomization until tube removal. Patients were permitted rescue medication as needed and completed an extra VAS assessment prior to taking any rescue medication; this was accounted for in the analysis by assuming that the "rescue" VAS measurement would have continued until the next scheduled VAS assessment. Visual analog scale scores were measured by 2 independent observers blinded to treatment group, with a protocol for resolving discrepant scores.

Pleurodesis Failure at 3 Months | Patients were classified as having pleurodesis failure if they required a further pleural intervention for relief of breathlessness on the same side as the pleurodesis in the 3 months after randomization. To reduce bias, the trial protocol allowed those with symptoms and a chest radiograph demonstrating 50% or more of the hemithorax occupied by fluid to have a further pleural intervention. Patients with symptoms and less than 50% of hemithorax occupied by fluid were referred for further pleural intervention only if the attending clinician discussed the case with a second clinician blinded to treatment group and consensus was reached regarding further treatment.

Secondary End Points

Secondary outcomes included change in pain over time; time to pleurodesis failure 6 months after randomization; pain scores at 4 and 12 weeks after randomization; volume of pleural fluid drained while the tube was in situ; number of times rescue medication was taken during the hospital stay; all-cause mortality up to 12 months; proportion of complications occurring during insertion of the chest tube; safety outcomes (including change from baseline to day 2 in hemoglobin, renal measures, and liver function); and frequency of serious and nonserious adverse events.

Statistical Analysis

Power Calculations

Sample size calculations were performed for both primary outcomes, and the one providing the larger sample size was used as the basis for the study. The larger sample size calculation related to the noninferiority comparison of the pleurodesis failure outcome.

Based on an acute pain trial comparing opiates with high-dose NSAIDs using similar methods,[18] which demonstrated an effect size of 7.2 (SD, 6.1), a total of 36 patients were required to demonstrate superiority in a factorial design (90% power; $\alpha = .05$; 10% not assessable).

For the noninferiority comparison of pleurodesis failure, talc pleurodesis was estimated to have a 20% failure at 3 months on the basis of previous randomized data on talc pleurodesis in malignant pleural effusion (summarized in evidence-based guidelines[3]). The acceptable margin of noninferiority of pleurodesis failure was based on clinical opinion and set at −15% based on a survey of 10 UK respiratory physicians who regularly provide care for patients with malignant pleural effusion. Using this margin with 90% power and 1-sided 5% significance and assuming 10% of patients would not be assessable, 320 patients were required to be randomized. Full details of statistical methods and other treatments are presented in Supplement 2 and Supplement 3.

Data Analysis

A complete statistical analysis plan was written and approved prior to database lock (Supplement 3). All analyses were preplanned per the trial protocol (Supplement 2).

Mean pain scores (superiority comparison) were analyzed by intention to treat (ITT), including all randomized patients with at least 1 recorded postrandomization VAS score and using multiple imputation. Treatment groups were compared for noninferiority of pleurodesis failure in both the ITT and per-protocol populations (preplanned). The ITT analysis included all randomized patients for whom a pleurodesis failure outcome was available and the per-protocol analysis included all randomized patients who had a chest tube inserted and received talc. Patients who died but did not require further drainage were not classified as having failures; deaths were accounted for in an analysis of competing risk against pleurodesis failure (see Supplement 3 for full definitions). Noninferiority was assessed using the lower bound only of the 1-sided 95% Wald confidence interval. All superiority analyses were 2-sided at the 5% level.

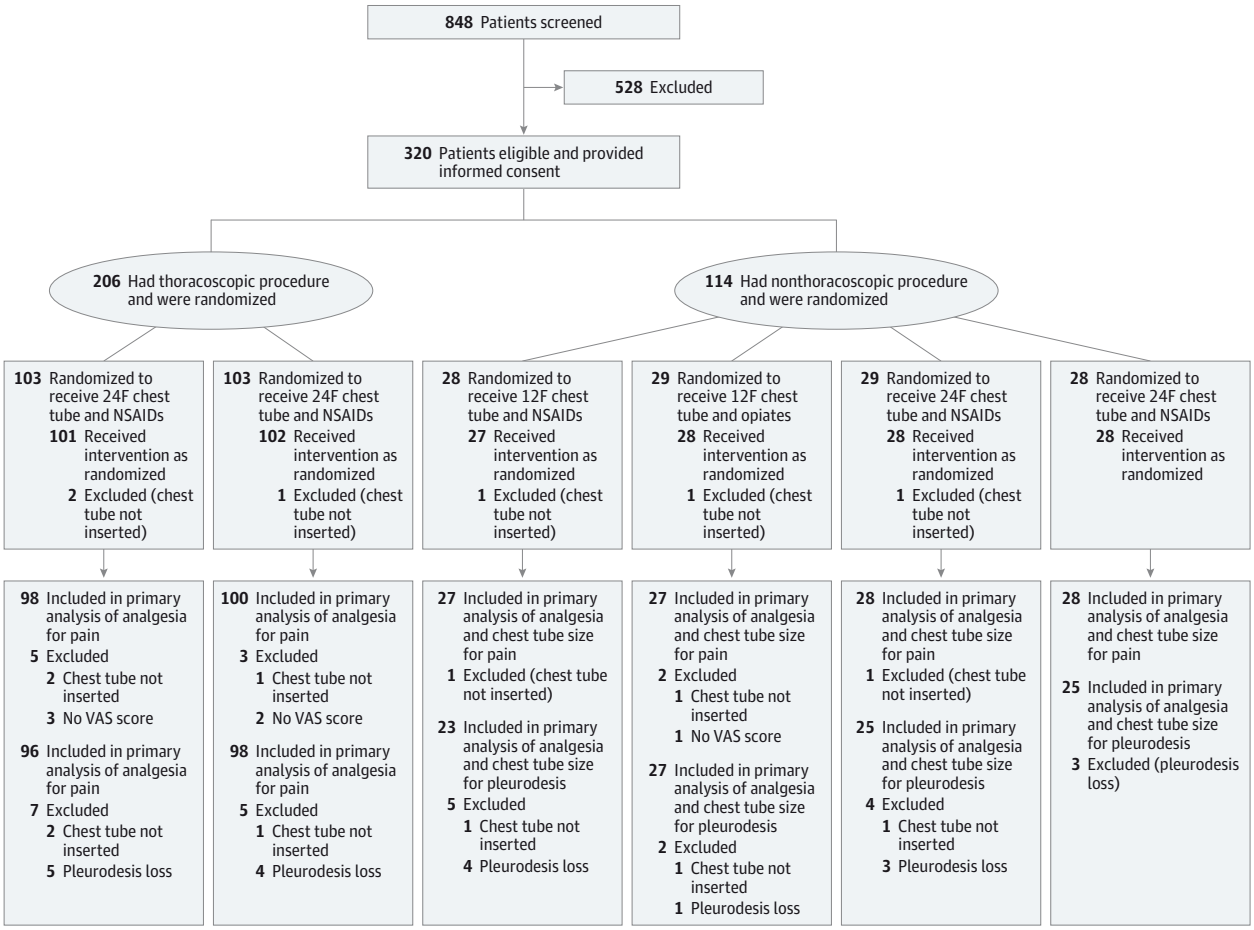
Because only patients not undergoing thoracoscopy were randomized to 24F vs 12F chest tubes, only nonthoracoscopy patients were included in the primary comparison of tube size for each outcome. A secondary comparison was made of 24F vs 12F chest tubes including all thoracoscopy and nonthoracoscopy patients. The groups receiving opiates and 24F chest tubes were considered the controls for all analyses.

An initial interaction test was conducted between drain size and analgesia for both primary outcomes. Multiple imputation was used to account for missing data for both outcomes. The average pain score was analyzed using a mixed-effects linear regression model with adjustment for minimization variables (histological tissue type, thoracoscopic procedure, and center). The absolute difference in the proportion of patients who had pleurodesis failure was calculated using a generalized linear model with a binomial family and identity link. Because of potential overstratification, minimization variables were not adjusted for.[19] Sensitivity analyses of the primary outcome were performed to test the robustness of the results, not accounting for rescue medication (pain), logistic regression and competing risks (pleurodesis failure), and with respect to missing data under a number of data "missing not at random" assumptions (Supplement 3). A secondary analysis was conducted suitable to a 4-group trial (Supplement 3).

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Figure 1. Flow of Patients Through the TIME1 Trial



NSAIDs indicates nonsteroidal anti-inflammatory drugs. Patients were simultaneously randomized to chest tube size and analgesia regimen in the nonthoracoscopic group. Reasons for screening failure were not recorded but included ineligibility and patient refusal. No VAS score refers to patients who did not complete a single visual analog scale assessment and pleurodesis loss refers to patients in whom data on pleurodesis efficacy was not available at follow-up. A total of 6 patients did not have chest tubes inserted.

Linear mixed-effects models with a random effect for center were used to assess continuous variables, and logistic regression was used for binary outcomes where appropriate. The number of times rescue medication was taken during a hospital stay was analyzed using negative binomial regression. Time to pleurodesis failure during the first 6 months after randomization was analyzed using competing risks. All analyses were conducted using Stata software, version 12.1 (Stata Corp).

Results

Patients

The trial flow diagram is presented in **Figure 1**. A total of 320 patients were recruited to the trial, of whom 201 (62.8%) were men; with a mean age of 71.8 years; and of whom 122 (38%) had effusion from metastatic cancer including lung; 9 (2.8%) had mesothelioma and 189 (59%) had malignancy identified at thoracoscopy, with histology taken at the time of thoracoscopy. A total of 160 patients were randomized to receive opiates and 160 to receive NSAIDs. Of 114 patients undergoing a nonthoracoscopic procedure, 57 were randomized to 12F and 57 to 24F chest tubes. Interaction tests were nonsignificant (P = .49 for pain score; P = .31 for pleurodesis failure), permitting factorial analysis for all outcomes. Baseline demographic and clinical characteristics of patients were similar in all treatment groups (**Table 1**), with the exception of an excess of men in the 24F chest tube group. The baseline pleural opacity occupied by the malignant pleural effusion on chest radiograph was similar across all groups.

Data Quality

The primary outcome measure for pain was available in 308 (96%) of 320 patients, and pleurodesis outcomes were available in 297 (93%) of 320 and 264 (83%) of 320 at 1 and 3 months following randomization, respectively (294 patients were included in the primary analysis) (Figure 1). During the first 3 months after randomization, 79 (25%) of the 320

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Table 1. Baseline Characteristics of the 320 Participants

Characteristics	Chest Tube Size		Analgesia	
	24F (n = 263)	12F (n = 57)	Opiates (n = 160)	NSAIDs (n = 160)
Demographics				
Female, No. (%)	84 (32)	35 (61)	58 (36)	61 (38)
Age, mean (SD), y	72.1 (10.0)	70.4 (11.9)	72.6 (9.9)	71.0 (10.8)
Diagnosis at baseline (minimization criteria), No. (%)				
Mesothelioma	6 (2)	3 (5)	3 (2)	6 (4)
Nonmesothelioma	74 (28)	48 (84)	58 (36)	64 (40)
Unknown at time of procedure	183 (70)	6 (11)	99 (62)	90 (56)
Thoracoscopic procedure, No. (%)				
Yes	206 (78)	0	103 (64)	103 (64)
No	57 (22)	57 (100)	57 (36)	57 (36)
Pleurodesis and pain, No. (%)				
Received analgesia in last 3 mo	111 (42)	33 (58)	67 (42)	77 (48)
Oral steroid use in last mo	24 (9)	11 (19)	18 (11)	17 (11)
Previous pleurodesis	11 (4)	7 (12)	12 (8)	6 (4)
Previous thoracocentesis	138 (52)	29 (51)	84 (53)	83 (52)
Visual analog scale score, median (IQR)				
Pain at baseline	3.5 (1-10.3)	10 (2.7-21.5)	4.0 (1.3-16)	4.0 (1.0-10.0)
Pain having cannula inserted	4.8 (2-13)	7.5 (2-19)	4.8 (2-13.6)	5 (1.8-13.5)
Baseline pleural opacity, mean (SD), % hemithorax occupied on chest radiograph[a]	43.4 (24.4)	51.6 (25.8)	44.0 (24.3)	45.9 (25.4)
Comorbidities, No. (%)				
Arthritis	42 (16)	11 (19)	30 (19)	23 (14)
Respiratory	53 (20)	12 (21)	35 (22)	30 (19)
Cardiac	101 (38)	26 (46)	55 (34)	72 (45)
Liver	11 (4)	3 (5)	6 (4)	8 (5)
Gastroesophageal	46 (17)	10 (18)	25 (16)	31 (19)
Excessive alcohol intake[b]	7 (3)	1 (2)	5 (3)	3 (2)
Immunosuppression	7 (3)	0	6 (4)	1 (1)
Renal	9 (3)	4 (7)	8 (5)	5 (3)
Diabetes	29 (11)	7 (12)	20 (13)	16 (10)
Neurological/ mental disability	13 (5)	4 (7)	8 (5)	9 (6)
Psychiatric	5 (2)	2 (4)	1 (1)	6 (4)
Other	73 (28)	21 (37)	45 (28)	49 (31)

(continued)

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Table 1. Baseline Characteristics of the 320 Participants (continued)

Characteristics	Chest Tube Size		Analgesia	
	24F (n = 263)	12F (n = 57)	Opiates (n = 160)	NSAIDs (n = 160)
Baseline laboratory measurements, mean (SD)				
Hemoglobin, g/dL	13.5 (1.8)	12.7 (1.8)	13.2 (1.7)	13.5 (2.0)
White blood cell count, /μL	8900 (3000)	9100 (2500)	9000 (3100)	8900 (2800)
Platelet count, 10^3/μL	333 (114)	340 (115)	333 (114)	336 (115)
Prothrombin time, s	13.9 (5.5)	14.9 (6.6)	13.8 (5.9)	14.5 (5.5)
aPTT, s	26.6 (8.0)	23.8 (6.9)	25.8 (8.3)	26.4 (7.5)
Albumin, g/dL	3.8 (0.6)	3.6 (0.6)	3.7 (0.6)	3.8 (0.7)
C-reactive protein, median (IQR), mg/L	26 (8-62)	28 (14-64)	28.5 (9-65)	26 (9-57)
Creatinine, mg/dL	0.97 (0.27)	0.93 (0.29)	0.98 (0.27)	0.95 (0.28)
Alanine aminotransferase, U/L	25 (15)	32 (29)	26 (19)	26 (17)
Alkaline phosphatase, median (IQR), U/L	105 (81-158)	113 (86-144)	100 (82-150)	113 (81-158)
Urea nitrogen, mg/dL	16.8 (9.2)	18.8 (8.1)	17.4 (6.7)	17.1 (11.2)
Respiratory rate, /min	18 (3)	18 (2)	18 (3)	19 (4)
Oxygen saturation, %	95 (3)	94 (3)	95 (3)	95 (3)
Blood pressure, mm Hg				
Systolic	133 (18)	129 (17)	133 (18)	132 (19)
Diastolic	78 (12)	76 (12)	77 (12)	78 (12)

Abbreviations: aPTT, activated partial thromboplastin time; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; VAS, visual analog scale.

[a] Radiological score derived from digital measurement of chest radiographs by previously established methods.[20]

[b] Excessive alcohol intake was defined as a formal clinician diagnosis of alcohol excess in the patient's medical notes or patient reported dependence on alcohol currently.

patients died. Mortality data were available for all patients at 12 months. For details on data quality, see eAppendix 1 in Supplement 1.

Primary End-Point Analysis

There was no significant difference in mean pain scores comparing NSAIDs with opiates while the chest tube was in place (mean VAS score in the NSAID group, 22.1 mm [SD, 16.9 mm] vs in the opiate group, 23.8 mm [SD, 15.8 mm]; adjusted difference in means, −1.5 mm; 95% CI, −5.0 to 2.0; P = .40) (**Table 2**). Rescue analgesia was used more frequently in the NSAID group (number of patients requiring rescue medication in the NSAID group, 61/160 [38.1%] vs in the opiate group, 42/160 [26.3%]; rate ratio, 2.1; 95% CI, 1.3-3.4; P = .003), with a low median number of doses per participant (interquartile range, 0-1).

There was significantly less pain with smaller vs larger tubes (mean VAS scores, 22.0 mm [SD, 16.6 mm] vs 26.8 mm [SD, 16.9 mm], respectively; adjusted difference in means, −6.0 mm; 95% CI, −11.7 to −0.2 mm; P = .04) (Table 2). There was no significant difference in the amount of rescue analgesia required according to tube size (rate ratio, 1.1; 95% CI, 0.38-3.18; P = .86). The difference in pain scores remained when analysis was repeated not accounting for use of rescue medication (mean VAS score for 12F tubes, 21.3 mm [SD, 15.8 mm]); for 24F tubes, 25.8 mm [SD, 16.9 mm]; adjusted difference in means, −5.6 mm; 95% CI, −11.2 to 0.02 mm; P = .05).

In the ITT analysis for pleurodesis failure at 3 months, NSAIDs met prespecified criteria for noninferiority because the lower bound of the 1-sided 95% confidence interval did not cross the 15% margin (failure rate: opiates, 30/150 (20.0%); NSAIDs, 33/144 (22.9%); difference, −3%; 95% CI, −10% to ∞). Smaller chest tubes had a higher failure rate (24F tubes, 12/50 [24.0%]; 12F tubes, 15/50 [30.0%]; difference, −6%; 95% CI, −20% to ∞) (Table 2 and **Figure 2**), failing to meet the 15% margin of noninferiority. The more stringent 97.5% confidence interval for pleurodesis failure gave similar results (Table 2). Including all patients (with and without thoracoscopy; preplanned secondary analysis) comparing tube size for pleurodesis failure, there remained an increased rate of pleurodesis failure using smaller tubes (failure rate: 24F tubes, 48/244 [19.7%]; 12F tubes, 15/50 [30.0%]; difference, −10%; 95% CI, −21% to ∞). The per-protocol analyses demonstrated similar results for pleurodesis failure (Figure 2 and eAppendix 8 in Supplement 1).

Details of how patients met the criteria for pleurodesis failure are given in eAppendix 9 in Supplement 1.

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Table 2. Primary and Major Secondary Outcomes: Factorial Comparison of Treatment Groups

Outcome Measures by Treatment Group	No. of Patients Analyzed	Outcomes	Treatment Effect (95% CI)	*P* Value
VAS pain score while tube in situ, to 5 d (superiority; ITT)				
Chest tube size				
24F	56	26.8 (16.9)[a]	−6.0 (−11.7 to −0.2)[a]	.04
12F	54	22.0 (16.6)[a]		
Analgesia				
Opiates	155	23.8 (15.8)[a]	−1.5 (−5.0 to 2.0)[a]	.40
NSAIDs	153	22.1 (16.9)[a]		
Pleurodesis failure at 3 mo (noninferiority; ITT)[b]				
Chest tube size				
24F	50	12 (24)[c]	−6 (−20 to ∞)[c,d,e]	.14[f]
12F	50	15 (30)[c]		
Analgesia				
Opiates	150	30 (20)[c]	−3 (−10 to ∞)[c,g,h]	.004[f]
NSAIDs	144	33 (23)[c]		
Secondary comparison of primary outcomes (all chest tubes, thoracoscopic and nonthoracoscopic; ITT)				
VAS pain score while tube in situ, to 5 days (superiority)				
Chest tube size				
24F	254	23.2 (16.3)[a]	−5.6 (−11.4 to 0.2)[a]	.06
12F	54	22.0 (16.6)[a]		
Pleurodesis failure at 3 mo (noninferiority; ITT)				
Chest tube size				
24F	244	48 (20)[c]	−10 (−21 to ∞)[c,d,i]	.24[f]
12F	50	15 (30)[c]		

Abbreviations: ITT, intention to treat; NSAIDs, nonsteroidal anti-inflammatory drugs; VAS, visual analog scale.

[a] Pain outcomes reported as mean (SD) score in millimeters on the VAS pain scale; treatment effect measured as mean difference in pain scores.

[b] Patients were classified as having pleurodesis failure if they required a further pleural intervention for relief of breathlessness on the same side as the pleurodesis in the 3 months after randomization.

[c] Pleurodesis failure outcomes reported as No. (%) of participants; treatment effect measured as percentage risk difference.

[d] Fails to meet noninferiority margin, preset at −15%.

[e] One-sided 97.5% CI is −23%; fails to meet the noninferiority margin.

[f] *P* value for noninferiority (1-sided test). Pain primary outcome analysis was adjusted for baseline pain score and the minimization variables.

[g] Meets noninferiority criteria.

[h] One-sided 97.5% CI is −12% to ∞; meets the noninferiority criteria.

[i] One-sided 97.5% CI is −24%; fails to meet the noninferiority margin.

Subgroup Analyses

There was no evidence of a differential treatment effect in any subgroups analyzed for pain or pleurodesis failure in either analgesic regimen or tube size comparisons (*P* > .10 for all interaction tests; data presented in eAppendix 2 in Supplement 1).

Secondary End-Point Results

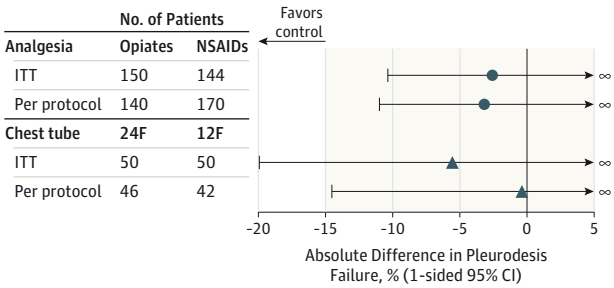
Change in Pain Over Time

Figure 3 shows changes in pain scores over time following randomization by treatment group. Over time, there was a nonsignificant reduction in pain comparing NSAIDs with opiates and a reduction in pain using 12F chest tubes compared with 24F chest tubes.

Time From Randomization to Pleurodesis Failure

Patients treated with opiates had a shorter time to pleurodesis failure compared with those treated with NSAIDs, but this did not reach statistical significance (time to pleurodesis failure: opiates, 48.9 days [SD, 46.3 days]; NSAIDs, 73.0 days [SD, 66.5 days]; hazard ratio, 1.1; 95% CI, 0.7-1.8; *P* = .69). Patients treated with a 12F chest tube had a shorter time to pleurodesis failure vs those treated with a 24F chest tube, but this also did not reach statistical significance (time to pleurodesis failure: 12F tubes, 31.6 days [SD, 20.3 days], 24F tubes, 61.3 days [SD, 57.8 days]; hazard ratio, 1.2; 95% CI, 0.6-2.5; *P* = .64). Kaplan-Meier data on time to pleurodesis failure censored for death are presented in **Figure 4**.

Figure 2. Noninferiority Comparison for Pleurodesis Failure by Treatment Comparisons (Analgesia and Tube Size) Using Intention-to-Treat (ITT) and Per-Protocol Analysis



The prespecified noninferiority margin was set at −15% for pleurodesis failure and only the lower bound of the interval was used to assess noninferiority. The shaded area represents the zone of noninferiority. The control group for analgesia is opiates and the control group for chest tube size is 24F.

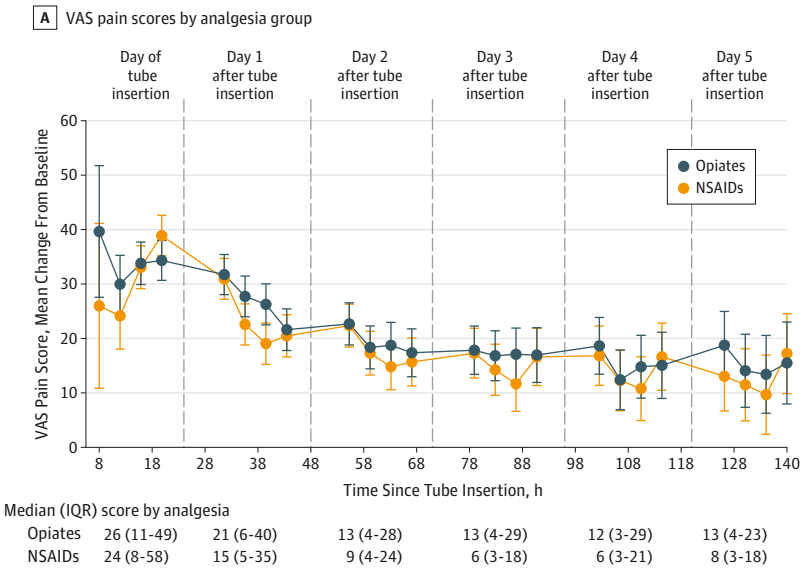
Pain Scores at 1 and 3 Months After Randomization

Pain scores at 1 month were not significantly different by analgesia and chest tube size groups (difference, −1.0 mm;

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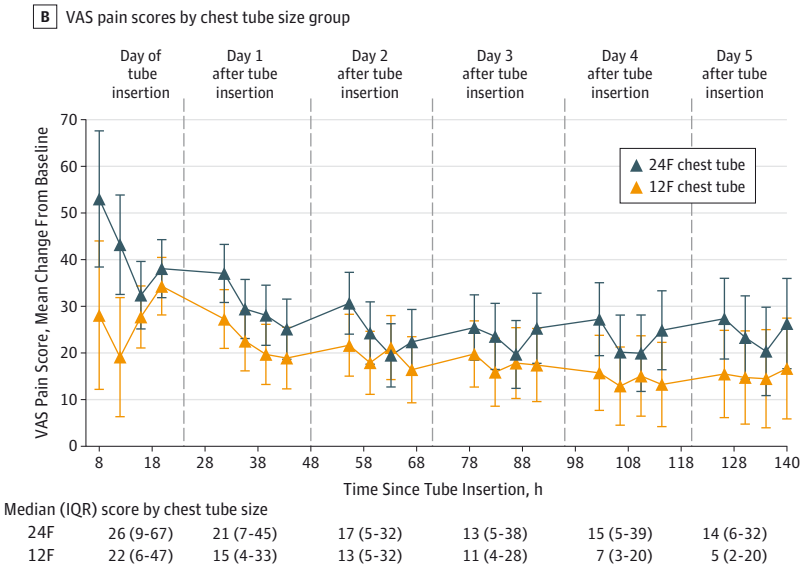
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Figure 3. Pain Trends Over Time After Chest Tube Insertion by Randomized Group



Median (IQR) score by analgesia

	Day of tube insertion	Day 1 after tube insertion	Day 2 after tube insertion	Day 3 after tube insertion	Day 4 after tube insertion	Day 5 after tube insertion
Opiates	26 (11-49)	21 (6-40)	13 (4-28)	13 (4-29)	12 (3-29)	13 (4-23)
NSAIDs	24 (8-58)	15 (5-35)	9 (4-24)	6 (3-18)	6 (3-21)	8 (3-18)



Median (IQR) score by chest tube size

	Day of tube insertion	Day 1 after tube insertion	Day 2 after tube insertion	Day 3 after tube insertion	Day 4 after tube insertion	Day 5 after tube insertion
24F	26 (9-67)	21 (7-45)	17 (5-32)	13 (5-38)	15 (5-39)	14 (6-32)
12F	22 (6-47)	15 (4-33)	13 (5-32)	11 (4-28)	7 (3-20)	5 (2-20)

Mean scores (error bars indicate SDs) are shown for each time point at which the visual analog scale (VAS) for pain was administered. Panel A compares pain scores between the control group (opiates) and patients receiving nonsteroidal anti-inflammatory drugs (NSAIDs); panel B compares pain scores between the control group (24F chest tubes) and patients receiving 12F chest tubes. Median numbers of patients contributing to the analysis were, for opiates, 89 (range, 8-148); NSAIDs, 84 (range, 5-149); 12F chest tubes, 40 (range, 5-52); and 24F chest tubes, 46 (range, 6-56). For details on the number of patients who contributed at each time point, see eAppendix 7 in Supplement 1. IQR indicates interquartile range.

95% CI, −6.4 to 4.4 mm; P = .72 for analgesia groups and difference, 7.7 mm; 95% CI, −3.3 to 18.6 mm; P = .17 for chest tube groups). Results were similar for both analgesia and chest tube size groups at 3 months (**Table 3**).

Volume of Pleural Fluid Drained and 3-Month Radiological Outcomes

Neither the volume of pleural fluid drained nor the area of chest radiographic opacity at 1 and 3 months after randomization differed significantly between tube size or analgesia treatment groups (Table 3).

All-Cause Mortality to 12 Months

Mortality rates were not significantly different between the analgesia groups (NSAIDs, 98/160 [61.3%]; opiates, 86/160 [53.8%]; adjusted odds ratio, 1.5; 95% CI, 0.9-2.3; P = .11) or between the chest tube size groups (12F tubes, 40/57 [70.1%]; 24F tubes, 43/57 [75.4%]; adjusted odds ratio, 1.4; 95% CI, 0.6-3.3; P = .48).

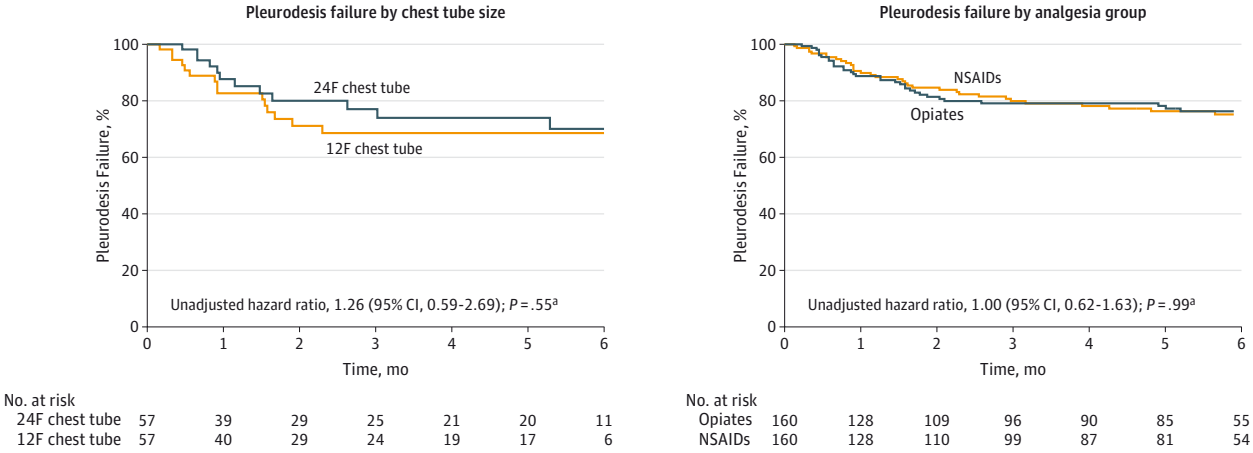
Adverse Events

There was no difference in serious or nonserious adverse events between the chest tube size and analgesia groups (**Table 4**). There was a nonsignificant excess of complications during tube insertion in the 12F tube group (24%) compared with the 24F tube group (14%; adjusted odds ratio, 1.9; 95% CI, 0.7-5.1; P = .20). Moderate or severe adverse events occurred in 18 patients in both the 12F and 24F tube groups and in 28 patients in both the NSAID and opiate groups (eAppendix 6 in Supplement 1). Safety blood measurements comparing base-

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Figure 4. Time to Pleurodesis Failure Between Randomization and 6 Months by Tube Size and Analgesia Strategy, Censored for Loss to Follow-up and Death



NSAIDs indicates nonsteroidal anti-inflammatory drugs.

[a] By Cox regression analysis.

line to day 2 after randomization were not significantly different between the treatment groups, with the exception of change in blood creatinine levels, which were statistically significantly elevated in the NSAID group but by a clinically insignificant margin (9 µmol/L adjusted difference in means; **Table 5**). There were no differences in the time the tube was in situ or the time spent in the hospital between the groups (eAppendix 5 in Supplement 1).

Adherence to Trial Interventions

The number of patients in the trial with a successful chest tube insertion was high and did not differ among treatment groups (12F tubes, 55/57 [96%]; 24F tubes, 56/57 [98%]; opiates, 158/160 [99%]; NSAIDs, 156/160 [98%]). The proportion of patients with a successful chest tube insertion and who received talc did not differ by analgesic regimen (opiates, 146/158 [92.4%]; NSAIDs, 147/156 [94.2%]) but did differ by tube size (12F tubes, 44/55 [80%]; 24F tubes, 52/56 [92.9%]). Smaller tubes were dislodged (before a clinical decision to remove) more frequently than larger tubes (12F tubes, 24/57 [42%]; 24F tubes, 74/263 [28%]).

Discussion

This trial is the largest study to our knowledge to specifically address analgesia and tube size for malignant pleural effusion pleurodesis in terms of pain experienced and pleurodesis success. The results challenge a number of assumptions about the optimal chest tube size and analgesic strategy for malignant pleural effusion pleurodesis and, by implication, current evidence-based guidelines such as the British Thoracic Society guideline, undertaken using SIGN methods.[3]

This study demonstrated that NSAIDs are not superior to opiates in the management of pain after tube insertion and pleurodesis. However, given in high doses for a short period, NSAIDs given after talc pleurodesis were safe, effective, and not inferior in terms of pleurodesis efficacy. Although NSAID use was associated with increased use of rescue medication compared with an opiate-based strategy in 12% of patients requiring a small number of doses, the resultant pain experienced was not significantly different between opiate-treated and NSAID-treated patients. The increased requirement for rescue analgesia in the NSAID group may be a result of these drugs providing less pain relief than opiates. However, the finding of the same mean pain scores in the opiate and NSAID groups, whether rescue analgesia was accounted for or not, may reflect the unblinded nature of the trial, with the potential for NSAID-treated patients to have had a greater perception of the need for rescue analgesia. These data suggest that NSAIDs can be used in patients undergoing pleurodesis if required. Also, in this study, despite the mean age of 71 years among participants, short-term use of high-dose NSAIDs was not associated with significant renal impairment or gastrointestinal adverse effects.

This trial also demonstrates that smaller (12F) chest tubes are associated with less pain than larger (24F) tubes. Although this difference was statistically significant and consistent (whether rescue analgesia was accounted for or not), the absolute difference in pain scores between smaller and larger tubes on average was small (6 mm) and was below the published minimum clinically significant threshold for a 100-mm VAS pain score (13 mm; 95% CI, 10-16 mm).[17] Thus, there is relatively little clinical benefit in terms of less pain from use of smaller chest tubes for malignant pleural effusion pleurodesis.

However, the results of this trial also demonstrate that smaller chest tubes may be inferior to larger chest tubes in terms of pleurodesis success, given a 15% margin of noninferiority. Although many previous case series and small

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Table 3. Secondary Outcomes[a]

Outcome Measures by Treatment Group	No. of Patients Analyzed	Outcomes	Treatment Effect, Mean Difference (95% CI)	*P* Value
Volume of pleural fluid drained while tube in situ (ITT)				
Chest tube size				
24F	55	3086 (1822)[b]	−241 (−878 to 397)	.46
12F	55	2879 (2074)[b]		
Analgesia				
Opiates	155	2733 (1726)[b]	190 (−190 to 571)	.33
NSAIDs	154	2891 (1931)[b]		
Chest radiograph opacity at 1 mo (ITT)				
Chest tube size				
24F	34	25.2 (17.9)[c]	−3.5 (−3.7 to 10.8)	.34
12F	30	28.2 (18.2)[c]		
Analgesia				
Opiates	100	26.0 (18.5)[c]	−1.2 (−5.9 to 3.5)	.62
NSAIDs	99	25.3 (18.1)[c]		
Chest radiograph opacity at 3 mo (ITT)				
Chest tube size				
24F	20	18.9 (17.0)[c]	6.2 (−2.9 to 15.4)	.18
12F	23	27.7 (23.9)[c]		
Analgesia				
Opiates	69	25.1 (20.9)[c]	−2.0 (−7.8 to 3.8)	.50
NSAIDs	65	21.9 (19.1)[c]		
VAS pain score at 1 mo (ITT)				
Chest tube size				
24F	32	3 (13-26)[d]	7.7 (−3.3 to 18.6)	.17
12F	32	6 (1-48)[d]		
Analgesia				
Opiates	117	7 (2-19)[d]	−1.0 (−6.4 to 4.4)	.72
NSAIDs	100	4 (2-18)[d]		
VAS pain score at 3 mo (ITT)				
Chest tube size				
24F	25	5 (2-20)[d]	−7.7 (−18.4 to 3.0)	.16
12F	21	4 (2-20)[d]		
Analgesia				
Opiates	96	6 (1-23)[d]	−1.3 (−6.2 to 3.6)	.60
NSAIDs	88	5 (1-18)[d]		

Abbreviations: ITT, intention to treat; NSAIDs, nonsteroidal anti-inflammatory drugs; VAS, visual analog scale.

[a] Pain outcome analysis was adjusted for baseline pain score and the minimization variables. Pleural fluid and x-ray outcomes were adjusted for baseline x-ray opacification and minimization variables.

[b] Outcomes for pleural fluid volume reported as mean (SD) volume in milliliters.

[c] Outcomes for chest radiograph opacity reported as mean (SD) percentage of hemithorax occupied.

[d] Pain outcomes reported as median (interquartile range) score in millimeters on the VAS pain scale.

comparative studies have suggested that smaller chest tubes are "as good as" larger ones for malignant effusion pleurodesis,[2,3] this is the first randomized study to our knowledge to specifically address this question using a noninferiority design. As a consequence of including thoracoscopy cases, for which only large-bore tubes are used, numbers of patients in the direct comparison of small-bore and large-bore tubes was limited; however, in this comparison, small tubes failed to meet noninferiority criteria, although this study was underpowered for this outcome because of the high number of patients undergoing thoracoscopies recruited to the study. On the basis of these data, performing a pleurodesis using a small tube according to current national guidelines[2,3] may reduce the likelihood of pleurodesis success compared with larger-bore tubes. Furthermore, larger direct comparison studies of small- and large-bore chest tubes are now required, but the current study poses important questions as to whether small-bore chest tubes are truly as efficacious as large-bore tubes for malignant pleural effusion pleurodesis.

The potential reasons for the 6% observed decrease in successful pleurodesis may include incomplete drainage; an increased unintentional displacement rate, thereby preventing adequate drainage after pleurodesis; and an increase in the frequency of patients unable to receive talc intrapleurally because of blockage of smaller tubes. Our data demonstrate that patients treated with smaller tubes were able to receive talc less often (80% vs 93%) and had a higher frequency of unintentional displacement of the chest tube (42% vs 28%). This is further supported by the slightly dif-

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Table 4. Serious, Nonserious, and Tube Insertion–Related Adverse Events

Events by Treatment Group	No. (%) of Patients With Event	Treatment Effect, Odds Ratio (95% CI)	*P* Value
Serious adverse events			
Chest tube size (n=57)			
24F	6 (11)	0.80 (0.2-2.9)	.73
12F	5 (9)		
Analgesia (n=160)			
Opiates	13 (8)	1.1 (0.5-2.4)	.84
NSAIDs	14 (9)		
Nonserious adverse events			
Chest tube size (n=57)			
24F	32 (56)	1.1 (0.5-2.3)	.84
12F	33 (58)		
Analgesia (n=160)			
Opiates	72 (45)	0.7 (0.4-1.1)	.11
NSAIDs	60 (38)		
Complications during tube insertion[a]			
Chest tube size			
24F (n=56)	8 (14)	1.9 (0.7-5.1)	.20
12F (n=55)	13 (24)		
Analgesia			
Opiates (n=158)	20 (13)	1.2 (0.6-2.4)	.56
NSAIDs (n=156)	22 (14)		

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

[a] Tube insertion complication overall frequencies were bleeding, n=5; repeat insertion required, n=11; pleural space not entered, n=2; syncope, n=5; and other, n=23. When more than 1 complication occurred in a single patient, it was recorded as a single complication.

Table 5. Safety Blood Measurement Outcomes

Outcomes by Treatment Group	Change, Mean (SD)	Treatment Effect, Mean Difference (95% CI)	*P* Value
Change in hemoglobin, day 0 to day 2, g/dL			
Chest tube size			
24F (n=34)	−0.3 (0.6)	0.1 (−0.3 to 0.5)	.52
12F (n=25)	−0.4 (0.7)		
Analgesia			
Opiates (n=106)	−0.4 (1.0)	−0.1 (−0.4 to 0.2)	.41
NSAIDs (n=103)	−0.7 (1.2)		
Change in creatinine, day 0 to day 2, mg/dL			
Chest tube size			
24F (n=34)	−0.08 (0.24)	4 (−7 to 15)	.45
12F (n=25)	0 (0.10)		
Analgesia			
Opiates (n=103)	−2 (12)	9 (4 to 15)	.001
NSAIDs (n = 104)	7 (26)		
Change in urea nitrogen, day 0 to hospital discharge, mg/dL			
Chest tube size			
24F (n=32)	2.8 (12.9)	−3.6 (−8.4 to 1.1)	.12
12F (n=22)	0.3 (5.9)		
Analgesia			
Opiates (n=70)	0.6 (8.4)	1.1 (−1.7 to 3.6)	.47
NSAIDs (n=54)	2.5 (10.6)		

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

ferent results from per-protocol and ITT analyses (Figure 2), which imply that if talc is successfully administered via a smaller tube, it results in reasonable pleurodesis success. Should it be the case, this represents a significant disadvantage of smaller-tube treatment. The reasons for these clinically important difference are not clear; it is unlikely, how-

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ever, to be related to insertion technique and experience with chest tubes, as all centers participating in this study have established pleural intervention practices, and protocolized management (including the use of intrapleural flushes with smaller tubes) was undertaken.

Although some of the observed difference in pleurodesis efficacy may have been due to the use of thoracoscopic talc poudrage (in which talc is administered after full drainage of the chest in a single procedure), patients undergoing thoracoscopic procedures were excluded from the primary data analysis of chest tube size for this reason, and therefore, the potential reduction in pleurodesis efficacy with smaller tubes appears to be real. Randomization in this study was minimized by thoracoscopic procedure, ensuring that pre hoc subgroup analysis was feasible. There was no evidence of an advantage to thoracoscopically delivered talc, although this was not a primary randomized study assessing this treatment mode, and ongoing trials should provide valuable information on this aspect of care.[21]

Larger tubes were associated with significantly more pain; whether this is related to the size of the traumatic injury required for chest tube insertion or related to insertion technique is not clear from our data. As all larger tubes were inserted using the blunt dissection technique and all smaller tubes inserted using the guide-wire technique, we were unable to address this issue. Whether using the guide-wire technique reduces pain but allows safer insertion of larger tubes requires further investigation.

There are important limitations to this study. First, this trial was not clinician- and patient-blinded, using "masked" drains and a double-dummy, double-placebo analgesic design, and this may have introduced bias in the assessment of pain. Second, as a consequence of recruiting patients undergoing thoracoscopy (in whom only a large-bore tube can be used), the number of patients in the primary comparison of chest tube size for pleurodesis efficacy was limited. Thus, it is likely that this analysis is underpowered, but it remains the largest study to directly address this question. Third, the power calculation for pain was based on a nonpleurodesis model of acute pain using similar assessment methods[18]; data on the pain caused by pleurodesis using these methods were not available during trial planning, and this limitation does not affect the validity of comparative treatment analyses for this study. Fourth, the noninferiority margin of 15% was based on a survey of clinical expert opinion rather than on empirical data, which were not available at the time of trial planning.

On the basis of this randomized trial, what should now be the recommended method of talc pleurodesis? There appears to be no advantage to NSAID-based analgesia but no reason to avoid use of these drugs for postpleurodesis pain. Thus, for patients at risk of opiate toxicity, NSAID-based analgesia is a reasonable treatment alternative with evidence of noninferior pleurodesis efficacy but modest increased use of rescue analgesia. There is now an argument for the use of large-bore chest tubes for malignant pleural effusion pleurodesis on the basis of data from this trial. Although larger tubes were associated with more pain than smaller tubes, this was not clinically significant, and it cannot now be assumed that 12F tubes are as effective as 24F tubes in providing long-term fluid control after pleurodesis, which is the treatment intent. It appears that there are no clinically significant advantages of use of smaller tubes for malignant pleural effusion pleurodesis and the potential to reduce pleurodesis success, despite their current widespread use and the recommendations in national guidelines. These data highlight the need for adequately powered studies addressing specific clinical management issues in common pleural diseases.

Conclusions

Among patients with malignant pleural effusions undergoing pleurodesis, the use of NSAIDs compared with opiates resulted in no significant difference in pain scores but was associated with more use of rescue medication while the chest tube was in place; however, NSAID use also resulted in noninferior rates of pleurodesis efficacy at 3 months. Among patients who did not undergo thoracoscopy, placement of 12F chest tubes compared with 24F chest tubes was associated with a statistically significant but clinically modest reduction in pain scores and failed to meet noninferiority criteria for pleurodesis efficacy. These results challenge current guidelines that advocate avoidance of NSAIDs and use of small chest tubes.

ARTICLE INFORMATION

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Author Contributions: Dr Rahman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Rahman, Lee, R. Davies, Nunn.
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