CHEST

The Impact of Gravity vs Suction-driven Therapeutic Thoracentesis on Pressure-related Complications

The GRAVITAS Multicenter Randomized Controlled Trial

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BACKGROUND: Thoracentesis can be accomplished by active aspiration or drainage with gravity. This trial investigated whether gravity drainage could protect against negative pressure-related complications such as chest discomfort, re-expansion pulmonary edema, or pneumothorax compared with active aspiration.

METHODS: This prospective, multicenter, single-blind, randomized controlled trial allocated patients with large free-flowing effusions estimated ≥ 500 mL 1:1 to undergo active aspiration or gravity drainage. Patients rated chest discomfort on 100-mm visual analog scales prior to, during, and following drainage. Thoracentesis was halted at complete evacuation or for persistent chest discomfort, intractable cough, or other complication. The primary outcome was overall procedural chest discomfort scored 5 min following the procedure. Secondary outcomes included measures of discomfort and breathlessness through 48 h postprocedure.

RESULTS: A total of 142 patients were randomized to undergo treatment, with 140 in the final analysis. Groups did not differ for the primary outcome (mean visual analog scale score difference, 5.3 mm; 95% CI, –2.4 to 13.0; $P = .17$). Secondary outcomes of discomfort and dyspnea did not differ between groups. Comparable volumes were drained in both groups, but the procedure duration was significantly longer in the gravity arm (mean difference, 7.4 min; 95% CI, 10.2 to 4.6; $P < .001$). There were no serious complications.

CONCLUSIONS: Thoracentesis via active aspiration and gravity drainage are both safe and result in comparable levels of procedural comfort and dyspnea improvement. Active aspiration requires less total procedural time.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT03591952; URL: www.clinicaltrials.gov.

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ABBREVIATIONS: REPE = re-expansion pulmonary edema; VAS = visual analog scale

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Thoracentesis is among the most common procedures performed in clinical medicine.[1-3] Although considered a low-risk procedure, complication rates > 5% have been reported and appear more common when large pleural fluid volumes are aspirated and perhaps when vacuum suction is used.[4,5] Multiple complications, including pneumothorax ex vacuo, re-expansion pulmonary edema (REPE), and chest discomfort, have been associated with increasingly negative pleural pressure developing as fluid is withdrawn if the lung is not fully re-expandable.[6-11] Pleural pressure lower than –20 cm H_2O has traditionally been considered excessively negative, based primarily on data obtained from early animal models.[3,8-10,12]

Despite the association between pleural pressure and complications, a recent trial of routine pleural manometry during therapeutic thoracentesis, which had been proposed as a possible safeguard against such complications, failed to show improvement in patient comfort or reduction in serious complications.[13] Another potential method to mitigate the risk of negative pressure-related complications is drainage by gravity, which may result in significantly less negative pleural pressure than aspiration by suction or vacuum. We hypothesized that gravity drainage would result in less chest discomfort, a common negative pressure-related complication of thoracentesis, compared with suction drainage in a randomized, single-blind fashion.

Patients and Methods

Study Design and Participants

This randomized controlled, single-blind trial was conducted at 10 US academic medical centers. Patients referred to interventional pulmonology for thoracentesis were screened. Eligible patients were ≥ 18 years old with symptomatic pleural effusions estimated at least 500 mL in volume, defined as such if one of the following criteria was met: effusion occupying at least one-third of the hemithorax on chest radiograph,[14] maximum anteroposterior depth of effusion at least one-third the anteroposterior dimension of the hemithorax on the axial CT image immediately superior to the dome of the hemidiaphragm,[15] or effusion spanning at least three interspaces on ultrasonography with a depth of at least 3 cm in one or more interspaces in a patient sitting upright.[16] Patients were excluded if effusions did not appear free-flowing due to septations or loculation present on pre-procedure imaging, they were unable to sit for the procedure, or they were unable to provide informed consent. All participants provided written informed consent. This study was approved by the institutional review boards at each participating center (e-Table 1).

Randomization

Patients were randomly assigned to thoracentesis with fluid drained by gravity (gravity group) or manual aspiration using a syringe (control group). The allocation sequence was generated by a computer, using permuted blocks of four and six, stratified by each institution, with a 1:1 allocation ratio. Allocations were assigned by opening a sealed opaque envelope prepared by a research assistant (L. R.) who did not participate in enrollment decisions. Envelopes were opened following placement of the thoracentesis catheter in the pleural space to prevent allocation bias on baseline measures. Patients were kept unaware of their assignment to gravity or suction as catheters were introduced into the posterior hemithorax and proceduralists remained behind the patient for the duration of the procedure.

Study Procedure

Patients were positioned in an upright seated position. Thoracic ultrasonography identified ideal catheter placement location. Overlying skin was anesthetized by local infiltration of plain 1% lidocaine prior to insertion of an 8-F over-needle-style catheter (Safe-T-Centesis [BD] or Arrow-Clarke Pleura-Seal [Teleflex]) under standard sterile precautions. In the suction arm, pleural fluid was aspirated actively by using a 60-mL syringe. In the gravity arm, the catheter was attached to a drainage bag placed approximately 100 cm below the catheter insertion site via straight tubing of the same length. If fluid did not spontaneously fill the tubing to start drainage into the bag, a syringe was used to prime the tubing with approximately 5 mL of pleural fluid.

Complete evacuation of the pleural space was the goal of all procedures. Drainage was stopped early for persistent chest discomfort consistent with excessively negative pleural pressure (pressure-like in the central anterior chest, neck, or jaw, worse with inspiration), intractable cough, worsening dyspnea, vagal reaction, or if other complications occurred.

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Reason for drainage termination, volume drained, and procedure time (catheter-in to catheter-out) were documented.

Patient-centered data were obtained by using 100-mm horizontal visual analog scales (VAS), with labels "No discomfort at all" at 0 mm and "Worst possible discomfort" at 100 mm. For queries regarding breathlessness, the word "breathlessness" replaced "discomfort." These scales are well validated for patient-reported pain and breathlessness measurements.[17-19] Patients were asked to rate their degree of overall chest discomfort and breathlessness on the day of the procedure as well as current degree of chest discomfort prior to procedure start, following placement of the thoracentesis catheter, prior to catheter removal, and immediately following catheter removal. Five minutes following catheter removal, patients indicated their overall degree of procedure-related chest discomfort from procedure start to that moment, as well as the current degree of breathlessness. At 24 h and 48 h postprocedure, patients were contacted to rate their degree of chest discomfort by providing a number from 0 to 100, with 100 indicating worst possible discomfort. The Modified Borg Scale for Dyspnea, well validated for dyspnea measurements in lung disease with a minimal clinically important difference of 1 unit,[20] was used to assess breathlessness preprocedure and 5 min, 24 h, and 48 h postprocedure.

All patients underwent postprocedure thoracic ultrasound to assess for the presence of more than scant remaining pleural fluid. They also underwent a chest radiograph to determine the degree to which lung re-expansion occurred and to assess for pneumothorax and REPE.

Outcomes

The primary outcome was patient-reported overall procedural chest discomfort assessed according to the VAS score 5 min postprocedure. This primary outcome, also used in a recent similar trial conducted by this group,[13] was chosen because it is clinically relevant, patient-centered, and chest discomfort represents the most frequent complication of thoracentesis that has been attributed to excessively negative pleural pressure.[6,7,21] Secondary outcomes were discomfort according to VAS score prior to catheter removal, immediately following catheter removal, and at 24 and 48 h; breathlessness according to the VAS and Borg scales at 5 min postprocedure and according to the Borg scale at 24 and 48 h postprocedure; volume drained; procedure duration; and frequency of complete lung re-expansion as assessed by using postprocedure thoracic ultrasound and chest radiograph. Postprocedure radiographs were also inspected for pneumothorax or REPE.

Statistical Analysis

Baseline VAS chest discomfort scores reported in the Second Therapeutic Intervention in Malignant Effusion (TIME2) trial[22] and previously reported VAS pain score minimum clinically important difference[17] were used to inform the power calculation. Using a two-sample Student t test, a sample size of 128 patients (64 in each group) was determined to have 80% power to detect a 15-mm decrease in the VAS chest discomfort score (SD, 30 mm) with gravity drainage with the probability of a type I error set at $\alpha = 0.05$.

Statistical analysis was conducted in R version 3.3.1 (R Foundation for Statistical Computing) according to a prespecified statistical analysis plan. Analysis was modified intention-to-treat, such that all patients with any procedure or outcome data were analyzed. Descriptive statistics included means, SDs, and ranges for continuous parameters, and percentages and frequencies for categorical parameters. Investigations for outliers and assumptions for statistical analysis (eg, normality and homoscedasticity) were made. Comparisons between the gravity and suction groups were made by using the Student t test for continuous variables and the χ^2 test for categorical variables. There were no prespecified subanalyses.

Two post hoc analyses were performed. Multivariable linear regression was used to assess the association between the primary outcome and drainage method with the adjustment of nonlinear effect of current chest discomfort preprocedure using a restricted cubic spline with

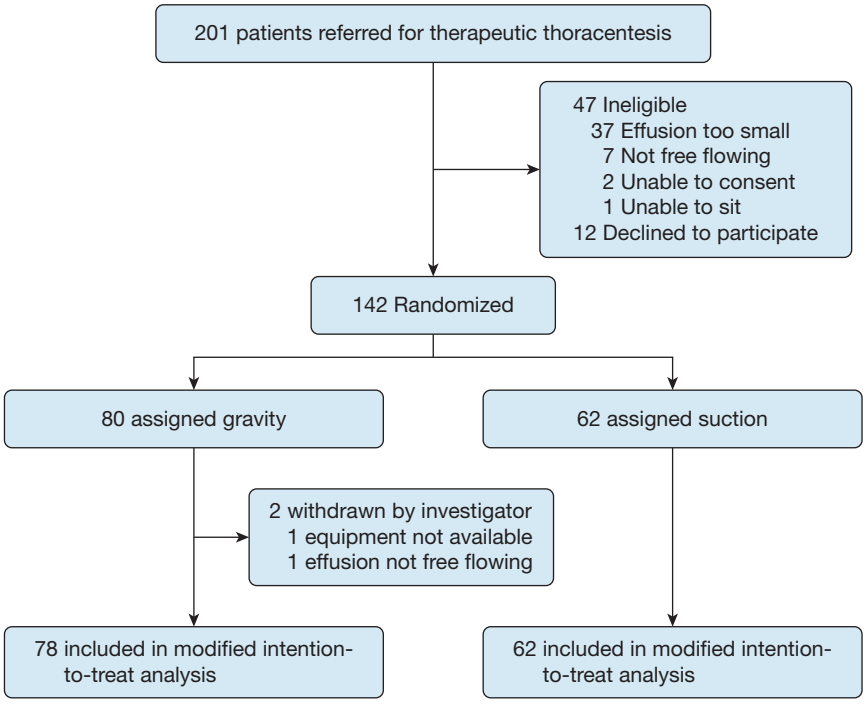

Figure 1 – *Trial profile.*

three knots. In addition, a per-protocol analysis of the primary outcome was conducted excluding suction procedures performed by any mechanism other than protocol-directed manual aspiration. A data monitoring committee was not established to oversee this trial because both methods of pleural fluid drainage studied are considered standard-of-care. The trial was registered at clinicaltrials.gov.[23]

Results

Between October 11, 2018, and April 5, 2019, a total of 201 patients were screened and 142 were randomized to undergo thoracentesis with gravity or suction drainage (Fig 1). Two subjects in the gravity group were withdrawn by investigators before any pleural fluid was removed or outcome data obtained; one was withdrawn for discovery of a non-free-flowing effusion requiring an alternative procedure and the other because equipment to perform the study procedure was unavailable. The final analysis included 62 patients who underwent gravity drainage and 78 who underwent aspiration via suction. This imbalance resulted from 10 sites enrolling simultaneously from distinct permuted block randomization schedules. Once the recruitment target was met, all sites immediately stopped enrolling; this imbalance represents a swing of eight allocations across all sites.

TABLE 1] Baseline Subject Characteristics

Characteristic	Suction (n = 62)	Gravity (n = 78)
Age, y	62.5 ± 14.0	65.1 ± 13.2
Male sex	28 (45%)	37 (47%)
Procedure setting		
Outpatient	33 (53%)	43 (55%)
ED	2 (3%)	1 (1%)
Inpatient, regular ward	27 (44%)	33 (42%)
Inpatient, ICU[a]	0	1 (1%)
Smoking status		
Current	5 (8%)	9 (11.5%)
Former	33 (53%)	42 (54%)
Never	24 (39%)	27 (35%)
Previous thoracentesis	27 (44%)	44 (56%)
With significant chest discomfort	8 (13%)	15 (19%)
Known effusion etiology	19 (31%)	17 (22%)
Malignant	15 (24%)	11 (14%)
Heart failure	2 (3%)	1 (1%)
Hepatic hydrothorax	2 (3%)	1 (1%)
Other[b]	0	4 (5%)
Comorbidities		
Malignancy	48 (77%)	51 (65%)
Heart failure	5 (8%)	10 (13%)
Chronic kidney disease	4 (6.5%)	11 (14%)
Cirrhosis	4 (6.5%)	6 (8%)

Data are presented as mean ± SD unless otherwise indicated.
[a]This patient was not mechanically ventilated.
[b]Other known effusion etiologies preprocedure: nonspecific pleuritis according to results of previous pleural biopsy (2), postcardiac surgery (1), and drug induced (1).

Patients assigned to each group were well matched on baseline characteristics (Table 1). Average chest discomfort on the day of the procedure did not differ between groups (mean difference in VAS scores, 3.9 mm; 95% CI, –5.6 to 13.5). Current chest discomfort immediately prior to procedure start differed between groups (suction VAS score, 22.9 ± 25.0 mm; gravity VAS score, 12.3 ± 18.1 mm).

The primary outcome of overall procedural chest discomfort measured by VAS 5 min postprocedure did not differ between the suction and gravity groups (mean difference in VAS scores, 5.3 mm; 95% CI, –2.4 to 13.0; $P = .17$) (Fig 2, Table 2). Likewise, there was no difference between the suction and gravity groups for any patient-reported secondary outcome, including intraprocedure or postprocedure VAS discomfort scores (Fig 3), postprocedure VAS and Borg dyspnea scores (Fig 4, Table 3), or pre-to-post procedure differences in VAS discomfort and dyspnea scores. Two post hoc analyses of the primary outcome were performed: one adjusting for current chest discomfort preprocedure and the other a per-protocol analysis excluding 11 suction procedures performed with continuous wall suction instead of protocol-dictated manual syringe aspiration. These analyses also found no difference between suction and gravity groups (e-Figs 1-3, e-Tables 2-3).

Primary and secondary outcomes were similar when the Wilcoxon rank sum test was used (e-Table 4). More than 1,500 mL was drained in 31 procedures (17 gravity, 14 suction) with no difference between groups on any outcome measures within this subset, and no complications occurred in these patients.

The volume of fluid drained in each group was equivalent (mean, 1,264 ± 724 mL suction vs 1,165 ±

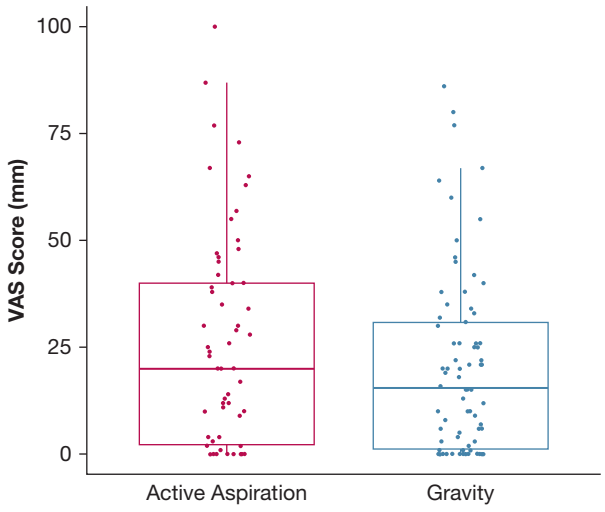

Figure 2 – *Comparison of overall procedural chest discomfort between the active aspiration and gravity groups assessed according to VAS score 5 min following removal of the catheter (primary outcome). Data are presented as medians and interquartile range.* VAS = *visual analog scale.*

543 mL gravity; mean difference, 99 mL; 95% CI, −113 to 310; $P = .89$). Procedure duration was significantly shorter in the suction group (mean duration, 10.5 ± 6.1 min vs 17.8 ± 9.7 min; mean difference, 7.4 min; 95% CI, 4.6 to 10.2; $P < .001$) (Fig 5, Table 4).

Reasons for cessation of thoracentesis and final diagnoses of all effusions are detailed in Tables 4 and 5. In both groups, drainage stopped spontaneously in approximately one-half of procedures; the other one-half were stopped early for chest discomfort, and a small minority were stopped for other reasons. Postprocedure ultrasound revealed more than scant residual pleural fluid in approximately one-half of patients in each arm, with similar reasons for drainage discontinuation between groups (e-Table 5).

No significant adverse events were observed. One pneumothorax was documented on a postprocedure chest radiograph in the suction group, with approximately 2 mm of apical pleural separation. During this procedure, a small amount of air was noted to be entrained via the thoracentesis catheter while attaching the drainage apparatus, and the pneumothorax had resolved several hours later. There were no instances of pneumothorax ex vacuo, expanding pneumothorax, REPE, or bleeding complication.

Discussion

This multicenter, randomized controlled, single-blind trial assessed two standard-of-care methods for draining pleural fluid during therapeutic thoracentesis with clinically relevant, patient-centered primary and secondary outcomes. We found no differences between active pleural fluid aspiration and gravity drainage related

TABLE 2] Preprocedure, Intraprocedure, and Postprocedure Chest Discomfort Scores

Variable	Suction (n = 62)	Gravity (n = 78)	Mean Difference[a]	95% CI	*P* Value
Preprocedure					
Average chest discomfort[b]	25.3 ± 27.0	21.4 ± 29.4	3.9	−5.6 to 13.5	.42
Current chest discomfort, pre	22.9 ± 25.0	12.3 ± 18.1	10.5	3.2 to 17.9	.005
During procedure					
Current chest discomfort, open	23.0 ± 24.1	15.1 ± 21.0	7.8	0.3 to 15.4	.04
Current chest discomfort, close	36.0 ± 28.8	32.8 ± 30.0	3.3	−6.7 to 13.2	.52
Current chest discomfort, post	33.3 ± 27.1	30.0 ± 27.7	3.3	−5.9 to 12.6	.48
After procedure					
Overall chest discomfort through 5 min post[c]	25.5 ± 25.0	20.2 ± 21.0	5.3	−2.4 to 13.0	.17
Chest discomfort through 24 h post	19.6 ± 28.8	18.7 ± 25.0	0.9	−8.4 to 10.3	.85
Chest discomfort through 48 h post	18.6 ± 25.5	17.2 ± 26.0	1.4	−7.8 to 10.6	.77
Pre-to-post change in VAS discomfort	11.0 ± 30.0	17.8 ± 31.3	−6.8	−17.4 to 3.8	.35
Change in VAS discomfort, pre-change to 5 min post- change	3.5 ± 28.9	8.0 ± 24.3	−4.5	−13.6 to 4.6	.31

Data are presented as mean ± SD visual analog scale (VAS) (0-100 mm) scores.
[a]Suction minus gravity.
[b]On the day of the procedure.
[c]Primary outcome measure.

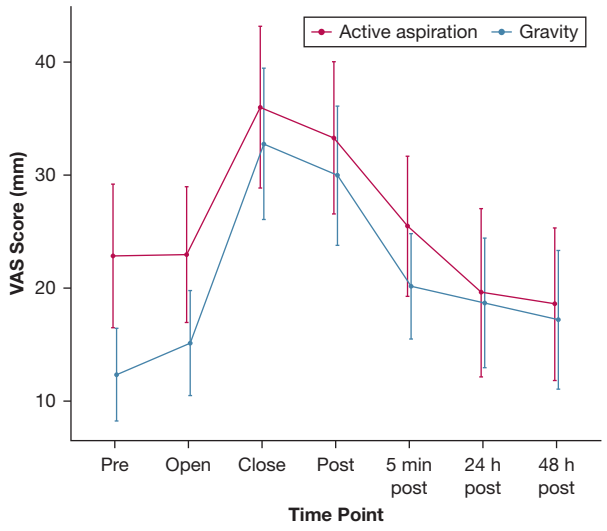

Figure 3 – *Preprocedure, intraprocedure, and postprocedure trends in VAS chest discomfort scores. Pre: immediately prior to catheter insertion. Open: immediately following catheter placement. Close: just prior to catheter removal. Post: immediately following catheter removed. 5 min Post: overall procedural chest discomfort measured 5 min following catheter removal. Data are presented as mean VAS scores and 95% CIs. See Figure 2 legend for expansion of abbreviation.*

to patient comfort, including chest discomfort measured by using the VAS or breathlessness measured by using the VAS and the Borg scale. In both groups, chest discomfort increased during the procedure then returned to preprocedure baseline approximately 24 h later (Fig 3), and breathlessness continued to improve through 48 h postprocedure (Fig 4). The only significant difference between groups was the time required to drain equivalent volumes of fluid, with gravity drainage requiring a mean additional 7.4 min. There were no significant

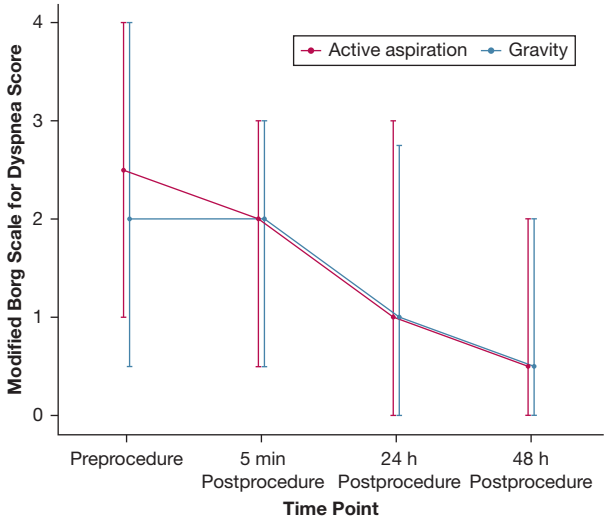

Figure 4 – *Preprocedure and postprocedure Modified Borg Scale for Dyspnea scores. Data are presented as medians and interquartile range.*

complications in either group. Both methods of pleural fluid drainage seemed safe and resulted in comparable levels of procedural comfort and improvement in dyspnea, with active aspiration requiring less overall time.

Major complications of therapeutic thoracentesis, including chest discomfort, pneumothorax ex vacuo, and REPE, have been associated with increasingly negative pleural pressures, occurring when fluid is excessively aspirated in the setting of nonexpandable lung.[3,6-10] The presence of nonexpandable lung, with a prevalence of 40% in a recent similar trial,[13] is difficult to predict prior to therapeutic thoracentesis. Recent work has focused on whether direct monitoring of pleural pressures via manometry might prevent pressure-related complications. This recent randomized trial found that routine use of a digital pleural manometer during therapeutic thoracentesis conferred no benefit.[13] The current study sought to evaluate whether changing the degree of negative pressure applied to the pleural space during therapeutic thoracentesis would improve patient comfort.

Despite the frequency with which thoracentesis is performed, and the association between pleural pressure and complications, optimal drainage methods have not been extensively studied. As a result, there is significant variation in drainage techniques, with intermittent suction via manual syringe aspiration, continuous suction via vacuum bottle or wall-based suction, and drainage to gravity all considered standard-of-care. These methods all apply negative pressure to the pleural space but to different and often variable magnitudes. Kelil et al[24] measured ex vivo pressures generated by evacuated bottle, 60-mL Luer Lock syringe, and wall suction with the regulator turned to maximal continuous suction. Maximum negative pressures measured were –963 cm H_2O, –802 cm H_2O, and –706 cm H_2O, respectively. Alraiyes et al[25] measured negative pressures during therapeutic thoracentesis using digital manometers positioned in-line between the thoracentesis catheter and drainage line; they noted maximal negative pressures of approximately –250 cm H_2O aspirating with a 60-mL syringe and –115 cm H_2O with an evacuated bottle. The gravity drainage method used in this study generated constant negative pressure of approximately –17 cm H_2O, significantly lower than all active-suction pleural fluid aspiration methods (e-Figs 4-5).

No previous studies have compared pleural fluid drainage by gravity vs active aspiration. Senitko et al[4] randomized 100 patients to undergo drainage by manual

TABLE 3] Preprocedure and Postprocedure Breathlessness Scores

Variable	Suction (n = 62)	Gravity (n = 78)	Mean Difference[a]	95% CI or χ^2	*P* Value
Preprocedure					
Average breathlessness, VAS[b]	40.8 ± 29.4	37.4 ± 30.5	3.4	−6.7 to 13.5	.51
Modified Borg Scale for Dyspnea score	3.10 ± 2.83	2.83 ± 2.66	0.26	−0.7 to 1.2	.64
After procedure					
Breathlessness, VAS, at 5 min postprocedure	21.0 ± 22.5	18.2 ± 20.6	2.8	−4.4 to 10.0	.45
Pre-to-post change in VAS breathlessness	−19.8 ± 32.8	−19.2 ± 33.6	−0.6	−11.8 to 10.6	.68
Modified Borg Scale for Dyspnea score, at 5 min postprocedure	1.90 ± 1.89	1.83 ± 1.73	0.07	−0.5 to 0.7	.90
Modified Borg Scale for Dyspnea score, at 24 h postprocedure	1.68 ± 1.59	1.67 ± 2.01	0.01	−0.6 to 0.6	.49
Modified Borg Scale for Dyspnea score, at 48 h postprocedure	1.54 ± 1.85	1.49 ± 2.14	0.05	−0.7 to 0.8	.47

Data are presented as mean ± SD. VAS = 0-100 mm. See Table 2 legend for expansion of abbreviation.
[a]Suction minus gravity.
[b]On the day of the procedure.

syringe aspiration or evacuated bottle and found more complications in the latter group, although some questioned whether this study was adequately powered. Sagar et al,[26] in a brief letter, reported a complication rate of 0.012% using maximal wall suction to aspirate pleural fluid. Kim et al[27] reported no increase in complication rates following the switch from evacuated container to wall suction in a prospective observational series involving 421 thoracenteses; objective chest discomfort measurements were not reported, however.

We hypothesized that gravity drainage would result in less chest discomfort. One criticism of intermittent pleural manometry-guided thoracentesis is the significant "blind time" between pleural pressure measurements, when highly negative pressures might be generated by active aspiration methods if the lung reaches its limit of normal expandability between measurements.[13,28] Excessively negative intrapleural pressures might be avoided by an aspiration mechanism that does not use a degree of suction in the excessively negative range. However, our findings suggest that this strategy does not protect against chest discomfort. There are several potential explanations for this finding. Although gravity drainage involves a significantly lower degree of suction, it still applies negative pressure to the

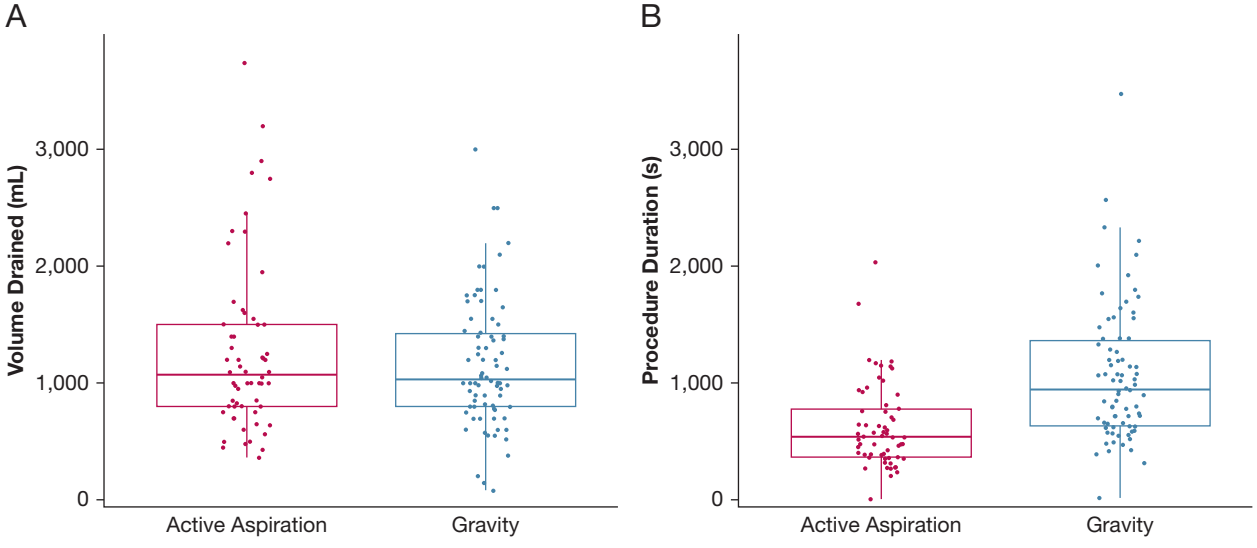

Figure 5 – *Comparison of volume drained and procedure duration between active aspiration and gravity groups. A, Volume drained. B, Procedure duration from catheter placement to removal. Data are presented as means and 95% CIs.*

TABLE 4] Procedure Data

Variable	Suction (n = 62)	Gravity (n = 78)	Mean Difference[a]	95% CI or χ^2	*P* Value
Volume drained, mL	1,264 ± 724	1,165 ± 543	99	−113 to 310	.89
Thoracentesis duration, min	10.5 ± 6.1	17.8 ± 9.7	−7.4	−10.2 to −4.6	< .001
Drainage discontinuation reason					
Stopped spontaneously	28 (45%)	34 (44%)			
Chest discomfort	30 (48%)	38 (49%)			
Intractable cough	1 (2%)	3 (4%)			
Increased dyspnea	2 (3%)	3 (4%)			
Vagal episode	1 (2%)	0			
Complications					
Nonexpanding pneumothorax	1 (2%)	0		$\chi^2 = 1.27$	.26
Residual postprocedure effusion[b]	32 (52%)	41 (53%)		$\chi^2 = 0.01$	.91

Data are presented as mean ± SD unless otherwise indicated.
[a]Suction minus gravity.
[b]More than scant residual pleural fluid on postprocedure thoracic ultrasound.

pleural space, and despite the studied gravity apparatus exerting negative pressure ex vivo below the threshold of "excessively negative," excessively negative pleural pressure could still develop in the breathing patient with nonexpandable lung due to swings in pleural pressure with respiration. In addition, the relation between intrapleural pressure and chest discomfort is inconsistent. In a large prospective series, Feller-Kopman et al[7] noted that only 22% of patients who developed chest discomfort had excessively negative pleural pressure, and 9% of patients with excessively negative intrapleural pressure had no symptoms. Others have noted the development of pneumothorax ex vacuo despite use of pleural manometry with avoidance of excessively negative pleural pressure.[21,29] Heidecker et al[21] suggested that local nonuniform stresses exerted on the visceral pleura, rather than global pressure within the pleural space, might explain these findings.

TABLE 5] Pleural Fluid Analysis and Final Effusion Diagnoses

Variable	Suction (n = 62)	Gravity (n = 78)
Exudate[a]	40 (64.5%)	45 (57.7%)
Transudate[a]	14 (23%)	19 (24%)
Effusion etiology		
Malignant	27 (43.5%)	27 (35%)
Heart failure	5 (8%)	5 (6%)
Chylothorax	1 (2%)	0
Hepatic hydrothorax	4 (6%)	5 (6%)
Chronic kidney disease	1 (2%)	3 (4%)
Parapneumonic	2 (3%)	1 (1%)
Other[b]	1 (%)	4 (%)
Could not be determined	21 (33%)	33 (42%)

[a]Pleural fluid analysis was not obtained in eight control effusions and 14 gravity effusions.
[b]Other etiologies included (n = 1 each): trapped lung with ex vacuo transudative effusion, multifactorial volume overload, drug-induced (dasatinib), and paramalignant inflammatory.

Of paramount importance in considering a randomized trial in which no difference was found between groups is whether a type II error has occurred. This trial was appropriately powered using a superiority design to detect a clinically meaningful difference in VAS discomfort score, with planned enrollment of at least 64 patients in each arm. Variability of the primary outcome did not exceed variability assumed for the power calculation (actual overall SD of 22.9 vs assumed SD of 30). We did note an imbalance in allocation away from the planned 1:1 ratio due to 10 sites enrolling simultaneously from distinct permuted block randomization schedules. Repeat power calculation using the final allocation numbers confirms that this trial remains appropriately powered (power of 83%). There were very few postrandomization exclusions, and complete outcomes data were available on all patients. Among 201 screened patients, only 47 (23%) were excluded prior to randomization, the majority of which (37 of 47) for effusions that were too small according to objective radiographic criteria, supporting the external validity of our findings.

Baseline characteristics were similar between groups, except for lower immediate preprocedure chest

discomfort in the gravity group. If gravity drainage was more comfortable within the predefined time points, as hypothesized, we should have seen lower chest discomfort scores on the primary outcome after starting at a lower baseline level of discomfort, and post hoc analysis adjusting for immediate pre-procedure chest discomfort concurred with the primary analysis. Furthermore, all secondary outcomes related to discomfort, including pre-to-post change in discomfort, failed to identify a difference between groups. Eleven thoracenteses allocated to suction were accomplished with continuous wall suction rather than protocol-directed manual syringe aspiration. Both methods have been shown to produce comparable levels of negative pressure as reviewed earlier, with one study associating continuous suction with more discomfort and a higher incidence of other complications.[4] If true, this scenario should also have biased toward finding a difference between these groups, which we did not, and post hoc per-protocol analysis excluding wall suction cases concurred with the primary analysis. Thus, we are confident on the basis of the data integrity that this study represents a true negative for the primary outcome analysis.

This study has several limitations. It was not powered to detect differences in REPE or pneumothorax ex vacuo, which would require prohibitively large sample sizes. Manometry was not used during thoracenteses in this trial, and thus the precise negative pressures being applied in vivo by the two studied methods is not known; however, based on previous data, this has not been shown to affect symptomatic outcomes and thus was deemed an unnecessary measurement. The most pertinent intraprocedure pressure measurement would be the pressure within the pleural space measured via independent catheter or channel from the drainage catheter, which was not practically feasible. It is possible that the postprocedure time points selected for discomfort measurements did not fully capture the degree of procedural discomfort experienced, although our data with highest discomfort just prior to catheter removal with a downward trend in discomfort scores thereafter suggest we are not missing a later peak in discomfort.

Conclusions

We conclude that pleural fluid drainage via suction and gravity drainage are equivalent in terms of patient comfort, with both methods increasing discomfort and relieving dyspnea by comparable magnitudes. Both also appear safe, with no significant complications occurring in this trial. Gravity drainage did require additional time to accomplish drainage, although proponents of gravity drainage note that this is "hands-off" time that some find more convenient. These two aspiration methods, one faster but "hands-on" and the other slower but more "hands-off," can be used interchangeably by individual providers according to their personal preferences and the clinical setting.

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Author contributions: R. J. L. and F. M. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. R. J. L., F. M., N. M. R., L. Y., and O. B. R. were responsible for study concept and design; R. J. L., S. S., H. B. G., O. B. R., L. R., J. K. P., Z. S. D., L. G. D., J. C. C., J. A., C. W., T. M. S., K. R. D., N. J., S. A., L. Y., F. M., D. F.-K., and H. L. were responsible for acquisition of data; R. J. L., F. M., N. M. R., H. C., R. W. L., C. G., J. T. H., S. S., H. G. B., J. K. P., J. C. C., L. Y., D. F.-K., and H. L. analyzed and interpreted the data; and R. J. L., F. M., N. M. R., and L. Y. drafted the manuscript. All authors participated in critical revision of the manuscript for important intellectual content and provided final approval to submit the final version of the manuscript and have agreed to be accountable for all aspects of the work.

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