Normal Saline Versus Hypertonic Saline for Airway STENT Maintenance

SALTY STENT Study

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Background: Mucus plugging is a common complication of airway stenting. There is no data or guidance on the best airway hygiene regimen and consequently wide practice variation exists.

Methods: This single-center, nonblinded, randomized, pilot study aims to evaluate the effectiveness and safety of nebulized 3% saline (3%S) versus normal saline (NS) in reducing the incidence of mucus plugging in adult patients that undergo central airway stent placement. Patients were enrolled immediately after stent placement and randomized to nebulized 3%S or NS (3 mL) 3 times a day. Patients were scheduled for surveillance bronchoscopy in 4 to 6 weeks. Unscheduled bronchoscopies due to symptomatic mucus plugging were recorded.

Results: From December 2022 to March 2024, 37 patients were screened, and 35 were enrolled. Four in the 3%S and 8 in the NS group did not undergo a surveillance bronchoscopy and were excluded from the final analysis. During surveillance bronchoscopy for the 3%S (n = 13) and NS (n = 10) groups, obstructive mucus plugging was noted in 7.7% versus 40%, granulation requiring intervention in 7.7% versus 10%, and > 25% circumferential biofilm in 0% versus 30%, respectively. In the 3%S versus NS groups, 0% versus 20% of patients required an unscheduled bronchoscopy due to mucus plugging. There were no side effects reported with the daily use of 3%S or NS.

Conclusion: Nebulized 3%S is safe and may be equally or more effective than NS in preventing obstructive mucus plugging in patients who undergo airway stenting. A larger blinded randomized controlled trial is necessary to confirm this finding.

Key Words: bronchoscopy, airway stents, mucus plug, nebulized saline, interventional pulmonology

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Airway stents offer a minimally invasive approach to establish airway patency in flow-limiting, symptomatic central airway pathologies, and are also commonly used to seal airway defects like fistulae. However, despite their widespread use in centers with interventional pulmonology and thoracic surgical expertise, due to the paucity of data and guidance on optimal airway stent maintenance ("hygiene") regimens there exists significant variation in practice across institutions.[1,2]

Mucus plugging after airway stenting occurs as the stent covers the airway epithelium's normal mucociliary clearance mechanism. Without this assistance, mucus can build up to occlude the stent, potentially leading to shortness of breath, lower respiratory infections, and even respiratory failure.[3] There are no data evaluating the use of humidification, mucolytics, expectorants, or cough assist devices after placing airway stents. In addition, no extrapolation on stent-related complication mitigation can be made from the scarce published data that clearly defines the use of a stent maintenance regimen.[4]

Nebulized normal saline (NS) is the most frequently used agent to prevent mucus plugging after airway stenting.[1] NS and its more concentrated versions do this by disrupting ionic bonds within the mucus gel, reducing cross-linking and entanglement, resulting in a reduction in viscosity.[5] In addition, hypertonic saline has been shown in vitro to reduce the formation of biofilm and growth of *Pseudomonas aeruginosa*, with increasing effectiveness in its more concentrated versions.[6] Consequently, simple and cost-effective saline nebulization is a mainstay in the treatment of patients with bronchiectasis to improve mucus clearance.[7] In both cystic fibrosis[8] and noncystic fibrosis[9] bronchiectasis, hypertonic saline is more effective than NS as airway maintenance therapy. However, these findings have not been studied in patients who have undergone airway stent placement. Bronchospasm has been reported with more concentrated saline formulations,[10,11] and caution with their use has been advised, particularly in patients with reactive airway diseases.

This pilot study aims to evaluate and compare the effectiveness and safety of 2 different nebulized regimens, NS or 3% saline (3%S), as airway maintenance therapy after airway stent insertion.

METHODS

This is a single-center, prospective, unblinded, randomized, pilot study that aims to evaluate the effectiveness and safety of 3%S versus NS in reducing the rate of obstructive mucus plugging in adult patients undergoing central airway stent placement. Other outcomes evaluated included biofilm formation, incidence of granulation tissue requiring intervention, stent migration, and medication-related side effects. Biofilm was assessed after suctioning out any luminal mucus and subjectively assessed simultaneously by 2 nonblinded bronchoscopists who reached a consensus and graded it

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based on the percentage area of the stent covered as seen in Figure 1: (1) 0% to 25%, (2) 26% to 50%, (3) 51% to 75% and (4) 76% to 100%. This study was approved by the Icahn School of Medicine institutional review board (IRB) (# 22-01107). See the complete protocol attached in Appendix A, Supplemental Digital Content 1, http://links.lww.com/LBR/A332.

Inclusion and Exclusion Criteria

All patients who underwent airway stent insertion by an interventional pulmonologist were screened for participation in the study. The inclusion criteria were age $\geq$ 18 years of age and undergoing a central airway stent insertion. The exclusion criteria included inability to provide informed consent, lobar or segmental stents, patients considered too ill to undergo a follow-up surveillance bronchoscopy, stent insertion as a trial for excessive central airway collapse (as the duration of these stents is only 1 to 2 weeks), and patients with a tracheostomy (as these patients can undergo frequent in-line suctioning that can affect the outcomes being assessed).

Consent, Enrollment, and Recruitment

Once eligible for the study, the benefits, risks, and study procedures were explained to the patients, and informed consent was obtained. Patients excluded from the study were considered a screen failure. The study protocol aimed to recruit all the patients who were eligible during a period of 15 months, beginning from the time of IRB approval. Since this was a pilot study, no target accrual was calculated.

Randomization

A ratio of 1:1 randomization was performed with random permuted blocks of 4 to randomize allocation between the intervention and control arms. The study was nonblinded, with both the investigator and the patients aware of the treatment that was being given.

Study Procedures

The bronchoscopy and stent insertion procedures were not part of the study protocol. Immediately after stent insertion, the patients were enrolled and randomized to NS or 3%S nebulized (3 mL) 3 times a day. Patients were scheduled for a surveillance bronchoscopy 4 to 6 weeks following stent insertion, during which data regarding complications were recorded. If a patient became symptomatic after the stent insertion and needed an unscheduled bronchoscopy, this was also recorded. Tolerability to the nebulized regimens was evaluated postprocedure in clinic or inpatient if they were admitted, and again prior to the surveillance bronchoscopy.

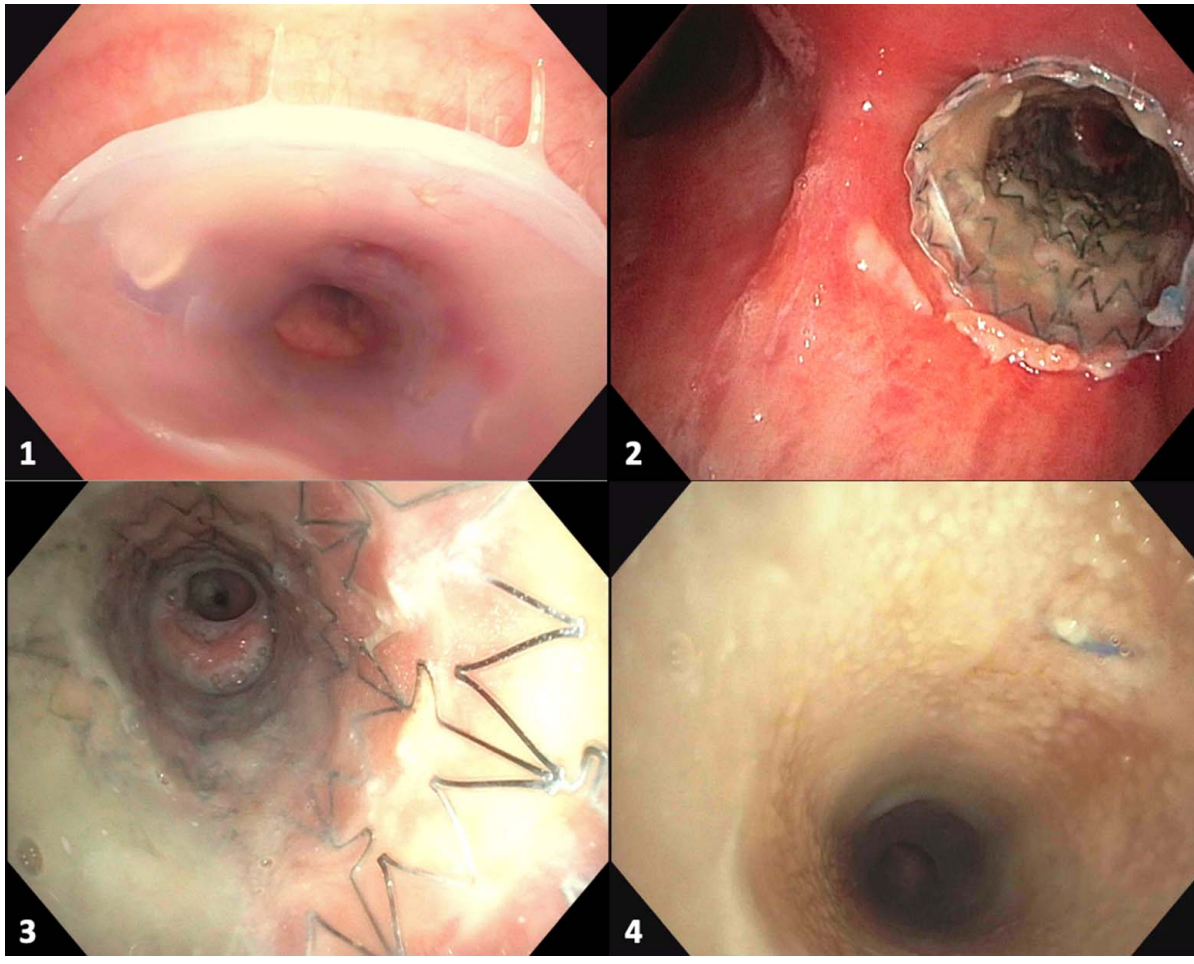

FIGURE 1. Grading of biofilm presence in airway stents (1) 0% to 25%, (2) 26% to 50%, (3) 51% to 75%, and (4) 76% to 100%.

Statistical Analysis

Power calculation was not possible. Only descriptive statistics were used. The randomization blocks and statistical analysis were done utilizing STATA (SE) 18.

RESULTS

From December 2022 to March 2024, 37 patients were successfully screened, of which 2 refused to participate. Of those randomized, another 12 were excluded from the final analysis (Fig. 2): 3 in the 3%S group and 6 in the NS group either died or were deemed too unwell to benefit from a surveillance bronchoscopy, 1 patient in the NS group had significant tumor growth into the stent (prohibiting complication evaluation during the surveillance bronchoscopy), and 1 patient in each group was lost to follow-up. There were no deaths due to complications related to the stent.

A total of 13 patients in the 3%S group and 10 in the NS group were included in the final analysis. Therefore, in a single center over 15 months, 94.6% (35/37) of eligible patients could be recruited to participate in the study, but only 65.7% (23/35) were able to complete the study.

In the 3%S group, the mean age was 57 years, 53.8% were females, and 23.1% had a diagnosis of cancer. In the NS group, the mean age was 64 years, 80% were females, and 60% had a diagnosis of cancer. A detailed list of the demographics and underlying etiologies is detailed in Table 1.

In the 3%S group (n = 13), 30.8% of the stents were tracheal, and 69.2% were bronchial; silicone stents were used in 84.6%, and self-expanding metallic stents (SEMS) in 15.4%. In the NS group (n = 10), 30% of the stents were tracheal, and 70% were bronchial; silicone stents were used in 60% and SEMS in 40%.

Outcomes

An unscheduled bronchoscopy (before the scheduled surveillance bronchoscopy) due to mucus plugging causing significant symptoms was needed in 0% in the 3%S group and 20% in the NS group. The two patients that needed an unscheduled bronchoscopy had fully covered SEMS, primary lung squamous cell carcinoma, stent location in the left main bronchus, and insertion times of 8 and 14 days, respectively. When comparing the findings of 3%S versus NS during the surveillance bronchoscopy, obstructive mucus plugging and granulation requiring intervention were noted in 7.7% versus 40% and 7.7% versus 10%, respectively. The underlying etiologies of the subjects with mucus plugging in the 3%S were benign (100%, n = 1), and in NS were malignant (75%, n = 3) and benign (25%, n = 1). Minimal biofilm covering 0-25% of the stent surface was noted in all patients in the 3%S group and 70% in the NS group; the remaining 30% in the NS group had > 25% biofilm noted. There were no instances of stent migration. There were no side effects reported with the daily use of 3%S or NS. A summary of these results is detailed in Table 2.

DISCUSSION

Airway stent utilization can be expected to increase in coming years given the expansion of interventional pulmonology.[12] Determining the most effective airway hygiene regimen to maintain stent patency should be a priority. We present the first randomized controlled study of two different nebulized saline regimens to prevent mucus plugging in patients who have undergone central airway stenting.

In our pilot study, we found a possibly lower incidence of obstructive mucus plugging noted either during scheduled surveillance bronchoscopy (7.7% vs. 40%) or necessitating an emergent bronchoscopy (0% vs. 20%) in the 3%S versus

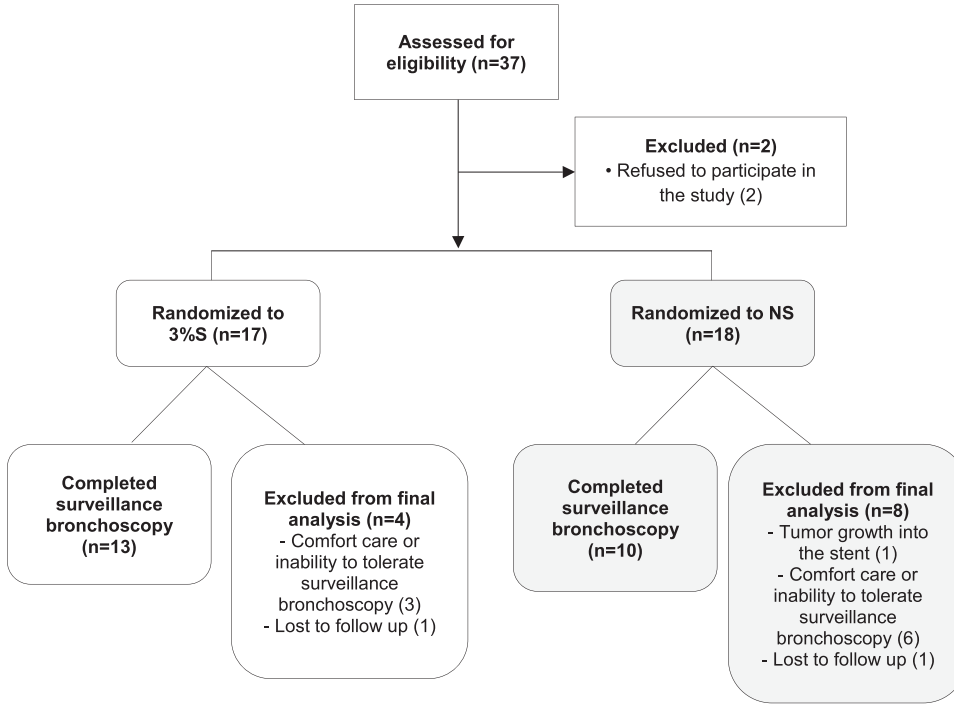

FIGURE 2. Flow diagram of patient analysis. 3%S indicates 3% saline; NS, normal saline.

TABLE 1. Demographics and Clinical Characteristics

	3% saline	Normal saline
Sample size (n)	13	10
Age (mean, range)	57 (28–87)	64 (56–72)
Gender, n (%)		
Male	6 (46.2)	2 (20)
Female	7 (53.8)	8 (80)
BMI (kg/m^2) (mean, range)	27 (20–46)	26.3 (18–34)
Smoking, n (%)		
Never	8 (61.5)	6 (60)
Previous	5 (38.5)	3 (30)
Active	0	1 (10)
mMRC, n (%)		
2	3 (23.1)	4 (40)
3	8 (61.5)	3 (30)
4	2 (15.4)	3 (30)
ECOG, n (%)		
1	2 (15.4)	0
2	5 (38.5)	6 (60)
3	5 (38.5)	4 (40)
4	1 (7.7)	0
Cancer diagnosis (n (%))	4, 30.8	6 (60)
Reason for stent insertion, n (%)	Symptomatic CAO = 12 (92.3) TEF = 1 (7.7)	Symptomatic CAO = 10 (100)
Location of stent		
	BI – 2 (15.3%) LMB – 1 (7.7%) RMB – 3 (23.1%) RMB + BI – 2 (15.3%) Trachea – 3 (23.1%) RMB + BI + RUL – 1 (7.7%) Trachea +/− LMB +/− RMB (Y) – 1 (7.7%)	BI – 3 (30%) LMB – 2 (20%) LMB + LUL + LLL – 1 (10%) RMB + BI – 1 (10%) Trachea – 1 (10%) Trachea +/− LMB +/− RMB (Y) – 2 (20%)
Types of stents		
SEMS - fully covered	(7.7)	4 (40)
SEMS - partially covered	1 (7.7)	0
Silicone - straight	9 (69.2)	4 (40)
Silicone - Y-shaped	2 (15.4)	2 (20)
Etiologies	Malignant (3, 23.1%) *Lung metastases* Esophageal SCC (2, 15.4%) Melanoma (1, 7.7%) Benign (10, 76.9%) Benign tracheal stenosis (1, 7.7%) Post TB bronchial stenosis (2, 15.4%) TBM (2, 15.4%) Lung transplant (5, 38.5%): Malacia (2), Stenosis (2) and Stenosis + Malacia (1)	Malignant (6, 60%) *Primary lung cancer* SCC (4, 40%) *Lung metastases* Anal SCC (1, 10%) Esophageal SCC (1, 10%) Benign (4, 40%) Benign tracheal stenosis (1, 10%) Sarcoidosis (1, 10%) Lung transplant (2, 20%): Stenosis (2)

BMI indicates body mass index; CAO, central airway obstruction; ECOG, Eastern Cooperative Oncology Group performance status; LMB, left main bronchus; mMRC, modified Medical Research Council dyspnea scale; SCC, squamous cell carcinoma; SEMS, self-expanding metallic stent; TB, tuberculosis; TBM, tracheobronchomalacia; TEF, tracheoesophageal fistula.

NS groups, respectively. Though this evaluation was not part of our initial protocol, we switched both the patients in the NS group that were found to have obstructive mucus plugging requiring an unscheduled bronchoscopy to 3%S and did not note a recurrence of mucus plugging on further surveillance bronchoscopy. There was no obvious relation of complications to either stent type or location; however, our small sample sizes do not allow accurate determination of this. Based on these results, we hypothesize that 3%S may be as or more effective than NS as an airway maintenance regimen. There are reports of bronchospasm in some (nonstent) studies that used inhaled concentrated saline formulations.[7,10,11] We did not encounter any reported side effects or issues with tolerability. However, our complication and compliance assessments were based on patient reports and not formalized using validated questionnaires. Tolerability should be an outcome evaluated in larger studies, to characterize the risk of bronchospasm more accurately in this population.

The effect of surveillance bronchoscopy was not assessed in this study. Despite conflicting evidence of its benefit,[13,14] it is part of our standard practice since it was shown in a recent study by *Lee* et al[13] that 60% of asymptomatic patients were found to have at least 1 stent-related complication during the surveillance bronchoscopy. In our study, despite the use of routine surveillance bronchoscopy with a standardized nebulized regimen to facilitate mucus clearance, 8.7% (2/23) of patients still

TABLE 2. Results of Surveillance Bronchoscopies

	3% saline	Normal saline
Sample size (n)	13	10
Obstructive mucus plug (n, %)	1, 7.7	4, 40
Need for emergency bronchoscopy (n, %)	0, 0	2, 20
Biofilm formation (n, %)		
0–25%	13, 100	7, 70
26%–50%	0, 0	1, 10
51%–75%	0, 0	1, 10
>75%	0, 0	1, 10
Obstructive granulation that required intervention (n, %)	1, 7.7	1, 10
Stent migration (n, %)	0, 0	0, 0

required an unscheduled bronchoscopy due to the development of acute respiratory symptoms secondary to mucus plugging.

Our study only evaluated the role of 2 concentrations of nebulized saline for stent maintenance therapy. No study has yet demonstrated the superiority of saline nebulization to doing nothing. Moreover, the additive role of bronchodilators like albuterol, expectorants like guaifenesin, mucolytics like acetylcysteine, or devices like flutter valves, has not been established and they are not part of our routine stent maintenance practice. Until further prospective analyses to determine their efficacy are carried out, we feel that the expectation of their effectiveness should be managed with caution.[1,2,15] We believe that our study may help better design future clinical trials that aim to evaluate the effectiveness of different airway hygiene regimens to maintain stent patency. The effect sizes that we demonstrated can be used to calculate power for determining the ideal sample size for a larger (ideally, multicenter) randomized clinical trial. In addition, we believe, even though single-centered, our study establishes the feasibility of recruitment of patients for such a study; the 34.3% dropout rate we noted should be factored into future study power calculations.

Our study has several limitations. The pilot design and small sample size prohibit any firm extrapolations from our data. The lack of blinding for both the investigators and patients, as well as the single-site design, introduces sources of bias. The short follow-up time of 4-6 weeks may be insufficient to assess complications or events that happen in the long term associated with airway maintenance, especially for patients who have long-term use of airway stents. Furthermore, for compliance with the prescribed nebulized regimens, we relied on patient reports and did not use a formal assessment tool. In addition, biofilm assessment, while performed by 2 providers, was still subjective. Moreover, the significance and consequences of varying degrees of biofilm remain unclear. Our results are relevant to adult patients with central airway stents and may not be extrapolated to lobar or segmental stents, and pediatric patients.

CONCLUSIONS

Nebulized 3%S is safe and may be as or more effective than NS to prevent obstructive mucus plugging in patients that undergo central airway stenting. Our study establishes the feasibility of recruiting patients for a larger, multicenter, blinded, randomized controlled trial to confirm our findings.

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