

Effects of Thrombolytic Agents on Tympanostomy Tubes Occluded by Blood Clots

Michael I. Orestes, MD; Bader Fileta, BS; Snezana Haymes, PhD; Scott E. Brietzke, MD, MPH

Objective: To investigate the efficacy of various topical applications in opening a clotted tympanostomy tube (TT) using an in vitro model.

Design: In vitro clinical trial.

Interventions: Fresh human blood was allowed to clot in the lumen of TTs. Seven agents were tested: 0.9% saline (control), 1-mg/mL alteplase, 100-U/mL unfractionated heparin, 3% hydrogen peroxide (H₂O₂), 3% acetic acid, 5% acetic acid, and a mixture of 3% H₂O₂ and 3% acetic acid. Each agent was added twice a day for 14 days to TTs that were incubated and humidified to simulate ear canal conditions. The tubes were analyzed with binocular microscopy to determine the status of the obstruction.

Results: A total of 16 trials per agent, including a saline

control, were performed. The saline control, alteplase, and heparin failed to open any TTs in any of the trials. Compared with the control, H₂O₂ also was not effective ($P=.23$). Acetic acid was increasingly effective, with a 3% concentration completely clearing 5 of 16 tubes and a 5% concentration completely clearing 11 of 16 tubes ($P=.006$). The addition of 3% H₂O₂ to 3% acetic acid did not significantly increase clearance ($P=.21$).

Conclusions: Thrombolytic agents and H₂O₂ were not effective in resolving TTs that were clotted with blood in an in vitro environment simulating the ear canal. Increasing concentrations of acetic acid are increasingly effective in this capacity.

Arch Otolaryngol Head Neck Surg. 2011;137(12):1228-1231

TYMPANOSTOMY TUBE (TT) placement is the most common reason for children to undergo general anesthesia in the United States. The most common adverse complication associated with TT placement is obstruction of the lumen, which occurs approximately 7% of the time, often causing accumulation of the middle ear effusion.¹ When this accumulation occurs early in the course of therapy, obstruction necessitates removal and replacement of the nonfunctioning TT. Repeated surgery results in additional costs to the hospital, which in 1 study ranged from \$200 to more than \$1000,² as well as additional complications from the use of anesthesia, including airway obstruction, emesis, agitation, and laryngospasm.³ Numerous treatment strategies have been developed to prevent obstruction, including oxymetazoline hydrochloride, ototopical antibiotic drops, and coated TTs.⁴ Also, various mucolytic agents to lyse mucoid obstructions, including vinegar and hyaluronidase solutions, have been studied.⁵ The components of TT obstruction have also been well studied, and, while mucoid obstructions were the most common type,

blood-based obstructions, which may also promote biofilm formation, were noted in a number of cases.^{6,7} A thorough literature search revealed only 1 study specifically addressing lysis of blood clots. That study showed improved clearing of blood clots with preparations of white vinegar (acetic acid) and hydrogen peroxide (H₂O₂) when compared with ototopical antibiotic drops.⁸ To our knowledge, there are no studies that have addressed the use of thrombolytic and anticoagulant agents in the treatment of TT obstruction due to blood clots. However, these agents have been successfully used to clear central lines and hemodialysis catheters that have clotted and no longer function.

METHODS

The study was fully approved by the institutional review board of Walter Reed Army Medical Center, Washington, DC, as an in vitro study. Human blood was obtained from the primary investigator (M.I.O.), who has type A Rh-positive blood, no history of coagulopathy, and was not taking any anticoagulant agents or platelet-inhibiting substances during the course of the experiment.

Author Affiliations: Departments of Otolaryngology (Drs Orestes and Brietzke) and Clinical Investigation (Mr Fileta and Dr Haymes), Walter Reed Army Medical Center, Washington, DC.

An experimental model was constructed to mimic the tympanic membrane (**Figure 1**). Paraffin wax was stretched across 6 well plates that had 30 mL of normal saline placed in the bottom of the ear well to provide humidification of the tubes. The TTs were inserted into the paraffin with a myringotomy knife and alligator forceps. Sheehy collar button tubes (fluoroplastic, blue with inner diameter of 1.27 mm) were used. Human blood (5 μ L) was placed into the lumen of each tube, and the tubes were incubated at 37°C for 24 hours to allow the blood to form a stable clot. The tubes were examined after formation of a clot to ensure that the clot completely obstructed the lumen of the tubes. Several extra tubes were prepared and were used to replace tubes in which the clot did not obstruct the lumen.

An agent (100 μ L) was then added to the prepared and clotted TT (**Figure 1**). Seven agents were tested: 0.9% saline (control), 1-mg/mL alteplase, 100-U/mL unfractionated heparin, 3% H₂O₂, 3% acetic acid, 3% H₂O₂ and 3% acetic acid, and 5% acetic acid. The agents were applied twice a day for 14 days, and the tubes were incubated at 37°C for the duration of the experiment. The tubes were then allowed to dry in the incubator for at least 48 hours and, once completely dry, were examined for evidence of clot lysis. The primary investigator, who examined the tubes, was blinded to the agents applied.

All tubes were examined under binocular microscopy with a standard otologic microscope and while backlit by a light box to determine the degree of clot lysis. The tubes were classified as completely obstructed, partially obstructed (partially patent), or completely patent (**Figure 2**). Those that were classified as partially obstructed had at least 1 portion of the lumen that was completely patent despite residual clot within the lumen. Those classified as completely patent had either minimal or no residual clot within the lumen. A total of 4 tubes were prepared to test each substance per trial, with a total of 4 trials, resulting in 16 total trials per substance.

The sample size of 16 tubes was selected based on a priori power analysis. An agent would need to unblock at least 50% of the ear tubes to be considered clinically useful vs control, for which it was assumed that none of the tubes would be opened. A sample size of 16 tubes results in 86% power to detect a 50% opening proportion of the test agent vs a 0 opening proportion of the control.

Stata version 8.2 software was used to perform the statistical analysis. The Fisher exact test was used to determine whether there was a significant difference in TT obstruction clearance between substances. $P = .05$ was considered significant.

RESULTS

Each of the 7 agents that were tested underwent 16 trials on 16 individual clotted TTs. After 2 weeks of treatment, the tubes were graded as obstructed, partially obstructed, or completely patent (**Figure 2**). **Table 1** shows the raw data. The saline control did not unblock any clotted TTs. Alteplase also did not dissolve any of the blood clots but, instead, caused a thickened residue to form over each tube, resulting in an increased obstruction. Heparin applied to the tubes was indistinguishable from saline. Three percent H₂O₂ caused the blood clots to change from dark-red to frothy white (**Figure 3**) but was mostly ineffective in relieving the obstruction. Three percent acetic acid and 5% acetic acid were increasingly successful at lysing the blood clots. The combination of 3% H₂O₂ and 3% acetic acid performed similarly to 3% acetic acid alone except that there were no partially obstructed tubes and the H₂O₂ turned the blood clots white.

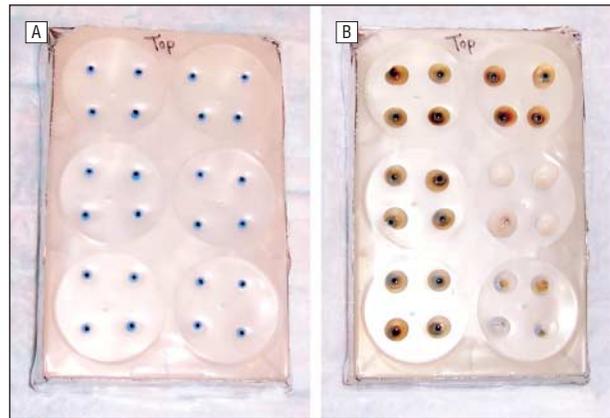


Figure 1. In vitro model of ear tubes. A, Model placed into a paraffin membrane simulating a tympanic membrane. B, Model after application of topical drops. The model was incubated and humidified to simulate ear canal conditions.

Table 2 shows the pertinent statistical comparisons between agents (Fisher exact test). Three percent H₂O₂ was not significantly better than the saline control ($P = .23$). However, the lack of difference between the saline control and the 3% hH₂O₂ could be attributable to power limitations with the sample size (post hoc power, 21.5%), and it is possible that 3% H₂O₂ is slightly better than control. Three percent acetic acid ($P = .002$) and 5% acetic acid ($P < .001$) were increasingly effective vs control, and 5% acetic acid was superior to 3% acetic acid ($P = .006$). The effect of the addition of 3% H₂O₂ to 3% acetic acid alone was not significant ($P = .21$), but this comparison was limited by power (post hoc power, 10.3%), and it is possible that the addition of H₂O₂ was slightly better than 3% acetic acid alone, but the combination of 3% acetic acid and H₂O₂ was not comparable to 5% acetic acid alone, which was superior ($P < .001$). Overall, 5% acetic acid was clearly the most superior agent in unblocking TTs with blood clots.

COMMENT

Obstruction of TTs due to blood clots is a frustratingly frequent cause of early TT failure, often leading to removal and replacement. Most research into unblocking TTs has involved the chemical removal of mucoid obstructions, which are the most common type of obstruction.^{5,6} However, this scenario often occurs after the tubes have been in place for an extended period, with benefit to the patient. Conversely, blood clot obstruction of TTs typically occurs early as a direct result of the placement procedure, and there has been little or no benefit from the TT at that point. We found only 1 previous study that evaluated chemical lysis of blood clots. That study showed that common agents such as H₂O₂ and acetic acid are superior to ototopical antibiotic drops at lysing blood clots.⁹ The purpose of our study was to expand the investigation regarding opening TTs that have been blocked by blood clots by examining the effectiveness of readily available agents with thrombolytic properties such as heparin and alteplase using an in vitro model. We also aimed to evaluate the effectiveness of increasing concentra-

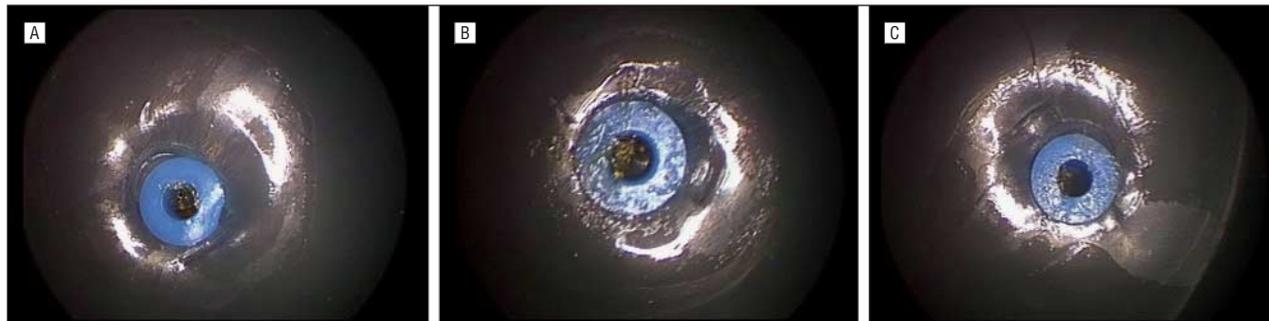


Figure 2. Grommet tube before and after application of topical agent. A, Magnified view (4-mm Hopkins rod) of grommet tube completely clotted with blood clot. B, Partial blockage of blood clot remaining after application of topical agent. C, Complete resolution of blood clot after application of topical agent.

Table 1. Raw Data

Agent	Completely Blocked	Partially Obstructed	Completely Patent
3% Acetic acid	8	3	5
5% Acetic acid	0	5	11
3% H ₂ O ₂	13	0	3
3% Acetic acid + 3% H ₂ O ₂	8	0	8
1-mg/mL alteplase	16	0	0
100-U/mL heparin	16	0	0
0.9% Saline control	16	0	0

Abbreviation: H₂O₂, hydrogen peroxide.

Table 2. Pairwise Comparisons

Agent	P Value ^a
3% H ₂ O ₂ vs 0.9% saline control	.23
3% Acetic acid vs 0.9% saline control	.002
5% Acetic acid vs 0.9% saline control	<.001
3% Acetic acid vs 5% acetic acid	.006
3% Acetic acid vs 3% acetic acid + 3% H ₂ O ₂	.21
5% Acetic acid vs 3% acetic acid + 3% H ₂ O ₂	<.001

Abbreviation: H₂O₂, hydrogen peroxide.

^aFisher exact test.

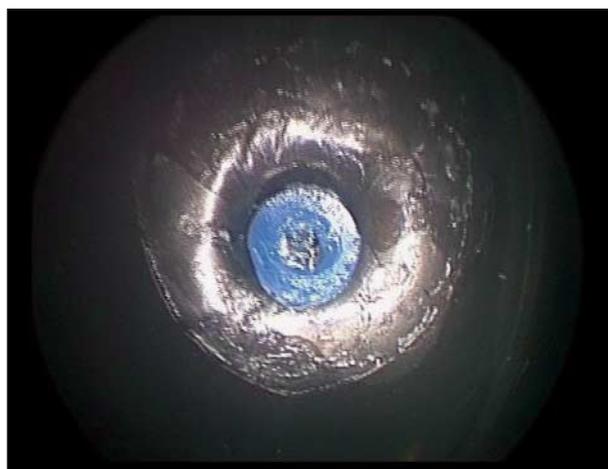


Figure 3. Magnified view (4-mm Hopkins rod) of grommet tube with blood clot after application of 3% hydrogen peroxide. Note that the blood clot has become white but the tube is still obstructed.

tions of acetic acid, which was found to be effective in the study by Burke et al.⁹

We originally hypothesized that alteplase would be effective at lysing blood clots given its utility in clearing blood clots from other systems such as central lines. However, owing to the viscosity of the chemical in solution, which because of surface tension prevented significant migration of the substance to the blood clot in the lumen of the TTs, alteplase was found to be ineffective. Heparin has a much lower viscosity than alteplase and appeared to enter the tubes but also had no effect on formed blood clots. There may also be a significant difference between the wet clot formed in central lines and hemodi-

alysis catheters and the dry clot formed in the present study. Also, alteplase is often forced against the clot physically when it is being pushed in the line, which would overcome the viscosity issue found in this study.

Like Burke et al,⁹ we found that acetic acid was effective at removing blood clots. We also found that increasing the concentration from 3% to 5% significantly increased the agent's ability to remove blood clots. In our study, 100% of the tubes that had 5% acetic acid applied had at least a partially patent lumen at the end of 14 days. We did not find that H₂O₂ was as effective at lysing blood clots by itself or when added to acetic acid. Furthermore, the H₂O₂ bleached the blood clot itself, which may make it more difficult to monitor via binocular microscopy in the office. Of note, however, when H₂O₂ was added, there were no partially obstructed tubes; it either completely cleared the blood clot or left a persistent obstructive film within the lumen of the tube.

Because acetic acid was found to be the most effective agent in this study, a discussion of the adverse effects of its use is appropriate. Acetic acid is commonly used in otology to treat otitis externa due to acid suppression of the growth of various microorganisms within the external auditory canal. We found only 1 study that specifically addressed the ototoxic effects of acetic acid alone.¹⁰ In that study, VoSol (2% acetic acid and 3% propylene glycol among other preservative ingredients) was compared with 2% acetic acid and hydrogen chloride. It was noted that both VoSol and 2% acetic acid applied directly to the round window caused acidification of perilymph, resulting in depression of endocochlear potentials. This was not observed with a nonorganic acid, such as hydrochloric acid. Also, both 4% and 13% concentrations of Burow solution (aluminum subacetate), which

is also commonly used in otology for its antimicrobial properties, did not cause a significant change in auditory brainstem response when applied to middle ear in chinchillas.¹¹ Burow solution is discussed herein because it includes acetic acid used in concentrations similar to or higher than those used in our study.¹² We know of only 2 cases¹³ of Burow solution causing hearing loss in humans, both of which were due to infusions into the middle ear cavity to treat otitis media with tympanic membrane perforations. Both patients experienced immediate sensorineural hearing loss, which resolved with some minimal residual high-frequency defect in 2 weeks. However, in another study showing the efficacy of Burow solution as an antimicrobial agent, administration to nonintact tympanic membranes and even injection of the solution into the middle ear space resulted in no adverse effects on hearing.¹² While it seems that acetic acid solutions would be both safe and effective at removing blood clots, both 3% and 5% acetic acid solutions have not been specifically tested, and more research into the safety of the administration of these compounds is required, especially if higher concentrations of acetic acid are to be used clinically. It should also be noted that a much smaller volume of the solution would actually reach the round window compared with the volumes that were used in the ototoxicity studies and cases described herein. A decreasing concentration of acetic acid could be used along the course of clinical treatment to reduce the risk of ototoxic effects as the blood clot is lysed. Furthermore, more research on nonorganic acids that do not penetrate the round window may be indicated.

Pain is also a concern with the administration of acetic acid. The use of Burow solution has been noted to cause pain.¹² Acetic acid has been implicated in pain on contact with middle ear mucosa; however, as noted by Burke et al,⁹ acetic acid contact with mucosa would imply tympanostomy tube patency and indicate that treatment could be stopped.

Our study was limited to testing only Sheehy collar button tubes because of their nonbeveled nature and relatively large diameter, which allowed improved visualization of clots in our nonangled tympanic membrane model. Furthermore, our model was performed with pure blood clots in an in vitro model, whereas clinical clots are also likely to contain some elements of bacteria, cerumen, and mucoid components. While we attempted to mimic clinical conditions by warming and humidifying clots, our model did not attempt to mimic the effects of eustachian tube function and other properties of a true middle ear space and ear canal. Our study also used a nonvalidated visual inspection method, as described herein; however, we believe that this method effectively simulated the clinical conditions in which obstructed tubes are evaluated.

In conclusion, topical thrombolytic agents were ineffective in opening TTs that were blocked by blood clots. Increasing concentrations of acetic acid were increasingly effective in opening blocked tubes. Hydrogen peroxide was mostly ineffective. Further studies into the clinical use of concentrated acetic acid are necessary before its widespread use for this clinical application.

Submitted for Publication: January 29, 2011; final revision received June 18, 2011; accepted September 28, 2011.

Correspondence: Scott E. Brietzke, MD, MPH, Department of Otolaryngology, Walter Reed Army Medical Center, Washington, DC 20307 (SEBrietzke@msn.com).

Author Contributions: Drs Orestes and Brietzke 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. *Study concept and design:* Orestes, Fileta, and Brietzke. *Acquisition of data:* Orestes, Fileta, and Haymes. *Analysis and interpretation of data:* Orestes and Brietzke. *Drafting of the manuscript:* Orestes, Haymes, Fileta, and Brietzke. *Critical revision of the manuscript for important intellectual content:* Orestes and Brietzke. *Statistical analysis:* Brietzke. *Obtained funding:* Orestes. *Administrative, technical, and material support:* Orestes, Fileta, Haymes, and Brietzke. *Study supervision:* Brietzke.

Financial Disclosure: None reported.

Funding/Support: The Department of Clinical Investigation of Walter Reed Army Medical Center provided funding for the purchase of the expendable equipment, including TTs and reagents, used in this study. Approval from the Department of Clinical Investigation to proceed with the research as well as to publish the manuscript was required as part of the institutional review board process.

Disclaimer: The views herein are the private views of the authors and do not reflect the views of the Department of the Army or the Department of Defense.

Previous Presentation: This study was presented as an oral presentation at the American Society of Pediatric Otolaryngology meeting; April 29–May 1, 2011; Chicago, Illinois.

REFERENCES

- Kay DJ, Nelson M, Rosenfeld RM. Meta-analysis of tympanostomy tube sequelae. *Otolaryngol Head Neck Surg.* 2001;124(4):374-380.
- Shiley SG, Lalwani K, Milczuk HA. Intravenous sedation vs general anesthesia for pediatric otolaryngology procedures. *Arch Otolaryngol Head Neck Surg.* 2003;129(6):637-641.
- Hoffmann KK, Thompson GK, Burke BL, Derkay CS. Anesthetic complications of tympanostomy tube placement in children. *Arch Otolaryngol Head Neck Surg.* 2002;128(9):1040-1043.
- Kumar VV, Gaughan J, Isaacson G, Szeremeta W. Oxymetazoline is equivalent to ciprofloxacin in preventing postoperative otorrhea or tympanostomy tube obstruction. *Laryngoscope.* 2005;115(2):363-365.
- Westine JG, Giannoni CM, Gajewski B, Antonelli PJ. Opening plugged tympanostomy tubes. *Laryngoscope.* 2002;112(8, pt 1):1342-1345.
- Westine JG, Giannoni CM, Antonelli PJ. Defining tympanostomy tube plugs. *Laryngoscope.* 2002;112(6):951-954.
- Mehta AJ, Lee JC, Stevens GR, Antonelli PJ. Opening plugged tympanostomy tubes: effect of biofilm formation. *Otolaryngol Head Neck Surg.* 2006;134(1):121-125.
- Malaty J, Antonelli PJ. Effect of blood and mucus on tympanostomy tube biofilm formation. *Laryngoscope.* 2008;118(5):867-870.
- Burke EL, Walvekar RR, Lin J, Hagan J, Kluka EA. Common agents used to unblock blood clots within tympanostomy tubes: an ex vivo study and review of literature. *Int J Pediatr Otorhinolaryngol.* 2009;73(12):1725-1728.
- Ikeda K, Morizono T. The preparation of acetic acid for use in otic drops and its effect on endocochlear potential and pH in inner ear fluid. *Am J Otolaryngol.* 1989;10(6):382-385.
- Serin GM, Ciprut A, Baylanççek S, Sari M, Akdaş F, Tutkun A. Ototoxic effect of Burow solution applied to the guinea pig middle ear. *Otol Neurotol.* 2007;28(5):605-608.
- Kashiwamura M, Chida E, Matsumura M, et al. The efficacy of Burow's solution as an ear preparation for the treatment of chronic ear infections. *Otol Neurotol.* 2004;25(1):9-13.
- Oishi N, Inoue Y, Saito H, Ogawa K. Burow's solution-induced acute sensorineural hearing loss: report of two cases. *Auris Nasus Larynx.* 2010;37(3):369-372.