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ORIGINAL RESEARCH

Intrapleural Instillation of Sodium Bicarbonate versus Urokinase in Management of Complicated Pleural Effusion: A Comparative Cohort Study

Niveen E Zayed[1], Karim El Fakharany[2], Mohammed Mehriz Naguib Abozaid[1]

[1]Department of Chest Disease, Faculty of Medicine, Zagazig University, Zagazig City, Egypt; [2]Department of Cardiothoracic Surgery, Faculty of Medicine, Zagazig University, Zagazig City, Egypt

Correspondence: Niveen E Zayed, Chest Department, Zagazig University, Faculty of Medicine, Sharkia Government, Zagazig City, 44519, Egypt, Tel +201024831444, Email Niveenzayed@yahoo.com; nezayed@zu.edu.eg

Aim: The main target is evacuation; however, with evidence about the value of intrapleural instillation of different fibrinolytic agents still under evaluation, our aim was comparing the effectiveness and safety of intrapleural instillation of sodium bicarbonate ($NaHCO_3$) in comparison with urokinase in patients with infected pleural effusion.

Methods: Our prospective cohort study included 40 patients with complicated empyema; the diagnosis was based on analysis of aspirated fluid in association with radiological and bacteriological culture. The patients were subjected to instillation of two different fibrinolytic agents; the first one was $NaHCO_3$, the second was urokinase.

Results: The commonest underlying chest infection that was visualized by CT was pneumonia 70%. Nearly half of cases had community-acquired infection (45%), and more than half of them (55%) had anaerobic infection, and only five cases had TB pleural effusion based on ADA-positive, tuberculin skin test in addition to Abram's needles closed biopsy. The rate of repeated therapeutic thoracentesis success in each group was 85%; 80% in $NaHCO_3$ group, and 90% in urokinase group, both of them was significantly equal, P=0.37. Moreover, the frequency of complications in all patients was less than 13%, hence hemothorax and iatrogenic pneumothorax was 12.5%, and only 10% of cases were admitted in ICU after the maneuver, with insignificant difference in between the groups. However, looking at the smaller rate of RTT failure of $NaHCO_3$ or urokinase, the logistic regression model showed that RTT–$NaHCO_3$ was insignificantly related to failure in both unadjusted and adjusted models, P=0.37 and 0.32, respectively, and only smoking habits increase the likelihood of failure 9-fold (OR=8.9, P=0.04) with respect to age, sex, and treatment methods.

Conclusion: The efficacy of repeated therapeutic thoracentesis (RTT) with intrapleural instillation of $NaHCO_3$ was effective and safe, the same as urokinase, with consideration that $NaHCO_3$ was much more available and affordable than urokinase.

Keywords: pleural infection, fibrinolytic agents, NaHCO3, urokinase

Introduction

Infected pleural effusion is a collection of pus in the pleural space, and is considered as a severe form of infection with mortality rate about 20%.[1] Commonly it happens as a consequence of pulmonary infection such as pneumonia and lung abscess, then a simple para-pneumonic fluid collection is formed,[2,3] and by the effect of both bacteria and white cell metabolism, the fluid is rapidly turned to purulent empyema, which is characterized by low pH and higher LDH enzyme level.[4] The pathophysiological degree of empyema is classified into three stages; the first is simple exudative fluid collection, the second is fibrinopurulent transformation, and the third is aggressive organization phase.[5,6] The important point of pathophysiological classification of empyema is to guide the process of treatment intervention, hence, the gold standard treatment strategy of infected pleural effusion is evacuation beside the good coverage of antibiotics; however, with formation of fibrinopurulent stage, the theory of using intrapleural fibrinolytic agents is introduced as an add-on therapy to minimize the need for surgical consequences if the classical treatment fails.[7–9] Several clinical trials and observational studies were conducted and introduced a different fibrinolytic therapy such as streptokinase, tPA, and

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DNase as a treatment option for complicated effusion.[10,11] Streptokinase and other fibrinolytic substances had the ability to destruct the fibrin threads, which subsequently leads to opening of the loculi, and eventually enhancing the fluid evacuation and healing.[12–14] However, this area of research is still growing, putting into consideration the safety and efficacy issues.

Sodium bicarbonate solution has potential antithrombotic and antimicrobial properties;[20,21] it has the ability to chelate calcium ions and thus inhibits the conversion of fibrinogen to fibrin.[20] Moreover, the antimicrobial ability of sodium bicarbonate may decrease the formation of bacterial biofilm, especially Gram-positive organisms as staphylococci in addition to decreasing its adherence.[22] Furthermore, the ionic abundance of $NaHCO_3$ may alter the membrane permeability of the bacteria, which further leads to modification of their structure to become less viable.[23] The present work was designed as an observational prospective cohort study to assess the safety and efficacy of sodium bicarbonate ($NaHCO_3$) as a promising fibrinolytic agent in comparison with urokinase in the treatment of complicated pleural effusion.

Patients and Methods

Patients and Study Design

A prospective cohort study that included 40 patients with infected pleural effusion was carried out through the period from June 2020 to January 2022 at the chest department of Zagazig University Hospital. The study included all patients above 18 years of age, with at least one of the following criteria that denote infected fluid. The first was frank pus aspiration, the second was fluid pH <7.2, the third was positive microbiological culture of the aspirated fluid, and the fourth was intrapleural loculation in the radiological examination. After written consent from all participants for publication of their data, the study has been approved from the ethical committee office of the faculty of medicine, Zagazig University in agreement with the Helsinki Declaration rules.

Data Collection

The data of the selected patients were collected in a spreadsheet and included all demographic characteristics and clinical, laboratory, radiological, and bacteriological findings, in addition to the outcome of cases, which stand for the success rate and the associated complications such as hemothorax, iatrogenic pneumothorax, and need for ICU admission for any reasons during intrapleural instillation procedures.

Fibrinolytic Instillation Protocol

The dose of urokinase was 100,000 UI, then diluted in 50 mL saline solution, while the $NaHCO_3$ ampule contains 50 meq in 50 mL. The fibrinolytic agents were instilled in the pleural space by the effect of gravity using pleural trocar at the end of thoracentesis. The thoracentesis was repeated to get rid of the accumulated fluid till the effusion was significantly decreased. The good outcome was defined as adequate pleural evacuation, improvement of clinical state, and control of systemic infection, in addition to enhancement of radiological picture.

Statistical Analysis

The data were collected and coded in an Excel spreadsheet, and the normality of data was examined using Shapiro–Wilk test using Minitab 17.1.0.0 for Windows (Minitab Inc., 2013, Pennsylvania, USA). Continuous data were represented as mean and standard deviation, and categorical data as number and percentage. The comparison between two means was done using an independent *t*-test, while the frequency comparison was made using the chi-square test. Logistic regression analysis was performed on the factors associated with RTT failure either with unadjusted or adjusted models. All tests were two-sided, and a *P* value below 0.05 was considered significant.

Results

General Characteristics of Patients

The study included forty patients with infected pleural effusion that were subjected to repeated therapeutic thoracentesis with instillation of two different materials; the first group (Group-A; n=20) was treated with $NaHCO_3$, while the second

group (Group-B; *n*=20) was treated with urokinase. The mean (SD) age of the patients was 52 (15) years, and more than half of them were male (55%). DM was the most frequent comorbidity followed by HTN and IHD (65%, 32.5%, and 12.5%, respectively). Additionally, nearly half of cases were currently smokers and had underlying chest disease (42.5% and 40%, respectively). However, the studied groups were matched as regarding all basic factors, although the Group-A had significantly higher percentage of cases with underlying chest disease (*P*=0.05, Table 1).

Radiological Findings and Biochemical Analysis

About 95% of cases had infected effusion with moderate to large amount that exceeded 1/2 of the thorax, and 55% of them showed loculation in US assessment, Figure 1.

Additionally, the commonest underlying chest infection that was visualized by CT was pneumonia (70%); consolidation and air bronchogram, Figure 2.

Furthermore, 8 cases showed cavity with different wall thickness. Irrespectively, both treatment groups were matched regarding all radiological factors, Table 2. All cases showed an exudative pattern regarding Light's criteria, and nearly half of cases had community-acquired infection (45%), while more than half of cases (55%) showed anaerobic infection. Five cases had TB pleural effusion based on ADA-positive, tuberculin skin test in addition to Abram's needles closed biopsy.

Consequence of Repeated Thoracentesis Treatment (RTT) and Factors Associated with Failure

As shown in Table 3, the rate of RTT success was 85%; 80% in the $NaHCO_3$ group, and 90% in the urokinase group, both of them significantly equal, *P*=0.37. However, all cases had developed fever after injection of $NaHCO_3$ and urokinase, and there were insignificant differences between them regarding the duration of fever, *P*=0.75. Moreover, the frequency of complication in all patients was less than 13%, thus hemothorax and iatrogenic pneumothorax occurred in 12.5%, and only 10% of cases were admitted in ICU after the maneuver, with insignificant difference between the

Table 1 General Characters of Patient's Groups

Factors	Group-A (*n*=20)		Group-B (*n*=20)		*P*
	Mean/*n*	SD/%	Mean/*n*	SD/%	
Age (years)	53	15.4	50	14.8	0.54†
Sex (male)	12	60	10	50	0.52⌊
Smoking	10	50	7	35	0.33⌊
DM	15	75	11	55	0.18⌊
HTN	7	35	6	30	0.73⌊
IHD	3	15	2	10	0.63⌊
Underlying chest disease	11	55	5	25	0.05⌊
COPD	5	25	1	5	0.07⌊
BA	3	15	2	10	0.32⌊
ILD	3	15	2	10	0.63⌊

Notes: The parametric data are presented as mean and standard deviation (SD), and categorical data as number and percentage (%). Group-A had significantly higher percentage of cases with history of underlying chest disease only. †Independent *t*-test; ⌊Chi-square test.

Abbreviations: Group-A, $NaHCO_3$ group; Group-B, urokinase group; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; COPD, chronic obstructive pulmonary disease; BA, bronchial asthma; ILD, interstitial lung disease; *n*, number; SD, standard deviation.

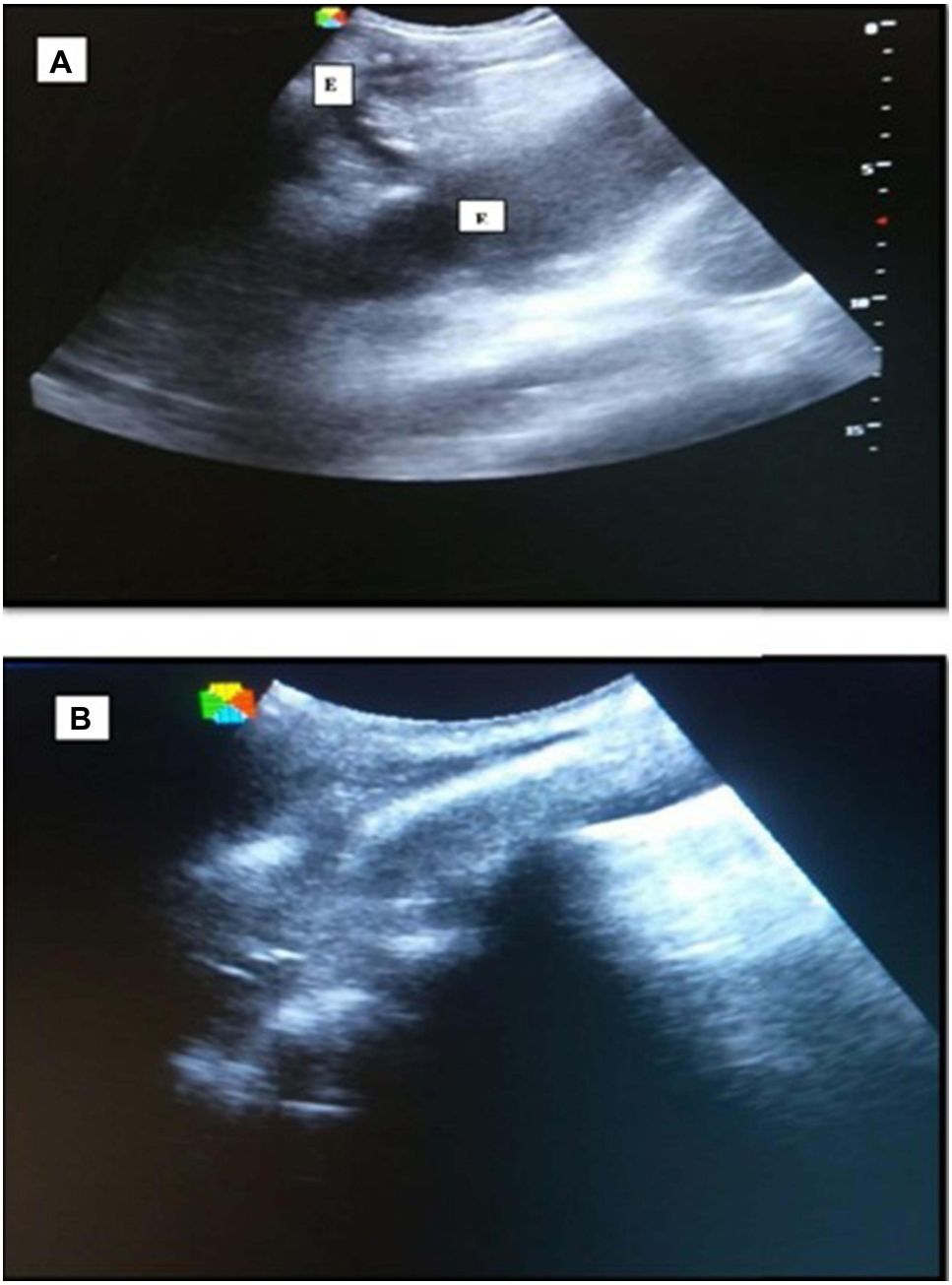

Figure 1 Thoracic ultrasound: (**A**) complex pleural effusion with loculation; (**B**) homogeneous effusion with septation after evacuation trial.

groups. The parametric data are presented as mean and standard deviation (SD), and categorical data as number and percentage (%), Table 3.

However, looking at the smaller rate of RTT failure of either $NaHCO_3$ or urokinase, the logistic regression model Table 4 showed that RTT–$NaHCO_3$ was insignificantly related to failure both in unadjusted and adjusted models, P=0.37 and 0.32, respectively, and only smoking habits increase the likelihood of failure 9-fold; OR=8.9, P=0.04 with respect to age, sex, and treatment methods.

Discussion

The risk of mortality among patients with pleural infection is higher, and it needs a strict and time-related treatment protocol to avoid the undesired surgery and complications.[7] The standard protocol for managing empyema is still undiscovered. The

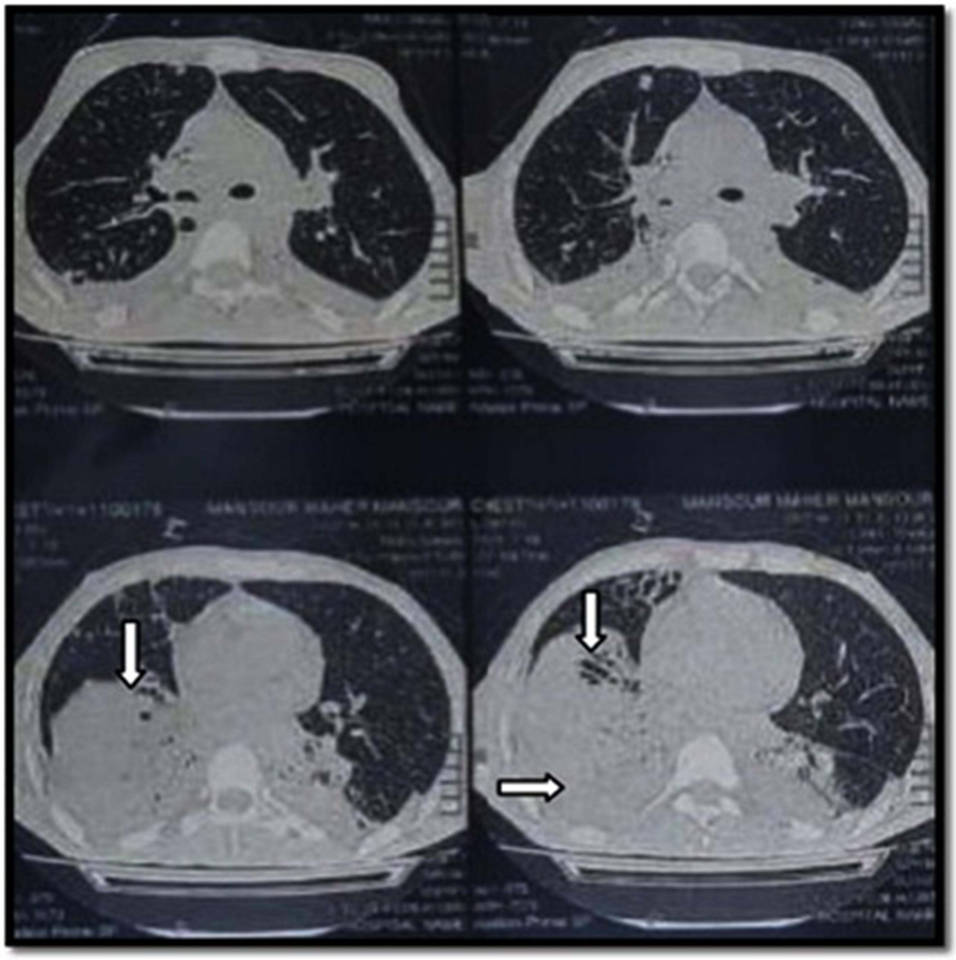

Figure 2 Chest computed tomography (CT). The arrows point to consolidation areas with air bronchogram and effusion.

present study aimed to introduce sodium bicarbonate as an add-on therapy in the treatment of complicated pleural infection, and we compared the performance of sodium bicarbonate with the previously used fibrinolytic agent "urokinase" regarding efficacy and safety. Urokinase as fibrinolytic agent had been used and evaluated in several observational studies as well as interventional trials with acceptable results regarding its efficacy and safety.[15–18] It was also associated with lower incidence

Table 2 Radiological and Biochemical Analysis of Infected Pleural Effusion

Factors	Group-A (*n*=20)		Group-B (*n*=20)		*P*
	Mean/*n*	SD/%	Mean/*n*	SD/%	
Location side					
LT	9	45	10	50	0.75[1]
RT	11	55	10	50	
Volume size					
Small (<1/3)	1	5	1	5	0.62[1]
Moderate (1/2)	11	55	8	40	

(*Continued*)

Table 2 (Continued).

Factors	Group-A (*n*=20)		Group-B (*n*=20)		*P*
	Mean/*n*	SD/%	Mean/*n*	SD/%	
Large (>2/3)	8	40	11	55	
Loculation	11	55	11	55	1[1]
Associated lung lesion	10	50	11	55	0.75[1]
Abscess	4	20	4	20	1[1]
Pneumonia	5	25	5	25	1[1]
Cystic lesion	1	5	2	10	0.5[1]
Effusion chemistry					
pH	6.95	0.164	6.955	0.161	0.92[†]
LDH	930	317	940	139	0.89[†]
Protein	4.125	0.265	4.27	0.325	0.13[†]
Glucose	16.5	8.06	19.15	8.22	0.31[†]
ADA (positive)	4	20	5	25	0.71[1]
Bacteriology					
Community acquired (yes)	8	40	10	50	0.52[1]
Gram-positive (yes)	10	50	5	25	0.11[1]
Gram-negative (yes)	5	25	9	45	0.18[1]
Anaerobic bacteria (yes)	8	40	14	70	0.05[1]
TB (yes)	3	15	2	10	0.63[1]

Notes: The parametric data are presented as mean and standard deviation (SD), and categorical data as number and percentage (%). [†]Independent *t*-test; [1]Chi-square test.
Abbreviations: Group-A, $NaHCO_3$ group; Group-B, urokinase group; LDH, lactate dehydrogenase; ADA, adenosine deaminase; TB, tuberculosis; *n*, number; SD, standard deviation.

Table 3 Treatment Complications and Outcomes

Factors	Group-A (*n*=20)		Group-B (*n*=20)		*P*
	Mean/*n*	SD/%	Mean/*n*	SD/%	
Duration of antibiotic (days)	19.35	3.28	20.75	4.96	0.3[†]
Complication					
Duration of fever (days)	6.85	2.76	6.55	3.33	0.75[†]
Hemothorax (yes)	1	5	4	20	0.15[1]
Iatrogenic pneumothorax (yes)	2	10	3	15	0.63[1]
ICU admission (yes)	1	5	3	15	0.29[1]
Outcome					
Success	16	80	18	90	0.37[1]

Notes: The parametric data are presented as mean and standard deviation (SD), and categorical data as number and percentage (%). [†]Independent *t*-test; [1]Chi-square test.
Abbreviations: Group-A, $NaHCO_3$ group; Group-B, urokinase group; *n*, number.

Table 4 Factors Associated with RTT Failure

Failure			
Factors	**OR**	**95% CI**	***P***
Unadjusted			
RTT–$NaHCO_3$	2.25	(0.3623, 13.9715)	0.37
Adjusted			
Age	0.96	(0.8905, 1.0450)	0.35
RTT–$NaHCO_3$	2.73	(0.3569, 20.9334)	0.32
Sex	0.24	(0.0251, 2.3746)	0.21
Smoking	8.94	(0.7651, 104.3946)	0.04
DM	0.74	(0.0831, 6.6039)	0.79
COPD	0.42	(0.0235, 7.5381)	0.55

Notes: For unadjusted model; Pearson; X^2=40, *P*=0.38. For adjusted model; Goodness-of-fit test: Hosmer–Lemeshow; X^2=3.29, *P*=0.91.
Abbreviations: OR, odds ratio; CI, confidence interval.

of bleeding and allergic response in comparison with streptokinase.[8,19] However, sodium bicarbonate solution has some potential properties regarding antithrombotic ability in addition to antimicrobial benefits.[20,21] The calcium ions are chelated by $NaHCO_3$, which subsequently inhibits the conversion of fibrinogen to fibrin.[20] As well, the antimicrobial ability of sodium bicarbonate may decrease the formation of bacterial biofilm, especially Gram-positive organisms as staphylococci, in addition to decreasing its adherence.[22] Furthermore, the ionic abundance of $NaHCO_3$ may alter the membrane permeability of the bacteria, which further leads to modification of their structure to become less viable.[23] The present data showed that the rate of successful thoracentesis in the $NaHCO_3$ group was 80% in comparison with 90% success rate in the urokinase group, with an insignificant difference, *P*=0.37. Additionally, considering undesired complications, bleeding during procedures had been recorded in only one case in the $NaHCO_3$ group, in contrast to 3 cases in the urokinase group. Moreover, iatrogenic pneumothorax was also recorded in 5 cases; 2 in the $NaHCO_3$ group and 3 in the urokinase group. The need for ICU admission was also recorded, with one case admitted in ICU in the $NaHCO_3$ group in contrast to 3 cases in the urokinase group. However, the differences between the two groups were insignificant, which means the capability of sodium bicarbonate in managing complicated pleural effusion was equal to the urokinase. The results regarding the efficacy of urokinase were supported by several studies,[15–19] but no previous study had used $NaHCO_3$ instillation with repeated thoracentesis as the present study. In spite of that, an Egyptian study suggested that the use of sodium bicarbonate lavage during medical thoracoscopy (MT) in treatment of complicated para-pneumonic effusion was beneficial, and the improvement rate reached 88%.[24] However, one of the strength points of our study was the use of sodium bicarbonate without invasive thoracoscopy, and even with frequent irrigation and thoracentesis, the overall outcome was acceptable. Another consideration that should be kept in mind, which made the sodium bicarbonate a potential alternative fibrinolytic agent, was its availability and affordability; additionally, its presence in different concentrations may open the window for future researchers to reach the optimal outcome. The current study had some limitation: the first was being a single-center study, which made some difference with other reports; the second was its small sample size, which made the generalization of the results much more restricted; however, more research using observational studies with larger cohorts was mandatory, in addition to designing a randomized control trial with a large scale of patients.

Conclusion

Sodium bicarbonate was a promising, affordable, and efficient fibrinolytic agent; it showed equal effectiveness and safety as urokinase in managing complicated pleural effusion.

Abbreviations

RTT, repeated therapeutic thoracentesis; SD, standard deviation; LDH, lactate dehydrogenase; tPA, tissue plasminogen activator.

Data Sharing Statement

The data sets utilized in this study are available upon reasonable request to the corresponding author.

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Disclosure

The authors declare no competing interests in this work.

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