Fu-Shan Xue, M.D., Nong He, M.D., Cheng-Wen Li, M.D. Beijing Friendship Hospital, Capital Medical University, Beijing, People's Republic of China (F.-S.X.). xuefushan@aliyun.com

This letter was sent to the corresponding author of the original article referenced above, with an invitation to submit a reply for publication. The author did not respond to the invitation.—Evan D. Kharasch, M.D., Ph.D., Editor-in-Chief

DOI: 10.1097/ALN.0000000000004451

References

1. Aarab Y, Ramin S, Odonnat T, Garnier O, Boissin A, Molinari N, Marin G, Perrigault PF, Cuvillon P, Chanques G: Pectoral nerve blocks for breast augmentation surgery: A randomized, double-blind, dual-centered controlled trial. Anesthesiology 2021; 135:442–53
2. Zhang Z, Xu H, Zhang Y, Li W, Yang Y, Han T, Wei Z, Xu X, Gao J: Nonsteroidal anti-inflammatory drugs for postoperative pain control after lumbar spine surgery: A meta-analysis of randomized controlled trials. J Clin Anesth 2017; 43:84–9
3. Dowell D, Haegerich TM, Chou R: CDC guideline for prescribing opioids for chronic pain–United States, 2016. JAMA 2016; 315:1624–45
4. Laigaard J, Pedersen C, Rønsbo TN, Mathiesen O, Karlsen APH: Minimal clinically important differences in randomised clinical trials on pain management after total hip and knee arthroplasty: A systematic review. Br J Anaesth 2021; 126:1029–37

(Accepted for publication November 15, 2022. Published online first on December 19, 2022.)

N-Acetylcysteine and Postoperative Atrial Fibrillation: Comment

To the Editor:

We read with interest the recent work of Amar *et al.*,[1] with the editorial by Karamnov and Muehischlegel[2] which demonstrated the feasibility and safety of an antioxidant, *N*-acetylcysteine, for the prevention of atrial fibrillation after thoracic surgery. We agree with Karamnov and Muehischlegel[2] that an anti-inflammatory approach using antioxidants reduces NADPH oxidase activity for postoperative atrial fibrillation, a plausible strategy for prophylaxis.[2] However, we have additional potential explanations for why there was no significant difference in the occurrence of postoperative atrial fibrillation in patients who did and did not receive perioperative *N*-acetylcysteine in the study of Amar *et al.*[1]

N-Acetylcysteine is an L-cysteine prodrug and glutathione precursor that, via L-cysteine conversion, helps scavenge oxygen-derived free radicals and binds metal ions into complexes, resulting in oxidative stress reduction.[3] However, as we showed in a previous study, which was done in rats and focused on the mesenteric artery, L-cysteine induces an oxygen-derived free radical, superoxide production mediated by NADPH oxidase in a high 95% oxygen condition.[4] In contrast, it does not cause redox derangement in a 50% oxygen mixture.[4] Therefore, the high oxygen exposure under one-lung ventilation during major thoracic surgery seems to cancel L-cysteine's beneficial role as a radical scavenger and to add oxidative stress. Nevertheless, we do not see any information regarding the inspiratory oxygen fraction in the work of Amar *et al.*,[1] and thus, *N*-acetylcysteine combined with a high oxygen condition during thoracic surgery may contribute to the results shown by Amar *et al.*[1] Also, previous studies indicated that a membrane-bound NADPH oxidase is the primary source of oxidative stress in human atrial fibrillation,[5] while inflammation (or cytokines) activates several subtypes of NADPH oxidase.[6] However, there are no clinically specific inhibitors of membrane-bound NADPH oxidase.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

The authors declare no competing interests.

Hiroyuki Kinoshita, M.D., Ph.D., Shingo Kawashima, M.D., Ph.D. Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan (H.K.). hkinoshi@krc.biglobe.ne.jp

DOI: 10.1097/ALN.0000000000004405

References

1. Amar D, Zhang H, Chung MK, Tan KS, Desiderio D, Park BJ, Pedoto A, Roistacher N, Isbell JM,

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/138/2/224/680482/20230200.0-00024.pdf by guest on 18 April 2024

Molena D, Milne GL, Meyers BF, Fischer GW, Rusch VW, Jones DR: Amiodarone with or without *N*-acetylcysteine for the prevention of atrial fibrillation after thoracic surgery: A double-blind, randomized trial. Anesthesiology 2022; 136: 916–26
2. Karamnov S, Muehischlegel JD: Inflammatory responses to surgery and postoperative atrial fibrillation. Anesthesiology 2022; 136:877–9
3. Pei Y, Liu H, Yang Yi, Yang Ya, Jiao Y, Tay FR, Chen J: Biological activities and potential oral applications of *N*-acetylcysteine: Progress and prospects. Oxid Med Cell Longev 2018: 2835787
4. Yasuda Y, Feng G-G, Li J, Nakamura E, Hayashi H, Sato M, Fujiwara Y, Kinoshita H: High oxygen modifies vasodilator effect of cysteine via enhanced oxidative stress and thromboxane production in the rat mesenteric artery. Pflugers Arch Eur J Physiol 2016; 468:1555–64
5. Kim YM, Zhang YH, Guzik TJ, Zhang YH, Zhang MH, Kattach H, Ratnatunga C, Pillai R, Channon KM, Casadei B: A myocardial Nox2 containing NAD(P)H oxidase contributes to oxidative stress in human atrial fibrillation. Circ Res 2005; 97:629–36
6. Takaishi K, Kinoshita H, Kawashima S, Kawahito S: Human vascular smooth muscle function and oxidative stress induced by NADPH oxidase with the clinical implications. Cells 2021; 10:1947

(Accepted for publication September 13, 2022. Published online first on November 4, 2022.)

N-Acetylcysteine and Postoperative Atrial Fibrillation: Comment

To the Editor:

We read the article by Amar *et al.*[1] with great interest. Their trial addressed whether *N*-acetylcysteine can prevent atrial fibrillation after thoracic surgery. A secondary analysis examined perioperative systemic markers of inflammation, oxidative stress, and the incidence of atrial fibrillation after discharge. We thank the authors for contributing to our understanding on this important topic. However, we have two questions regarding subgroup analysis.

First, the primary endpoint analysis included surgical procedures such as open thoracotomy, minimally invasive video-assisted thoracoscopic, robotic-assisted approaches, and Ivor Lewis esophagectomy. However, there was not a subgroup analysis by surgical modality. Of note, the incidence of postoperative atrial fibrillation is influenced by the extent of lung resection[2] and by the operative site (left more than right lobectomy).[3] Moreover, lobectomy removes more lung tissue than segmentectomy, which may induce myocardial hypoxia, thereby triggering atrial fibrillation.[2,4] A subgroup analysis of *N*-acetylcysteine effect according to surgical approach may be informative.

Second, the conclusion that *N*-acetylcysteine did not result in lower systemic markers of inflammation and oxidative stress should be interpreted with caution given the lack of power to identify these secondary outcomes. Perioperative drugs such as opioids and dexmedetomidine may affect intraoperative stress and inflammatory response. Oxycodone, for instance, has antioxidant and anti-inflammatory properties that protect against surgical stress by inhibiting the production of proinflammatory cytokines and lipid peroxidation.[5] Therefore, it would be of interest to perform a more comprehensive analysis of potential pharmacologic influence on the results.

Postoperative atrial fibrillation is an important clinical outcome in patients undergoing noncardiac thoracic surgery, and there is growing interest in its prevention and treatment. However, multiple factors contribute to postoperative atrial fibrillation and inflammatory response. If there is substantial heterogeneity of these risk factors in the study population, risk-stratified analysis is especially important for enhancing the credibility of clinical trials.

Research Support

Supported by Zhongshan City Social Welfare project No. 2020B1002.

Competing Interests

The authors declare no competing interests.

Junlin Wen, Ph.D., Weizhao Huang, M.D., Binfei Li, M.D.
Zhongshan People's Hospital, Zhongshan Hospital of Sun Yat-Sen University, Zhongshan, China (J.W.).
junlin1224med@163.com

DOI: 10.1097/ALN.0000000000004406

References

1. Amar D, Zhang H, Chung MK, Tan KS, Desiderio D, Park BJ, Pedoto A, Roistacher N, Isbell JM, Molena D, Milne GL, Meyers BF, Fischer GW, Rusch VW, Jones DR: Amiodarone with or without *N*-acetylcysteine for the prevention of atrial fibrillation after thoracic surgery:

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/138/2/224/680482/20230200.0-00024.pdf by guest on 18 April 2024

A double-blind, randomized trial. Anesthesiology 2022; 136:916–26
2. Ueda T, Suzuki K, Matsunaga T, Takamochi K, Oh S: Postoperative atrial fibrillation is less frequent in pulmonary segmentectomy compared with lobectomy. Gen Thorac Cardiovasc Surg 2018; 66:95–100
3. Xin Y, Hida Y, Kaga K, Iimura Y, Shiina N, Ohtaka K, Muto J, Kubota S, Matsui Y: Left lobectomy might be a risk factor for atrial fibrillation following pulmonary lobectomy. Eur J Cardiothorac Surg 2014; 45:247–50
4. Ishibashi H, Wakejima R, Asakawa A, Baba S, Nakashima Y, Seto K, Kobayashi M, Okubo K: Postoperative atrial fibrillation in lung cancer lobectomy—Analysis of risk factors and prognosis. World J Surg 2020; 44:3952–9
5. Cheng W, Wang M, Liu P, Zhao S, Liu X, Wang X: Protective effects of dexmedetomidine and oxycodone in patients undergoing limb ischemia–reperfusion. Med Sci Monit 2019; 25:9073–84

(Accepted for publication September 13, 2022. Published online first on November 4, 2022.)

N-Acetylcysteine and Postoperative Atrial Fibrillation: Reply

In Reply:

We thank Dr. Kinoshita and Dr. Kawashima,[1] and Dr. Wen, Dr. Huang, and Dr. Li[2] for their comments and their interest in our work. In the comments from Kinoshita and Kawashima,[1] they speculate that exposing our patients to a high fraction of inspired oxygen during one-lung ventilation negated the potential antioxidant effects of *N*-acetylcysteine during the 48 h after surgery. In our study, *N*-acetylcysteine was started only 1 to 2 h after the patient arrived at the postanesthesia care unit, where they had been receiving oxygen, by nasal cannula in most cases and occasionally by face mask, with varying degrees of inspired oxygen (typically in the range of 30 to 40%). In our practice, oxygen administration is usually titrated off as long as the patient is able to maintain an oxygen saturation measured by pulse oximetry greater than 94% on room air. Most lung-resection patients at our center are ambulating the day after surgery; among the patients in our study,[3] some were discharged from the hospital upon completion of 48 h of *N*-acetylcysteine or placebo infusions. Although Dr. Kinoshita's and Dr. Kawashima's work in experimental animals is very interesting, it cannot be assumed that these findings apply to humans, nor is it warranted to speculate on which of the mechanisms that they identify apply to postoperative patients.

Dr. Wen, Dr. Huang, and Dr. Li suggest the performance of a subgroup analysis by surgical modailty.[2] However, because of the small number of patients within the groups and the lack of power to do so, we did not perform a secondary subgroup analysis of the incidence of atrial fibrillation by type of surgery, whether open or minimally invasive. We have previously shown that the extent of lung resection affects the incidence of atrial fibrillation, and it is for this reason that we included patients who underwent anatomical lung or esophageal resection.[4] However, on the basis of our work—and the recommendations from the American Association for Thoracic Surgery task force on this topic—we disagree that the side of surgery affects the incidence of atrial fibrillation.[5,6] We also disagree with the authors' assertion that our finding of a lack of effect for *N*-acetylcysteine on inflammatory or oxidative stress markers is attributable to a lack of power. First, the number of patients in each of the randomized groups in our study was not small, and both groups were well balanced in terms of demographic and surgical characteristics. Second, all patients participated in an institutional enhanced recovery pathway and received similar intraoperative and postoperative opioid analgesics. Finally, the inflammatory and oxidative marker data were well distributed and did not require log transformation before statistical analysis. Considering that our use of *N*-acetylcysteine or placebo was intravenous over the course of 48 h and was started in the postanesthesia care unit long after intraoperative drugs, such as dexmedetomidine, were used, we do not believe that these pharmacologic agents influenced our findings.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

Dr. Jones serves as a consultant for AstraZeneca (Cambridge, United Kingdom) and on a Clinical Trial Steering Committee for Merck (Kenilworth, New Jersey). The other authors declare no competing interests.

David Amar, M.D., Mina K. Chung, M.D., David R. Jones, M.D.
Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, New York (D.A.). amard@mskcc.org

DOI: 10.1097/ALN.0000000000004407

References

1. Kinoshita H, Kawashima S: *N*-Acetylcysteine and postoperative atrial fibrillation: Comment. Anesthesiology 2023; 138:222–3

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/138/2/224/680482/20230200.0-00024.pdf by guest on 18 April 2024

2. Wen J, Huang W, Li B: *N*-Acetylcysteine and postoperative atrial fibrillation: Comment. Anesthesiology 2023; 138:223–4
3. Amar D, Zhang H, Chung MK, Tan KS, Desiderio D, Park BJ, Pedoto A, Roistacher N, Isbell JM, Molena D, Milne GL, Meyers BF, Fischer GW, Rusch VW, Jones DR: Amiodarone with or without *N*-acetylcysteine for the prevention of atrial fibrillation after thoracic surgery: A double-blind, randomized trial. Anesthesiology 2022; 136:916–26
4. Amar D, Zhang H, Tan KS, Piening D, Rusch VW, Jones DR: A brain natriuretic peptide-based prediction model for atrial fibrillation after thoracic surgery: Development and internal validation. J Thorac Cardiovasc Surg 2019; 157:2493–9.e1
5. Amar D, Roistacher N, Rusch VW, Leung DH, Ginsburg I, Zhang H, Bains MS, Downey RJ, Korst RJ, Ginsberg RJ: Effects of diltiazem prophylaxis on the incidence of atrial arrhythmias after thoracic surgery. J Thorac Cardiovasc Surg 2000; 120:790–8
6. Frendl G, Sodickson AC, Chung MK, Waldo AL, Gersh BJ, Tisdale JE, Calkins H, Aranki S, Kaneko T, Cassivi S, Smith SC, Darbar D, Wee JO, Waddell TK, Amar D, Adler D: 2014 AATS guidelines for the prevention and management of perioperative atrial fibrillation and flutter for thoracic surgical procedures: Executive summary. J Thorac Cardiovasc Surg 2014; 148:772–91

(Accepted for publication September 13, 2022. Published online first on November 4, 2022.)

Liposomal Bupivacaine *versus* Dexamethasone: Comment

To the Editor:

A recently published article in Anesthesiology reported results from a randomized trial that compared the analgesic effectiveness of interscalene brachial plexus block with liposomal bupivacaine to standard bupivacaine with perineural dexamethasone.[1] This article by Kim *et al.*[1] concluded that the two study drugs provided similar analgesia with no differences in opioid consumption. However, the article contains a statistical error that led to an incorrect conclusion on the primary outcome measure, and the relationship between pain intensity scores and opioid rescue medication was not fully considered.

In this blinded study, 112 adult patients undergoing ambulatory arthroscopic shoulder surgery were randomized to receive an interscalene brachial plexus block with either an admixture of 10 ml (133 mg) liposomal bupivacaine and 5 ml 5% bupivacaine or an admixture of 15 ml 0.5% bupivacaine and 4 mg dexamethasone. The primary outcome was the average numerical rating scale pain scores at rest during 72 h. The primary analysis evaluated whether liposomal bupivacaine was noninferior to bupivacaine with dexamethasone at a margin of 1.3 points.[2,3] Additional outcomes included opioid consumption, patient satisfaction, and duration of sensory and motor block at predefined time points up to 7 days postsurgery.

The article reported that the mean ± SD numerical rating scale pain score during the first 3 postoperative days was 2.4 ± 1.9 in the liposomal bupivacaine group and 3.4 ± 1.9 in the bupivacaine with dexamethasone group, with a mean difference of −1.1 (95% CI, −1.8 to −0.4; $P < 0.0001$ for noninferiority). The article concluded that liposomal bupivacaine was not superior to bupivacaine with dexamethasone (one-sided $P = 0.998$). However, this conclusion and associated P value are incorrect because the upper bound of the 95% CI for the difference between groups excludes 0 in favor of liposomal bupivacaine.[4] The P value of 0.998 actually corresponds to a test of superiority (with a null value of 0) for bupivacaine with dexamethasone over liposomal bupivacaine. The correct P value for a one-sided test of superiority of liposomal bupivacaine is 0.002, which is statistically significant. Therefore, the conclusion that the treatments provided similarly effective analgesia is not supported, because liposomal bupivacaine demonstrated both noninferiority and superiority to bupivacaine with dexamethasone. Notably, a treatment demonstrates superiority to a comparator when the CI excludes 0, even when a noninferiority study design is used (fig. 1).[5,6]

The analyses presented in the article by Kim *et al.*[1] did not consider the important relationship between pain intensity scores and rescue medication. Consider, for example, a clinical trial of two analgesics in which patients randomized to receive the less effective analgesic study drug required more opioid rescue medications to achieve satisfactory pain control. The difference between the treatment groups in pain intensity scores over time will be attenuated owing to greater rescue medication use in the group that received the less effective study drug. Therefore, assessments of analgesic effectiveness must consider both pain intensity scores and the amount of rescue medication that supplemented the study drug to achieve those scores.

The trial used a stepwise approach to opioid rescue pain medication based on patient-reported pain severity (*i.e.*, tramadol for mild or moderate pain and oxycodone or intravenous hydromorphone for severe pain). Kim *et al.*[1] noted that there were no significant differences in opioid consumption at specific time points (*i.e.*, in the postanesthesia care unit and on postoperative days 1, 2, 3, 4, and 7). However,

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/138/2/224/680482/20230200.0-00024.pdf by guest on 18 April 2024