Pounds of Prevention but Only Ounces of Cure

The Need for More Research on the Treatment of Postoperative Nausea and Vomiting

Jai N. Darvall, M.B., B.S., M.Epid., F.A.N.Z.C.A., F.C.I.C.M., Kate Leslie, M.B., B.S., M.D., F.A.N.Z.C.A.

Surprisingly, despite a plethora of trials examining postoperative nausea and vomiting prophylaxis in a variety of patients, surgeries, drug combinations, and doses, there has been very little research assessing treatment. This is especially amazing given the incidence of postoperative nausea and vomiting in patients who have not received prophylaxis (10 to 80% depending on risk) and the requirement for "rescue" after failed prophylaxis (up to 30% in high-risk patients).[1] Given the global volume of surgery, estimated at more than 300 million operations per annum, it is likely that, on any given day, hundreds of thousands of patients worldwide are vomiting, retching, or experiencing nausea after anesthesia. This has important implications for patients, anesthesiologists, and health services, and more research is urgently required.

"...there is a lack of high-quality, randomized controlled trials of postoperative nausea and vomiting treatment, with or without preceding prophylaxis..."

In this issue of the Journal, Habib *et al.*[2] report on rescue treatment with the dopamine antagonist amisulpride, an antipsychotic currently being reevaluated for antiemetic effects. They randomized 702 patients with postoperative nausea and vomiting after failed prophylaxis with 5 hydroxytryptamine-3 antagonists, dexamethasone, and/or scopolamine to a placebo, 5 or 10 mg of amisulpride. Complete response (defined as no emesis or rescue antiemetic for 24 h after administration, excluding emesis in the first 30 min) occurred in 42% of patients receiving 10 mg of amisulpride and 28% of patients receiving placebo (odds ratio, 1.8; 95% CI, 1.2 to 2.6). The 5-mg dose showed no significant benefit over placebo. This is the first randomized placebo-controlled trial proving the effectiveness of a rescue treatment for postoperative nausea and vomiting after failed prophylaxis with a different agent.

The reasons for the weak evidence base for postoperative nausea and vomiting treatment for this are multifactorial. Economics of scale are likely to appeal to the pharmaceutical industry; because many more units will be prescribed for prophylaxis than for treatment, clinical trials proving that an antiemetic is effective for prophylaxis rather than treatment may be more cost-effective. In addition, clinical trials assessing treatment need to enroll many more patients than will ultimately be randomized, particularly if effective prophylaxis is given and/or lower-risk patients are included. The cost of closely following patients who never develop postoperative nausea and vomiting may be considerable. This makes trials of old drugs even less attractive than trials of new ones. Finally, design of rescue treatment trials is complicated with respect to the choice of prophylactic drugs (which should be different from the treatment drugs) and the choice of an active or inactive comparator.

Despite these barriers, a handful of trials of the effectiveness of various postoperative nausea and vomiting treatments have been completed, mostly in the 1990s. A 2001 systematic review included 18 placebo-controlled trials in patients who did not receive prophylaxis.[3] Eleven of these trials tested 5 hydroxytryptamine-3 receptor antagonists, three tested propofol, and one trial each tested domperidone, midazolam, isopropyl alcohol vapor, and an neurokinin-1 receptor antagonist. The 5 hydroxytryptamine-3 receptor antagonists proved effective, with relative risks for early rescue ranging between 1.6 and 2.2 and numbers needed to treat ranging between 3.0 and 4.7. Evidence for the other treatments was limited by small numbers of patients.

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Accepted for publication October 31, 2018. From the Department of Anaesthesia and Pain Medicine, Royal Melbourne Hospital, Melbourne, Australia (J.N.D., K.L.); Royal Melbourne Hospital Clinical School (J.N.D.), Centre for Integrated Critical Care Medicine (J.N.D., K.L.), and Department of Pharmacology and Therapeutics (K.L.), Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, Australia; and Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia (K.L.).

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Even fewer prospective studies of rescue treatment after failed prophylaxis have been conducted. Habib and Gan[4] previously conducted a randomized controlled trial of ondansetron *versus* droperidol prophylaxis with nonprotocolized rescue treatment and demonstrated the benefit of promethazine compared with repeat administration of ondansetron or droperidol. This is consistent with other studies showing that rescue treatment after failed prophylaxis with an agent from the same class is ineffective. Finally, Meyer *et al.*[5] conducted a randomized controlled trial of 92 patients receiving two different 5 hydroxytryptamine-3 rescue medications for postoperative nausea and vomiting, with nonprotocolized prophylaxis (including 5 hydroxytryptamine-3 antagonists) administered in a quarter of the patients, and demonstrated the superiority of dolasetron over ondansetron. In summary, therefore, high-quality evidence for the effectiveness of many widely used drugs for rescue is lacking, particularly after failed prophylaxis.

Ethical dilemmas inevitably arise when studying an unpleasant event that has already happened, related to the use of placebos and the timing of subsequent treatment should the intervention fail. The thorny subject of placebo controls in antiemetic trials is longstanding, with arguments for and against dating back over 20 yr. Habib *et al.*[2] justify their use of a placebo because "no agent has previously been shown in a prospective trial to be more effective than placebo for treating postoperative nausea and vomiting in patients who have failed prophylaxis." While this is true, we would argue that an active comparator (such as a 5 hydroxytryptamine-3 antagonist) could have been considered, in light of the strong evidence that these agents are effective as prophylaxis and as treatment in patients who have not received prophylaxis and their extremely widespread use in clinical practice.[1] This would have involved protocolizing prophylaxis to exclude ondansetron as well as dopamine antagonists, leaving dexamethasone and a range of less commonly used drugs. Nevertheless, the authors have managed to conduct a trial that is rare in the modern era: comparison of a treatment for postoperative nausea and vomiting against placebo. Such studies are useful in helping inform noninferiority margins for future noninferiority trials of postoperative nausea and vomiting treatments (for which there is a pressing need); however, they do not provide us with an estimate of how well amisulpride compares with the drugs that we use daily in our clinical practice.

More high-quality research is required both to evaluate currently used antiemetics and to investigate novel treatments. Nonpharmacologic options deserve consideration. For example, only low-quality evidence exists for the effectiveness of aromatherapy, with uncertainty about whether patients receiving aromatherapy need fewer antiemetic medications for treatment of postoperative nausea and vomiting. A similar lack of high-quality evidence exists for acupuncture, with studies almost exclusively assessing its role in prevention rather than treatment. Future research into treatment for postoperative nausea and vomiting should also seek to evaluate specific issues. Many previous trials have focused on emesis, possibly because nausea is considered a less severe symptom and is more difficult to measure. We believe that investigators should follow the admirable lead of Habib *et al.*[2] and assess the effect of treatment on nausea and emesis separately, because the effect of rescue medication on each may differ. We also commend Habib *et al.*[2] for measuring nausea on an ordinal scale, rather than as a binary outcome. As any sufferer of nausea will attest, there are "many shades of green." Improvements to the work of Habib *et al.*[2] for future studies could include protocolizing antiemetic prophylaxis to ensure precise application of the guidelines,[1] the prespecification of statistical testing of secondary endpoints, health economic assessment, and inclusion of more patient-reported outcomes, such as quality of recovery and patient satisfaction.

In conclusion, there is a lack of high-quality, randomized controlled trials of postoperative nausea and vomiting treatment, with or without preceding prophylaxis, despite such medication being administered to tens of millions of patients globally each year. Habib *et al.*[2] have demonstrated that amisulpride is effective when compared with placebo as a rescue antiemetic after failed prophylaxis with drugs from a different class. This study addresses a huge gap in our clinical evidence base, and more such research is urgently required.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Leslie: kate.leslie@mh.org.au

References

1. Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, Watcha M, Chung F, Angus S, Apfel CC, Bergese SD, Candiotti KA, Chan MT, Davis PJ, Hooper VD, Lagoo-Deenadayalan S, Myles P, Nezat G, Philip BK, Tramèr MR; Society for Ambulatory Anesthesia: Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2014; 118:85–113
2. Habib A, Kranke P, Bergese S, Chung F, Ayad S, Siddiqui N, Motsch J, Leiman D, Melson T, Diemunsch P, Fox G, Candiotti K: Amisulpride for the rescue treatment of post-operative nausea and/or vomiting in patients failing prophylaxis: A randomized, placebo-controlled phase III trial. Anesthesiology 2019; 130:203–12

3. Kazemi-Kjellberg F, Henzi I, Tramèr MR: Treatment of established postoperative nausea and vomiting: A quantitative systematic review. BMC Anesthesiol 2001; 1:2
4. Habib AS, Gan TJ: The effectiveness of rescue antiemetics after failure of prophylaxis with ondansetron or droperidol: A preliminary report. J Clin Anesth 2005; 17:62–5
5. Meyer TA, Roberson CR, Rajab MH, Davis J, McLeskey CH: Dolasetron *versus* ondansetron for the treatment of postoperative nausea and vomiting. Anesth Analg 2005; 100:373–7

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George S. Bause, M.D., M.P.H., Honorary Curator and Laureate of the History of Anesthesia, Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.