Bleeding risk and dexamethasone use in children undergoing tonsillectomy

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BLEEDING RISK AND DEXAMETHASONE USE IN CHILDREN UNDERTAKING TONSILLECTOMY

To the Editor: Dr Gallagher and colleagues1 examined the risk of bleeding associated with dexamethasone administered to children undergoing tonsillectomy. The authors concluded that dexamethasone was not associated with bleeding requiring reoperation, using a noninferiority threshold of 5%.

Gallagher et al1 applied the same threshold of 5% to all bleeding end points (any bleeding, bleeding requiring rehospitalization, reoperation due to bleeding) to indicate noninferiority. We agree that an increase of 5% in level I bleeding (any bleeding) might not necessarily be of clinical relevance. However, an increase of 5% in level III bleeding (ie, those needing a reoperation) is quite different.

Bleeding after tonsillectomy requiring reoperation is a potentially life-threatening complication and therefore constitutes major harm. It is an important difference if 0.6% (as reported in their placebo group) or 5.6% of children need to be reoperated on; this difference in event rates corresponds to a number needed to harm of 20. We believe that for this end point, the inferiority margin should have been set at a lower level (eg, 1.5%), which would have required a much larger number of patients to be randomized.

In addition, the study by Gallagher et al1 strictly avoided nonsteroidal anti-inflammatory drugs (NSAIDs), presumably because of their additional bleeding risk. However, after tonsillectomy, the increase in the risk of reoperation due to bleeding when exposed to NSAIDs has been shown to be about 1.6% (an increase from 1.1% with placebo to 2.7% with NSAIDs).2

The study by Gallagher et al1 fails to prove that dexamethasone is safe in children undergoing tonsillectomy; we share the viewpoint of Plante et al3 that systemic steroids should not be used routinely in this setting.

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In Reply: In noninferiority trials, the margin of noninferiority must be determined based on both statistical reasoning and clinical judgment.1 We think both criteria were satisfied in our study. The chief concern by Dr Czarnetzki and colleagues was that the same noninferiority threshold of 5% was applied to all bleeding end points and that this level was too high for level III bleeding. These concerns were at the center of our decision to choose level III bleeding rates as our primary end point and to power the study based on these rates and not on the comparison between the means of all types of bleeding events.

Our approach to developing the noninferiority margin combined composite data from the literature, institutional data, and clinical experience. We sought to balance the preponderance of benefit of a single dose of perioperative dexamethasone with the potential implications of a bleeding event leading to a return to the operating room. All of these factors combined resulted in a noninferiority margin of 5%.

The selection of a noninferiority margin is crucial to the study design and we acknowledge that various arguments exist to select a tighter margin. However, we feel that this is an acceptable level in our health care system given the ready access to care during the postoperative period and the relative infrequency of postoperative bleeding requiring operative intervention.

We did not use NSAIDs in our protocol to ensure uniformity across surgeons. At the time of trial development, the surgeons in our study used NSAIDs postoperatively in variable ways. We acknowledge the reported hemorrhage concern with NSAIDs, but also note that the American Academy of Otolaryngology–Head and Neck Surgery recently recommended that NSAIDs be considered in postoperative pain management strategies.2 In the interest of standardization at the time of study design, we elected to not use NSAIDs.

The decision of whether to use perioperative dexamethasone in children undergoing tonsillectomy is a balance be-

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between the potential benefits and harms. We believe that the small additional risk that might be incurred due to a single dose of perioperative dexamethasone is balanced by the well-documented postoperative benefits.

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Disclaimer: The views expressed in this letter are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the US government.

To the Editor: Dr Bangalore and colleagues1 reported that the use of β-blockers was not associated with a lower risk of composite cardiovascular events in patients with coronary artery disease (CAD) risk factors only, known prior myocardial infarction (MI), or known CAD without MI. We agree that the effectiveness of a drug may be altered when diagnosis and treatment advance over time. For example, today CAD less often leads to necrotic and scarred myocardium than decades ago.1 However, we have concerns about this study.

First, it is unusual to perform an observational study to assess the effectiveness of a drug when large RCTs and meta-analyses already have shown its effectiveness.2 In observational studies, treatment groups may differ in prognosis, and correction of unknown or unmeasured prognostic characteristics (confounders) is difficult. Observational studies are meant for generating hypotheses or detecting rare adverse effects but not for assessing effectiveness. Initially, the authors mentioned that “the analyses were exploratory in nature,” but later they suggested that their results could change clinical practice.

Second, only 36% of patients with β-blocker use and 74% without β-blocker use were included in the propensity score–matched analysis, accepting a caliper width of 0.6 SD of the propensity. Even with a very large caliper (0.2 is common in propensity score–matched analyses),3 only about half of all patients could be matched. This suggests that patients in whom β-blockers were likely to be effective based on clinical judgment instead were excluded. The online tables showed important effect modification by heart failure in the group of patients with a known MI, with a hazard ratio of 0.75 for all-cause mortality with β-blocker use.

Third, exact exposure should be defined to allow insight into whether immortal time bias could have occurred.4 Fourth, it would have been better to present a time-dependent analysis and not ever vs never β-blocker use because exposure to a drug will not be constant over time.

Fifth, bias due to unobserved confounding, notably by atrial fibrillation, renal dysfunction, or chronic obstructive pulmonary disease, cannot be ruled out.

To provide an answer to the question of whether β-blockers are no longer effective in reducing cardiovascular disease and mortality in the modern era of reperfusion plus statin and antiplatelet use, an RCT is needed rather than an observational study.

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