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Letter to the Editor

Letter to Editor: Intraarticular Vancomycin Reduces Prosthetic Infection in Primary Hip and Knee Arthroplasty

Dear Editor,

Burns et al. recently published their study titled "Intra-articular Vancomycin Reduces Prosthetic Infection in Primary Hip and Knee Arthroplasty," which investigated the clinical benefits of intraarticular antibiotic (IAA) vancomycin solution in reducing periprosthetic joint infection (PJI) rates after total knee arthroplasty (TKA) and total hip arthroplasty (THA).[1] This was a retrospective observational study of a single-surgeon case series, with data extraction from the Australian Orthopaedic Association National Joint Registry. The study design involved the definition of a "pre-intraarticular antibiotic" cohort and a cohort receiving IAA, and comparison of surgical site infection/PJI rates between the 2 cohorts. Surgeries were performed by the same surgeon, but across 4 different surgical centers. The study concluded that intraarticular vancomycin solution reduced infection rates after primary hip and knee arthroplasty, as reflected in the study title. However, in light of our own experience from a large volume randomized controlled trial, we are skeptical about the results and inferences drawn from this retrospective study. Our concerns are described in following sections.

Firstly, there seems to be heterogeneity in perioperative protocols over the period that surgeries were performed. Most cases received intravenous vancomycin in both groups, in addition to IV cefazolin, which is not a widely accepted regimen. Even so, it is mentioned in the discussion that the use of IV vancomycin was stopped after the findings of the Australian Surgical antibiotic prophylaxis trial. However, it is not clear whether this change occurred after this study period and whether every patient in the retrospective review received the same prophylaxis over time. There is again confusion regarding the differential use of IV vs topical tranexamic acid in this study population, which needs to be clarified.

Second, it is mentioned that all knee and hip prostheses were cemented using tobramycin impregnated cement, which is again not standard practice in the world, and is a major confounding factor. The use of antibiotic impregnated cement can potentially alter local concentrations of antibiotics, and theoretically reduce SSI/PJI risk. Most of the world practices uncemented THAs, where this approach is not applicable and hence findings of the study may not be generalizable.

Third, there are some concerns with the results and their interpretation. In Table 2 by Burns et al [1], the Australian Orthopaedic Association National Joint Registry data showed that for the pre-IAA period of January 2010 and December 2017, 489 TKAs were performed with 6 revisions for infection (1.2%), and 694 THAs were performed with 5 revisions for infection (0.7%); and in the IAA group, there were no infections in 214 TKRs and 1 infection in 517 THAs (0.2%). While the incidence of PJI was significantly reduced for all joints that underwent a procedure in the IA group ($P = .03$), separate analyses for TKA ($P = .11$) and THA (0.19) approached but did not reach significance. There was no statistically significant difference when comparing the cohorts individually with regard to TKA or THA. However, the authors claimed a statistically significant reduction in PJI when looking at combined reduction for all joints ($P < .05$). The difference seems very marginal, and combining hip and knee complications to justify statistical significance is not appropriate, as individually there is no difference when knee PJI or hip PJI are considered separately.

The ideal statistical test for assessment would be a Fisher exact test for the PJI comparison tables which have small sample frequencies of less than 5. The chi-square reported *P*-values for TKA and THA separately failed to demonstrate any statistically significant difference and even when looking at a combined reduction in PJI using a chi-square test with Yates correction gives a value of 0.068 which is statistically insignificant. The high number needed to treat value of 111.1 signifies that the intervention is unlikely to have any positive impact in the outcomes.

Recent publications have commented on the fragility of statistical analyses pertaining to low incidence complications such as PJIs.[2,3] Fragility Index and Fragility Quotient may be better modalities to assess the trend of PJI in all future research. Hence, the results have to be interpreted with caution. The discussion mentions the systematic review by Heckmann et al., and that it reported significant reductions in PJI with the use of intrawound vancomycin.[4] However, that was not the conclusion of that review. They actually reported that it may be beneficial; however, the studies included in that review are all retrospective with a low quality of evidence. That is the reason why that same review called for level-1 evidence in the form of a randomized controlled trial to help establish higher quality evidence on this important topic.

In our own experience, which is one of the only published randomized controlled trials on the topic of local antibiotic powder, we found no clinical benefit and increased complications with the use of vancomycin. Vancomycin was an independent risk factor to develop prolonged wound drainage and wound healing issues.[5] Another prospective study on the efficacy of vancomycin powder in THA, also had worse outcomes in the local antibiotic group with vancomycin powder.[6] The authors of the study under discussion also published their report on the safety of intraarticular vancomycin solution in arthroplasty, reporting that is safe without

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renal toxicity and high local concentrations.[7] Whether the use in solution form is superior to the powder form and/or reduces PJI rates, and safety from a wound healing perspective have to be evaluated with a large volume randomized controlled trial in the future.

Considering the factors discussed above, attributing the very small difference in PJI rate reported to the use of vancomycin solution seems far-fetched. Future studies should be adequately powered, prospective, randomized, and with very strict inclusion/exclusion criteria with standard perioperative protocols. The study title and conclusion are misleading, and the results do not truly support the statement that intraarticular vancomycin reduces PJI rates after hip and knee arthroplasty. It is important to strive for reductions in PJI rates; however, surgeons must keep antibiotic stewardship in mind before implementing changes in prophylactic practices to prevent the danger of antimicrobial resistance.

Conflicts of Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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CRediT authorship contribution statement

Praharsha Mulpur: Writing – review & editing. **Tarun Jayakumar:** Validation, Writing – original draft. **A.V. Gurava Reddy:** Supervision, Writing – review & editing.

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