Puzzling posology: was the bevacizumab regimen in recurrent glioblastoma misreported?


In those early days, the optimal bevacizumab dosage in this indication was still uncertain, and physicians proceeded cautiously, especially in real-world practice. Consequently, some initially dosed bevacizumab at 5 mg/kg fortnightly, as Virginia Stark-Vance had in her seminal study;\(^7\) they subsequently raised the dose to 10 mg as data from larger Phase II clinical trials accrued.\(^1,2,4–8\)

However, while researching the topic, I was puzzled that the aforementioned JNS paper by Ali et al. reported bevacizumab being dosed at 5 mg or 10 mg per square meter (m\(^2\)) every 2 weeks,\(^1\) rather than per kilogram (kg) body weight, as is standard and labelled (https://www.gene.com/download/pdf/avastin_prescribing.pdf). It is surely an elusive typographic error; nevertheless, it would be worthwhile publishing a formal erratum, not only to correct the scientific record, but also to avoid potential confusion or inadvertent propagation by other non-experts besides myself who refer to that paper.

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References

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Is preoperative hypoalbuminemia really a risk factor associated with acute kidney injury and mortality after brain tumor surgery?

TO THE EDITOR: With interest, we read the article of Kim et al.\(^1\) assessing the association of preoperative hypoalbuminemia with acute kidney injury (AKI) and mortality after brain tumor surgery in a retrospective study (Kim K, Bang JY, Kim SO, et al: Association of preoperative hypoalbuminemia with postoperative acute kidney injury in patients undergoing brain tumor surgery: a retrospective study. J Neurosurg [epub ahead of print May 5, 2017].

\(^{1}\) Kim et al. J Neurosurg 128:1260–1272, 2018
According to the multivariable logistic regression analysis and Cox proportional hazards model used in the study, these authors show that a preoperative serum albumin level of < 3.8 g/dl is independently associated with postoperative AKI and mortality. Strengths of this study are a relatively large sample size and its use of appropriate statistical methods to determine the association of preoperative serum albumin level with postoperative AKI. Given that AKI is significantly associated with increased mortality rate after neurosurgery, the findings of this study have potential implications. However, this study is a retrospective analysis, which potentially introduces a number of confounding variables. Other than the limitations described in the discussion section of the paper, we note several issues of this study that were not well addressed.

First, one main aim of this study was to assess the association of preoperative hypoalbuminemia with postoperative AKI. However, patients were arbitrarily stratified into two groups based on preoperative serum albumin levels (< 3.8 g/dl and ≥ 3.8 g/dl). In clinical practice, the cutoff value of serum albumin level used for diagnosis of hypoalbuminemia is < 3.5 g/dl. That is, this study actually does not evaluate the association of true preoperative hypoalbuminemia with postoperative AKI. Thus, it would be better if the title of the article was changed to “Association of preoperative serum albumin levels with postoperative AKI in patients undergoing brain tumor surgery.”

Second, the multivariable logistic regression analysis showed that preoperative hemoglobin level was not an independent risk factor for postoperative AKI. However, only comparing mean preoperative hemoglobin levels between patients with preoperative serum albumin levels < 3.8 g/dl and ≥ 3.8 g/dl may have limited clinical value for prediction of postoperative AKI. In fact, preoperative anemia is highly prevalent in patients undergoing noncardiac surgery and has been shown to be an important risk factor for postoperative AKI. Furthermore, postoperative anemia is also strongly associated with AKI after noncardiac surgery. In a comparison with patients who did not have a decrease in postoperative hemoglobin, a decrement of 1.1–2.0 g/dl was associated with an adjusted hazard ratio (HR) for AKI of 1.51 (95% confidence interval [CI], 1.15–1.98), and a decrement of ≥ 4.0 g/dl with an adjusted HR of 4.7 (95% CI 3.6–6.2) for AKI.

Third, in this study, intraoperative lowest mean arterial pressure (MAP) was recorded and was significantly different between patients with two preoperative serum albumin levels, but was not identified as a risk factor for postoperative AKI. Most importantly, the readers were not provided with the occurrences of intraoperative hypotension, which is a known causative factor of postoperative AKI. The available evidence indicates that even a short duration of an intraoperative MAP < 55 mm Hg can result in postoperative AKI. In particular, the combination of intraoperative anemia, transfusion, and hypotension can synergistically act to increase the risk of postoperative AKI.

Fourth, this study showed that a preoperative serum albumin level of < 3.8 g/dl was independently associated with postoperative mortality. We noted that the median follow-up duration for the overall patient population was 4.1 years, and 36.5% of patients underwent glioma and metastatic tumor operations. However, the types of brain tumors were not included in the multivariable Cox proportional hazards model identifying independent risk factors for postoperative survival. In fact, patients with a preoperative serum albumin level < 3.8 g/dl were older and were more likely to have hypertension and diabetes mellitus, and have a lower preoperative hemoglobin level than patients with a preoperative serum albumin level ≥ 3.8 g/dl. In our opinion, no matter how refined the adjustment is for differences in health status and comorbid burden, it is never possible to ensure a complete adjustment for differences between patients with two preoperative serum albumin levels. A preoperative serum albumin level < 3.8 g/dl may be only an overall manifestation of worse health status and greater comorbid burden that can markedly increase postoperative morbidity and mortality. A “kitchen-sink” approach of adjusting for all available variables using multivariable analysis may lead to overadjustment and therefore bias the true effects of a lower preoperative serum albumin level itself on postoperative mortality. Thus, we argue that great caution must be taken when interpreting the association between a preoperative serum albumin level of < 3.8 g/dl and postoperative mortality, as it has great inherent bias that cannot be overcome by statistical adjustment.

**References**