Perioperative Use of Gabapentinoids: Comment

To the Editor:

It was a pleasure to read the article from Verret *et al.* in a recent issue of Anesthesiology.[1] The main prerequisites of a high-quality systematic review were met; however, some considerations about the patient, intervention, comparison, and study design approach applied and the conclusion of the review must be addressed. The main outcomes of the meta-analysis pooled results of highly divergent procedures, from endoscopic procedures to major surgeries. A relevant issue in both the Enhanced Recovery after Surgery and the Perioperative Surgical Home doctrines is the specificity of surgical route standardization.[2,3] The possibility of another analgesic regiment being used in the comparator group is another concern. The use of gabapentin was compared with antidepressants, opioids, ketamine, nonsteroidal anti-inflammatory drugs, corticosteroids, benzodiazepines, neuroleptics, anticonvulsant, α_2-adrenergic receptor agonists, paracetamol, melatonin, and placebo. The use of each of these agents incites completely different conclusions, and—with the exception of the placebo—would not give any idea about the effectiveness of the studied intervention when pooled.

Beyond the clinical heterogeneity, the statistical heterogeneity is also a major issue. The inconsistency (I^2) over 75% (considerable heterogeneity according the Cochrane Handbook for Systematic Reviews of Interventions) found in every acute and subacute pain summary measure of the review confirms the previous considerations.[4] Its high level of statistical heterogeneity is considered a prohibitive feature when considering performing a meta-analysis in many systematic review protocols and raises many concerns about the conclusions of the review announced by the authors. That statistical heterogeneity must dictate how the results are understood and reflects the aforementioned clinical heterogeneity.

The inclusion of unequal study populations and comparison groups increased the precision of the estimates, while it also reduced the applicability of the results. The low certainty of evidence rated for the primary outcomes implies that the true effect is probably markedly different from the estimated effect.[5] The assumption that further research is unlikely to change the conclusion about the effectiveness of gabapentinoids in early postoperative analgesia is consistent with the trial's sequential analysis, but does not contemplate the clinical and statistical heterogeneity between the included studies.

Competing Interests

The author declares no competing interests.

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Perioperative Use of Gabapentinoids: Comment

To the Editor:

Gabapentinoids, including gabapentin and pregabalin, bind to the α2δ1 subunit of calcium channel (α2δ1) to relieve neuropathic pain.[1] Although gabapentinoids are among the most effective medications to treat chronic neuropathic pain,[2] their use in managing postoperative acute pain has been controversial. A recent meta-analysis of 281 randomized controlled trials by Verret *et al.* shows that gabapentinoids do not provide clinically significant analgesic effect for postoperative acute pain.[3] It would be of great interest to discuss the potential mechanism behind why gabapentinoids have limited effect in postoperative acute pain.

α2δ1 is constitutively expressed in dorsal root ganglion. Its expression is greatly induced after nerve injury,[4] and the upregulated α2δ1 is transported from dorsal root ganglion sensory neurons to spinal cord.[5] Because α2δ1 is a subunit of the voltage-activated Ca^{2+} channel complex, it has been postulated that gabapentinoids work through modulating Ca^{2+} channels. However, gabapentinoids do not alter the activity of Ca^{2+} channels, suggesting that the effect of gabapentinoids in treating pain is independent from the regulation of Ca^{2+} channel activity.[6,7]

Chen *et al.* recently discovered a novel mechanism through which gabapentinoids relieve neuropathic pain.[7] They found that α2δ1 binds to *N*-methyl-D-aspartate (NMDA) receptor in both rodent and human to enhance its activity in spinal cord after nerve injury, and gabapentin prevents α2δ1-mediated NMDA receptor hyperactivity.[7] Importantly, baseline α2δ1 does not facilitate spinal cord NMDA receptor activity, but the upregulated α2δ1, like after nerve injury, is associated with the enhanced spinal cord NMDA receptor activity and neuropathic pain behavior.[7] Notably, α2δ1 does not contribute to the acute pain immediately after nerve injury. In preclinical models, it takes up to 2 days for α2δ1 to be fully upregulated after nerve injury,[4] and knocking down α2δ1 has no effect on neuropathic pain behavior within the first 2 days after nerve injury, even though it attenuates pain behavior at later time points.[7] Taken together, Chen *et al.* have revealed a new mechanism in which gabapentinoids reduce neuropathic pain by inhibiting spinal cord NMDA receptor hyperactivity mediated by upregulated α2δ1.

The role of the NMDA receptor in many pain conditions, including postoperative pain, has been well recognized.[8] The interaction between α2δ1 and the NMDA receptor explains why gabapentinoids are effective in treating chronic neuropathic pain, but not postoperative acute pain. In chronic neuropathic pain, α2δ1 is upregulated to enhance NMDA receptor activity in spinal cord to produce neuropathic pain, and gabapentinoids prevent the interaction between the upregulated α2δ1 and NMDA receptor to relieve neuropathic pain. In healthy uninjured state, the interaction between baseline α2δ1 and the NMDA receptor is minimal, and gabapentinoids have no influence on baseline NMDA receptor activity in spinal cord. It takes time for α2δ1 to be fully induced after injury, so during the perioperative period it is likely that α2δ1 remains at or near baseline level with minimal interaction with the NMDA receptor. As a result, perioperative gabapentinoids, especially administered before surgical injury, have limited effects on spinal cord NMDA receptor activity to reduce acute pain immediately after surgery. Furthermore, as gabapentin treatment does not prevent α2δ1 upregulation after nerve injury,[5] it is also unlikely that perioperative gabapentinoids can prevent chronic postoperative pain, consistent with meta-analysis from Verret *et al.*[3]

In conclusion, gabapentinoids disrupt the interaction between the upregulated α2δ1 and NMDA receptor to inhibit spinal cord NMDA receptor hyperactivity in treating chronic neuropathic pain. As the acute postoperative pain precedes injury-induced α2δ1 upregulation, and gabapentinoids have no effect on the NMDA receptor without α2δ1 upregulation, perioperative gabapentinoids do not have clinically significant impact on postoperative pain.

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Competing Interests

The authors declare no competing interests.

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Perioperative Use of Gabapentinoids: Reply

In Reply:

We thank Dr. Araujo[1] for his interest on our systematic review about the perioperative use of gabapentinoids for the management of postoperative acute pain.[2] The main purpose of a systematic review with meta-analyses is to synthesize treatment effects considering all available data. By pooling data from different trials, the power to detect a differential effect is increased. Trials included in a systematic review frequently present some degree of clinical heterogeneity. However, not considering these trials in pooled analyses, as suggested by Dr. Araujo, would diminish our collective ability to both answer important research questions and understand the modifiers of important treatment effects.

In our systematic review, we carefully considered potential sources of clinical heterogeneity among the included trials. First, we performed subgroup analyses to explore whether clinical heterogeneity or methodologic aspects of included trials could explain our findings and the observed statistical heterogeneity. As such, if a differential effect existed based on clinical factors, this effect would have been observed. We observed no such influence according to the type of drug used, dose regimen, duration of the intervention, type of surgery, or postoperative care pathway. We also observed that statistical heterogeneity was minimally attributable to the type of coanalgesia and the risk of bias in trials. The type of comparator was also not associated with the direction and magnitude of the treatment effect. Importantly, 90% of the trials included in our systematic review were conducted with placebo and not with an active comparator. Second, to mitigate the influence of heterogeneity, we used random effect models for our analyses. These models consider that results from individual trials may deviate from the true intervention effect due to sampling error and further assume that sources of variance may explain differences in effect across trials.

We also evaluated the certainty of the evidence based on Grading of Recommendations Assessment, Development, and Evaluation methodology, the recommended approach in knowledge synthesis methods.[3] Accordingly, the summary estimates of our primary outcomes measure were considered to be of low certainty, meaning that the true effect may be different to the one observed. We must, however, understand that the certainty of the evidence in this instance was downgraded by the high proportion of trials at high or unclear risk of bias. Considering that trials at low risk of bias showed a smaller treatment effect (or none at all) of the intervention, it is thus very plausible that our results overestimate the true analgesic effect of gabapentinoids. Since the observed effect is already shown to not be clinically significant and our trial sequential analyses demonstrated that our sample size was substantially larger than the required sample size to evaluate the observed effect, additional trials evaluating the analgesic effect of the perioperative use of gabapentinoids are not required.

We also thank Drs. Su and Guan[4] for their interest in our work on the perioperative use of gabapentinoids.[2] The hypothesis raised in their letter explaining the absence of a clinically significant analgesic effect of gabapentinoids for the management of postoperative acute pain is interesting and is in accordance with our findings.

The main mechanism of action of gabapentinoids is hypothesized to be the binding of $\alpha_2\delta$-1 subunit of calcium channel in the central nervous system and the dorsal root ganglion.[5,6] The absent or minimal upregulation of $\alpha_2\delta$-1 subunit in the acute perioperative period is an interesting hypothesis that could explain the lack of clinically significant analgesic effect from gabapentinoids for the management of acute pain condition. Although the exact role of the minimal upregulation from $\alpha_2\delta$-1 in the postoperative period is unknown, we agree that this concept deserves further considerations.

Competing Interests

The authors declare no competing interests.

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Fasting Duration and Blood Pressure in Children: Comment

To the Editor:

We read with interest the article by Simpao *et al.*[1] regarding the association between clear fluid fasting duration and postinduction low blood pressure in anesthetized children. In this retrospective analysis, the authors reported that, among children (0 to 18 yr) who underwent inhalational induction of anesthesia for elective surgical procedures, longer duration of clear fluid fasting was associated with increased risk of postinduction low blood pressure during the surgical preparation. Despite the clinical relevance of the topic and the elegant study design, certain methodologic issues require clarification.

First, although the exposure (fasting duration) was collected as a continuous variable, the authors transformed this continuous variable into categorical groups using some clinically useful, though arbitrary, cutpoints. The statistical limitations of this approach must be highlighted. As elegantly assessed by the authors, the association between clear fasting time and low blood pressure was not linear. In this setting, percentile categorizations can misrepresent the dose–response relationship between the exposure and outcome because instead of accounting for the nonlinearity, the cutpoints are merely identified according to the distribution of the primary predictor.[2,3] This may result in the lumping together of subjects with different risks of low blood pressure, thus violating the assumption of no differences in risk of the outcome between groups. For instance, children in the 6- to 8-h group had a 22% (1.55/1.27) relative higher odds of low blood pressure, relative to children in the 4- to 6-h group, yet both groups have been lumped into the 4- to 8-h category. Similarly, children in the 10- to 12-h group had a 17% (1.16/0.99) relative higher odds of low blood pressure, relative to children in the 8- to 10-h group, yet both groups have been lumped into the 8- to 12-h category. These departures of 22% and 17% appear to be meaningful, given the context of the study, because the highest relative excess in the odds ratio was 33%. In addition, the authors adopted an open-ended categorization of patients with clear fasting time greater than 12 h (alternatively greater than 14 h in the sensitivity analysis). This cutpoint of 12 h (14 h in the sensitivity analysis) may be too far from the most extreme value and may hide important effects. For example, the risk of low blood pressure among children with clear fasting time greater than 18 h (corresponding to about 2.5% of the study population) is unknown because it was averaged with those of the other children in the greater than 12-h group.

Second, it appears that about 60% of the study cohort received coinduction of anesthesia with propofol or an intravenous opioid, and 12% of subjects received a neuraxial block (type not stated). Given that propofol coinduction and neuraxial anesthesia are known causes of hypotension under anesthesia, the observed associations do not disambiguate the effect of fasting from the expected hypotensive effects of propofol and/or neuraxial anesthesia. Therefore, the interpretation of the authors' findings would benefit from a sensitivity analysis by separating patients who received propofol from their counterparts who did not receive propofol.