opioid-sparing effects, the resultant analgesia is short-lasting and of questionable clinical significance in the management of opioid-naive surgical patients.

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# Ketamine Analgesia: Not All Patients or Surgeries Seem to Be Equal

## To the Editor

I read with a great interest the recent article of Brinck et al[1] with the accompanying editorial from Bhatia et al.[2] Brinck et al[1] deserve praise for their impressive work, indeed the largest published study (189 patients) among randomized, controlled studies aimed to detect a putative, preventive effect of perioperative ketamine infusions, that is, intended to avoid persistent postsurgical pain. Not less than 24 such studies have been conducted since the seminal work of de Kock et al[3] in 2001, only 1, but using ketamine added within a PCA regimen, claiming a bigger cohort (352 patients).

Yet this very sophisticated work, as Bhatia et al[2] write, raises more questions than it provides answers. I am not sure that starting the ketamine infusion long before the beginning of surgery would have significantly changed the final results: it has been demonstrated that ketamine has no preemptive effect, that is, its administration before incision is not more effective than after incision.[4] This is the consequence of the so-called use-dependence: the ketamine molecule can rich the PCP site only if the canal of the NMDA receptor has been previously opened, which is presumably not the case before the beginning of surgery, especially in opioid-naive patients. In contrast, pursuing the infusion after the surgery, on the first or even the second postoperative day may perhaps have been of value.

But the most intriguing fact is that Brinck et al[1] choose to administer a very high dose of ketamine; the highest dose administered within the above-mentioned studies, in fact. As often pointed out, ketamine studies are difficult to compare, because administration schemes are always completely different, making heterogeneity the rule. That is why I undertook a work simulating the obtained ketamine plasmatic concentrations for each administration scheme of the 24 above-mentioned studies (Figure). This makes the comparison possible within the shambles of quite heterogenous boluses, infusion rates, and durations of administration. The calculations use the Domino pharmacokinetic model, available to download as a Microsoft Excel tool on the Demed website (http://www.demed.be/downloads.htm).

On average, when ketamine "works" (ie, results in a significant decrease of persistent postsurgical pain, 8 studies), plasmatic concentrations attained during surgery, and maintained afterward, are significantly higher (nearly double area under the curve, Mann-Whitney *U* test: $P < .001$), than in negative studies (16 studies), raising the interesting possibility of a dose effect. Indeed, the recent Podcast study showed that a single bolus (1 $mg \cdot kg^{-1}$) at the beginning of surgery is unable to decrease postoperative pain or postoperative opioid needs.[28]

But what is obvious, is that in some instances (series, patients, surgery… surgeons?) even high concentrations do not work at all. This is the case for the Dualé et al[29] study, where the ketamine bolus was 1 $mg \cdot kg^{-1}$ and infusion rate 1 $mg \cdot kg^{-1} \cdot h^{-1}$ with an infusion of 1 $mg \cdot kg^{-1} \cdot 24\ h^{-1}$ maintained for 3 days.[29] And this is also the case for Brinck et al[1] study, were esketamine presumably twice as potent as racemic ketamine, was used, providing a perioperative concentration equivalent to >500 $ng \cdot mL^{-1}$ of racemic ketamine. A lack of statistical power may be invoked, but most probably, as Dualé points out, ketamine cannot prevent neuropathic pain induced by surgical damages of the nerves! In contrast, some studies convey positive results, where ketamine concentrations are at the bottom of the therapeutic range (20 $ng \cdot mL^{-1}$ in Suzuki's study[5]), raising the possibility of false-positive results (type 1 errors).

In conclusion, we should probably consider that perioperative ketamine efficacy is based on efficient plasmatic concentrations (at least 100 $ng \cdot mL^{-1}$)[30]

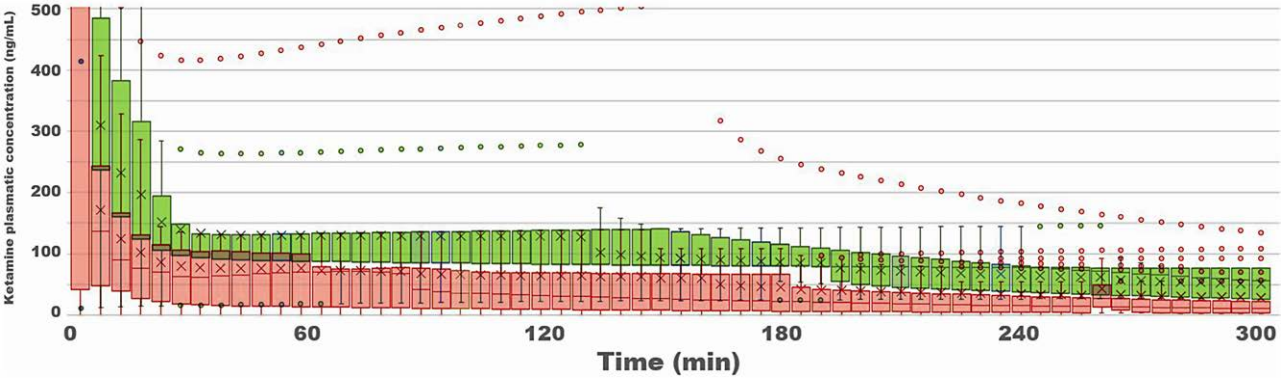


**Figure.** Ketamine plasmatic concentrations have been simulated for 5 h (intraoperative and early postoperative periods) according to the Domino model for each study administration scheme. The median, first and third quarters, and extreme values are represented as box-plots. The crosses represent the weighed means taking into account each study size. A total of 226 patients received ketamine in the 8 positive studies (De Kock et al,[3] Suzuki et al,[5] Perrin and Purcell,[6] Remérand et al,[7] Aveline et al,[8] Nielsen et al,[9] Liu et al,[10] Kang et al[11]) and 694 in the 16 negative studies (Katz et al,[12] Hayes et al,[13] Dualé et al,[14] Ryu et al,[15] Joseph et al,[16] Mendola et al,[17] Wilson et al,[18] Crousier et al,[19] Sveticic et al,[20] Dullenkopf et al,[21] Sen et al,[22] Spreng et al,[23] Bilgen et al,[24] Peyton et al,[25] Shanthanna et al,[26] Czarnetzki et al[27]). The concentrations provided in the positive studies (green) are significantly higher ($P < .001$) than those provided in the negative studies (pink), but extreme values show that some studies escape the average behavior.

maintained during the entire surgical procedure and presumably during the early postoperative period, with the sad reality that some patients or surgeries will sometimes not benefit from perioperative ketamine administration.

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## In Response

We thank Professor White[1] and Professor Mion[2] for their interest in our study on ketamine.[3] It is an honor to acknowledge the early contribution of Professor White[1] to the still-ongoing effort to clarify the clinical disposition of ketamine in acute postoperative pain. Ketamine trials on postoperative pain are difficult to compare, because administration schemes often vary, resulting in high clinical heterogeneity. Additionally, there are very few multiple-dose studies.[3] Ketamine is said to be more efficient in conditions with more intense pain.[4] Therefore, we pursued evaluating the effect of 2 different doses of intraoperatively administered S-ketamine on analgesic outcomes and adverse events after lumbar fusion surgery, a type of surgery that is often followed by severe postoperative pain.[5] We chose an intraoperative administration regimen over a single preincisional dose as it is postulated that ketamine requires an opened *N*-methyl-D-aspartate-receptor channel to adhere the phencyclidine binding site.[6] However, intraoperative intravenous S-ketamine during lumbar fusion surgery failed to show any benefit on postoperative pain outcomes in opioid-naive patients. This finding is contradictory to the earlier lumbar surgery studies, where ketamine has been shown to have an effect in patients with a previous opioid use.[7]

We wholeheartedly agree with Professor Mion[2] that all patients and all surgeries are not alike: patient characteristics, such as earlier exposure to opioids, amount of tissue and nerve damage and other surgical factors, and the concentration of ketamine isomers and metabolites in circulation and in the effect site are important determinants of the effect on postoperative pain. We believe that there are still unanswered questions regarding the analgesic effects of ketamine. Recently, Robu and Lavand'homme[8] suggested targeting the affective component of pain with ketamine, possibly enhancing postoperative recovery.[6] This could be achieved by exploring ketamine among those surgical patients with known psychological risk factors for pain and who therefore are more susceptible to intense postoperative pain.

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