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## Ketamine in PCA: what is the effective dose?

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### EDITOR:

Although adding ketamine to patient-controlled analgesia (PCA) with morphine has proven to be safe and has shown numerous advantages, like significant lessening of morphine consumption or lessening of opioid adverse effects, these beneficial effects are far from constantly encountered. The recent randomized study of Aubrun and colleagues published in the Journal did not show any advantage of adding 0.5 mg ketamine to a 1 mg morphine bolus during postoperative period of major gynaecological surgery [1].

Javery and colleagues first found, in 1996, a significant lessening of pain scores (2.3 vs. 4.5) and of morphine consumption (51 vs. 26 mg) when ketamine was directly added to the morphine PCA using a syringe (ketamine and morphine, 1 mg mL<sup>-1</sup> each). Morphine sparing resulted in less nausea, itching and urinary retention [2]. Again in 1999, a randomized study by Adriaenssens and colleagues detected a significant lessening of mean morphine consumption – 28 vs. 54 mg during the first postoperative 48 h. Ketamine was not added into the PCA, but as a 2.5 µg kg<sup>-1</sup> min<sup>-1</sup> infusion [3]. There was significantly less nausea in the ketamine group. The study by Guignard and colleagues in 2002 showed that a ketamine bolus dose of 0.15 mg kg<sup>-1</sup> followed by an infusion of 2 µg kg<sup>-1</sup> min<sup>-1</sup> reduced perioperative remifentanyl consumption and morphine

consumption (46 vs. 69 mg) in the postoperative period following abdominal surgery [4].

However in 2001, a double-blind randomized trial by Reeves and colleagues concluded that small-dose ketamine combined with PCA morphine (ketamine and morphine, 1 mg mL<sup>-1</sup> each) provided no benefit to patients undergoing major abdominal surgery. Analgesic efficacy was not improved, neither was opioid consumption, but patients in the ketamine group performed worse in cognitive testing and had a relative risk of experiencing vivid dreams of 1.8 [5]. In 2002, Murdoch and colleagues did not find any benefit in the addition of ketamine to morphine in PCA for gynaecological surgery [6].

The well-designed study of Aubrun and colleagues contributes to the controversy. As the authors stated, several facts may explain the negative findings. Pain levels in the control group were not very high and morphine consumption was rather low (perhaps because of the concomitant use of a non-steroidal anti-inflammatory drug). As a consequence, the NMDA (*N*-methyl-D-aspartate) channel was not likely to stay in the open state. But we do think that the main problem resides in the chosen ketamine bolus of 0.5 mg mL<sup>-1</sup>. Since ketamine dosing is closely linked to morphine PCA consumption, it may be predicted that the less the morphine consumption, the less the ketamine administration. Actually, patients received a mean dose of 44 ± 16 mg ketamine during the 48 postoperative first hours in Aubrun and colleagues's study. Because, in the smallest dose range the ketamine effective dose is not less than 2 µg kg<sup>-1</sup> min<sup>-1</sup>, equivalent to 6–10 mg h<sup>-1</sup> in patients weighing 50–80 kg, we suggest that no effect could be expected from a dose of less than 1 mg h<sup>-1</sup>.

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The absence of any psychic side-effect clearly supports such an explanation.

In most studies, the ketamine dose associated with morphine in PCA must be regarded as very low. We do not share Svetcic and colleagues's conclusions [7] that a combination of morphine with ketamine should be in a ratio of 1:1. We believe that an effective ketamine dose should probably be in the 5–10 mg h<sup>-1</sup> range. On the other hand, clinical daily practice may teach us that boluses as small as 5 mg may rarely result in significant psychological side-effects. From these pragmatic considerations, we conclude that the ketamine bolus dose associated with a PCA bolus of 1 mg morphine should probably average 3 mg. We actually have an experience, although limited, with this dosage, which occasionally results in marked sedation, but seems quite effective.

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