

Adding Midazolam to Ketamine in the Pediatric Emergency Department – It Doesn't Add Up

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Ketamine is widely used in the emergency department to facilitate painful procedures in children. Important adverse events associated with ketamine include respiratory depression (hypoxia, apnea and laryngospasm), emergence reactions (recovery agitation, hallucinations and “bad dreams”) and vomiting. Co-administration of benzodiazepines, most commonly midazolam, has been touted to reduce the incidence of the unpleasant emergence reactions associated with ketamine use.

In the current issue of *Indian Pediatrics*, Dilli, *et al.*(1) report on their randomized, controlled trial comparing ketamine alone to ketamine plus midazolam given intravenously to 99 children undergoing lumbar puncture in a pediatric emergency department in Ankara, Turkey. They conclude that the combination of ketamine plus midazolam compared to ketamine alone was superior in terms of shorter onset of sedation (2.6 versus 3.4 minutes, $P=0.01$), reduced emergence reactions (6.3% versus 19.6%, $P=0.04$) and higher parental satisfaction ($P=0.001$, no specific data reported). They also note that adding midazolam to ketamine did not increase the frequency of adverse event and there was a trend towards reduced nausea/vomiting (14.6% versus 27.5%, $P=0.08$).

Should clinicians routinely add midazolam to ketamine when used intravenously to sedate children for painful procedures? The results of this study by Dilli, *et al.* seem to indicate that we should. Let us briefly explore other published pediatric ketamine trials to help shed additional light on this question.

Two randomized, controlled trials have previously been published comparing ketamine with

and without midazolam in children in the emergency department setting(2,3). Both reported no measurable benefit of such adjunctive therapy with midazolam in preventing emergence reactions. Sherwin, *et al.*(2) randomized 104 children to receive adjunctive midazolam versus placebo during ketamine sedation. No difference was found between the treatment groups in the incidence of recovery agitation(2). Wathen, *et al.* (3) randomized 266 children sedated with intravenous ketamine to receive midazolam intravenously or no midazolam. They found that the overall incidence of emergence phenomena was not affected by the addition of midazolam. However, the addition of midazolam was associated with a 6-fold increase in the incidence of agitation (35.7% versus 5.7%) in children >10 years of age. Also, the addition of midazolam led to an increased incidence of hypoxia (7.3% versus 1.6%), but a decreased incidence of emesis (9.6% versus 19.4%). Finally, no significant difference in parental or physician satisfaction was reported between the two treatment groups.

Roback, *et al.* (4) retrospectively reviewed 2,609 sedations performed in their pediatric emergency department. Similarly, they found that respiratory adverse events were more common with the combination of ketamine/midazolam compared to ketamine alone (odds ratio [OR] 1.72; 95% confidence interval [CI] 1.11-2.65) and vomiting was less frequent (OR 0.50, 95% CI 0.30-0.85). In the study by Dilli, *et al.*(1), there was definitely a trend towards increased oxygen desaturation, increased hypotension, and reduced nausea/vomiting in the ketamine plus midazolam group.

We should remain cautious in interpreting the conclusions of Dilli, *et al.* Although they report statistically significant faster onset of sedation with

the combination of ketamine plus midazolam compared to ketamine alone, the difference of 0.8 minutes is not clinically significant, given the additional time required to draw up and administer the adjunctive agent. Also, the reported onset of action of ketamine of 3.4 minutes in the Dilli, *et al.* study is significantly longer than that commonly reported for ketamine (30-45 seconds)(5).

Despite the findings of Dilli, *et al.*, the preponderance of the evidence from larger trials in the medical literature does not support the routine addition of midazolam to intravenous ketamine sedation. Although such adjunctive use does appear to reduce the rate of emesis associated with ketamine sedation, it does not appear to reduce the frequency of emergence reactions and it increases adverse respiratory events(6). Nevertheless, a large multi-institutional study or meta-analysis of prior ketamine trials will be necessary to definitively put this issue to rest. In the meantime, clinicians seeking to reduce the incidence of emesis associated with ketamine sedation should consider administering ondansetron 0.15 mg/kg(7).

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