Ketofol for Procedural Sedation Revisited: Pro and Con

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Ketamine and propofol are both core emergency department (ED) procedural sedation agents.[1] Their concurrent administration—referred to by the portmanteau "ketofol"[2]—is widespread and based on an alluring premise of synergy. Ketamine is sympathomimetic and could theoretically mitigate propofol-associated respiratory depression and hypotension. Propofol is a sedative with antiemetic properties and could hypothetically counter the ketamine-associated recovery agitation and emesis. Furthermore, ketamine adds analgesia to the purely sedative action of propofol.[2]

In 2011, we debated the merits of the ketofol combination.[2] Subsequently, 2 large, well-designed, randomized, controlled trials[3,4] have provided compelling evidence on which to substantively advance this discussion. We therefore update these pro and con positions, with our preexisting biases against (S.M.G.), for (G.A.), and neutral (B.S.K.). Summary arguments are show in the Figure.

PREVIOUS EVIDENCE

The research before the 2 new trials, summarized elsewhere,[2] consists of multiple smaller and often nonblinded studies that have generally found that adding ketamine to propofol permits lower total doses of propofol to be administered and causes less hypotension, with similar procedural efficacy and provider satisfaction.

Two randomized controlled trials[5,6] have shown conflicting results about airway and respiratory adverse events. David and Shipp[5] found no differences in respiratory events between ketofol and propofol and, secondarily, observed a trend toward more consistent sedation depth with ketofol. Messenger et al[6] observed significantly fewer respiratory events with ketofol compared with propofol; however, this result is confounded because the propofol-only group received a large dose (1.5 μg/kg) of fentanyl 2 minutes before propofol administration, resulting in an unusually high incidence of oxygen desaturation (77%). Typical recommendations advise not to administer opioids and propofol concurrently because of the known potentiation of respiratory depression.[7]

TWO NEW TRIALS

In a recent randomized double-blind trial, Andolfatto et al[3] compared ketofol 1:1 versus propofol alone and found similar efficacy, patient satisfaction, and provider satisfaction. They observed a similar incidence of airway and respiratory adverse events, and of hypotension leading to treatment. The ketofol group had slightly more recovery agitation (7% versus 0%) and required significantly less repeated dosing during the procedure (20% versus 44%), lending support to the earlier suggestion by David and Shipp[5] of more consistent sedation depth. Andolfatto et al[3] also observed a trend toward slightly longer recovery time with ketofol (8 versus 6 minutes).

In this issue, Miner et al[4] report a meticulous 3-arm randomized trial comparing propofol alone with 2 different ketofol formulations: 1:1 and 1:4 ketamine to propofol. They found the 3 groups to be similar in terms of airway and respiratory adverse events, efficacy, patient-reported pain or recall, and patient satisfaction. They observed that the nadir systolic blood pressure was slightly higher with either ketofol formulation (both 122 mm Hg) compared with propofol (115 mm Hg) and that recovery time was slightly shorter for propofol: 6 minutes versus 10 and 8 minutes for 1:1 and 4:1 ketofol, respectively. There was more recovery agitation in the 1:1 group: 21% versus 8% and 10% for propofol and 4:1, respectively. The investigators were unable to reproduce the evidence of more consistent sedation described by David and Shipp[5] and Andolfatto et al.[3]

These new studies update areas of previous uncertainty. First, ketofol does not reduce airway and respiratory adverse events relative to propofol—even with different formulations. Second, in healthy adult ED patients the reduction of hypotension is slight and any such hypotension rarely leads to intervention. Third, ketofol recovery time appears slightly longer than with propofol. Fourth, patient satisfaction is similar no matter which agent

Pro

Ketofol is safe and effective in the ED setting and mitigates propofol-induced hypotension, providing an extra level of reassurance for patients with impaired cardiovascular reserve. The analgesia provided by ketamine obviates the need for and inherent risks of coadministered opioids, whereas propofol blunts ketamine-associated emesis.

Con

Multiple randomized controlled trials confirm that ketofol does not provide superior sedation to propofol and does not reduce clinically important adverse effects. Indeed, adding ketamine complicates things (why 2 drugs rather than 1?) and can cause recovery agitation. Why use ketofol when propofol is just as safe and effective?

Figure. Summary arguments for ketofol sedation.

or formulation is used. Fifth, the data about sedation depth consistency are conflicting, and ketofol introduces ketamine-associated recovery agitation in some patients.

Given this new evidence, what are the best current arguments for ketofol pro and con?

PRO ARGUMENT

Ketofol is well established as a safe and effective ED deep sedation strategy. Ketamine adds analgesia to propofol sedation without the hypoventilatory synergy that results from coadministered opioids; thus, with ketofol emergency physicians can provide deep sedation equivalent to that with propofol but without worry about suboptimal analgesia or ketamine-associated emesis because propofol is antiemetic.

Ketofol successfully blunts propofol-induced hypotension, which, although rarely problematic in healthy patients, may present risk to those with impaired cardiovascular reserve or volume depletion. Ketofol thus may be advantageous in the elderly, or in settings of trauma, hypovolemia, sepsis, or other serious infections. This is corroborated by a recent study in which ketofol improved anesthesia induction hemodynamics in elderly patients, with less need for blood pressure support.[8]

The accumulation of ketamine, relative to propofol, from repeated ketofol boluses is not clinically important because recovery times with ketofol are only slightly longer compared with those with propofol (median of 2 to 4 more minutes). Such extended effect may be clinically advantageous for procedures requiring more prolonged painful stimulation (eg, abscess incision and drainage, cast molding) and may lessen the need for repeated sedative boluses.

Of the 3 trials examining sedation depth consistency, one found ketofol to be superior,[3] one noted a trend in this direction,[5] and the third had a negative result.[4] Thus, the balance of the literature tilts toward improved sedation consistency with ketofol.

In summary, emergency physicians facile with ketamine and propofol can use the features of each component drug to adapt to specific clinical circumstances. Ketofol does not present any hazards relative to propofol and exhibits theoretical advantages. Further focused research will help to define specific benefits for ketofol in ED practice.

CON ARGUMENT

The evidence shows that ketofol demonstrates no compelling advantage over propofol. Ketofol does not provide superior sedation and does not reduce clinically important adverse events, but adds complexity (why 2 drugs when monotherapy is just as good?) and introduces ketamine-specific adverse events.

The evidence of more consistent sedation observed by David and Shipp[5] and Andolfatto et al[3] was not confirmed by Miner et al[4] at either 1:1 or 4:1 dosing and would appear to represent a modest attribute of unclear clinical importance. Furthermore, providers and patients are just as happy with propofol.

The hemodynamic effects of ketofol are clinically unimportant in healthy patients because the observed blood pressure differences are trivial[4] and do not alter ED interventions for hypotension.[3] Propofol-induced hypotension is essentially always transient in patients without serious underlying disease.[4] Although reports suggest safety for ketofol in the elderly,[3] there are theoretical risks of ketamine's exacerbating underlying coronary artery disease.[9]

Propofol and opioids should not be coadministered to avoid hypoventilatory synergy; however, this does not require adding ketamine. Instead, opioids can be titrated before the procedure to attain sufficient analgesia.[3,7]

The pharmacokinetic basis for coadministration is controversial because propofol is shorter acting than ketamine. Repeated ketofol boluses may result in high total doses of ketamine, which may prolong sedation.

In summary, ketofol is effective and not harmful; however, emergency physicians should not assume that adding ketamine provides any objective benefit over propofol. It is possible that researchers will ultimately identify subsets of patients for whom ketofol may present a measurable advantage; however, there is no evidence to confirm this.

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