Ketofol for Procedural Sedation? Pro and Con

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In an old Reese’s Peanut Butter Cups television commercial, 2 snacking pedestrians collide and their respective treats—peanut butter and chocolate—inadvertently mix. Both parties sample the blend with unexpected pleasure, and the narrator then pitches the slogan, “Two great tastes that taste great together.” Ketamine and propofol are 2 extremely common agents used for emergency department (ED) procedural sedation, with each having well-documented safety and efficacy. But do these 2 drugs work better together?

The combination of ketamine and propofol, referred to by the portmanteau “ketofol,” is currently all the rage. According to Internet and physician buzz, a large number of EDs in North America have adopted this combination as their primary sedation regimen. Much of this popularity has been fueled by anecdote rather than solid research. This is reminiscent of the dramatic entry of propofol a decade ago into emergency medicine, in which clinical application surged far ahead of the science. Ultimately, the original enthusiasm for propofol was properly validated, but will ketofol enjoy the same outcome? Other popular anecdotal therapies were later discredited, eg, aminophylline for asthma, antishock trousers for traumatic hypotension, high-dose epinephrine in cardiac arrest.

The concept of ketofol has immediate allure because of its intriguing synergistic premise. These 2 completely different sedatives exhibit clinical features that appear to balance each other’s deficits. Propofol is a superb sedative but lacks the analgesia that ketamine can amply provide. Respiratory depression and hypotension are the principal adverse events of propofol; perhaps the sympathomimetic ketamine mitigates them. Vomiting and hallucinatory recovery reactions are the principal adverse events of ketamine; perhaps the antiemetic and hypnotic properties of propofol mitigate them.

In this editorial, we debate the pros and cons of ketofol, with our preexisting biases against (S.M.G.), for (G.A.), and neutral (B.K.). Summary arguments are show in the Figure.

PREVIOUS ED EVIDENCE

Four ED ketofol case series1-4 studies and 1 randomized controlled trial5 predate this issue of Annals.

The authors of the 4 observational case series describe their experiences favorably and relate efficacy and safety parameters typical of other ED sedation regimens (Table 1). All 4 case series report near-perfect satisfaction ratings from staff or parents.

A key observation from these studies is the use of individual doses lower than typical monotherapy with either drug (Table 1). Deep sedation with propofol alone often begins with 1 mg/kg and ultimately requires 1.5 to 2 mg/kg or more6,7; however, with ketofol these authors performed painful procedures with half of this dosing. When ketamine is used alone, 1.0 to 1.5 mg/kg is typically required to attain the dissociative state8; however, in these series doses well below this, and frequently subdissociative, appear sufficient. Such lower dosing could be explained in 2 ways: either there is synergy between the 2 drugs or these authors might be satisfied with lighter sedation. Although the latter option seems unlikely, given the high satisfaction scoring, a major limitation of these case series is their absence of sedation depth documentation.

In a small previous ED randomized controlled trial, Messenger et al9 found fewer adverse events with ketofol compared with propofol (Table 2). However, this result is difficult to interpret because the control group received a large dose of fentanyl (1.5 μg/kg) 2 minutes before propofol administration, resulting in an unusually high incidence of oxygen desaturation (77%). Typical recommendations are to not administer opioids and propofol concurrently because of their known potentiation of respiratory depression.6

PREVIOUS EVIDENCE FROM OUTSIDE THE ED

Ketofol research outside the ED setting is difficult to interpret because of a confounding diversity of settings, indications, doses, comorbidities, and patient age ranges. The controlled trials are essentially all small and underpowered and at substantial risk of bias caused by nonblinding because it is difficult to mask the characteristic nystagmus and muscular hypertonicity of ketamine.
Ketofol is nothing more than standard propofol sedation in which fentanyl analgesia is replaced with subdissociative ketamine. There is no compelling evidence that the combination reduces respiratory depression or produces superior sedation to either drug alone and no evidence that its effect on hemodynamics and total propofol dose is clinically important. Why not use just 1 drug instead of 2? 

**Figure.** Summary arguments for ketofol sedation.

Regarding efficacy, the non-ED studies show no compelling evidence that ketofol provides superior sedation quality relative to propofol monotherapy.\(^9,10\) Seven small controlled trials of ketofol versus propofol alone support the concept of synergy because similar sedation quality could be achieved with lower doses of propofol and ketamine.\(^11-17\) Three other trials, however, failed to confirm such an effect.\(^18-20\)

Regarding safety, the most consistent and convincing data from these non-ED reports are that the sympathomimetic effects of ketamine blunt propofol-induced hypotension or prevent it altogether.\(^11,13,16,18,21,22\) However, the importance of this effect appears limited because the magnitudes of the observed differences were small\(^9\) and transient propofol-induced hypotension is rarely of clinical consequence even without ketamine.\(^6,7,23\)

Respiratory depression is the far more important propofol-associated adverse event, but here the non-ED data are conflicting. Four studies found no difference in airway and respiratory adverse events between ketofol and propofol\(^15,16,18,21\) and 2 others found only subclinical capnographic or oximetry changes.\(^14,19\) In a dose-response study, ketamine had no influence on the dose of propofol required to cause apnea.\(^16\) Two meta-analyses describe these data as inconclusive.\(^9,10\) Ketamine should not be expected to independently offset propofol-induced respiratory depression, for although it preserves spontaneous ventilation, it is not a respiratory stimulant.\(^8\) Rather, any lessened respiratory depression with ketofol should be attributable to a reduced total propofol dose.\(^11,12,14,15\)

Two non-ED reports observed more negative effects with ketofol compared with propofol that can be attributed to adding ketamine, ie, recovery agitation,\(^15,20\) nausea and vomiting,\(^20\) and delayed discharge.\(^20\)

**NEW EVIDENCE**

In this issue of *Annals*, there are 2 well-designed ED randomized controlled trials that shed substantial light on the relative merits of ketofol (Table 2). One compares ketofol with ketamine alone,\(^24\) and the second, to propofol alone.\(^25\) These trials echo the main themes from the 3 previous ED case series that ketofol is effective, safe, and satisfying to providers. Indeed, the paramount outcomes of procedural success and respiratory depression were statistically similar in both trials.

In their comparison of ketofol to ketamine alone for pediatric fracture reduction, Shah et al\(^23\) observed that ketofol significantly reduced total sedation time by 3 minutes, a difference unfortunately of minimal clinical importance. Of more practical interest, however, was that there was less vomiting, with an estimated number needed to benefit of 10 (95% confidence interval 6 to 50). Accordingly, propofol appears comparable to ondansetron in reducing ketamine-associated vomiting.\(^26\)

In the second trial, David and Shipp\(^25\) compared ketofol to propofol and, like Shah et al,\(^24\) observed similar procedural success and safety. As has been previously reported in non-ED settings,\(^11-17\) they observed that the ketofol group required substantially less total propofol (median 100 mg versus 175 mg). Unlike the previous trials, however, they scored serial sedation depth and confirmed its similarity between groups, which refutes the possibility suggested earlier that lighter sedation could explain the differential propofol requirement. Accordingly, this new trial provides the most compelling evidence to date that the sedative effects of propofol and subdissociative ketamine are indeed synergistic. Such synergy would not necessarily be expected, given their entirely different mechanisms of action, because propofol is a central nervous system depressant and ketamine is a dissociative agent.

An additional provocative observation is that, despite requiring substantially less propofol, the ketofol group trended toward more consistent sedation depth. David and Shipp\(^25\) observed that lightening sedation by a score point occurred less frequently with ketofol (31 versus 64 times) and in fewer patients (29 versus 45). Thus, less erratic sedation depth with ketofol can explain the apparent trend. Bolus dosing of the ultrashort-acting propofol will result in peaks and valleys of clinical effect, and the data from David and Shipp\(^25\) suggest that subdissociative ketamine bridges the propofol gaps and promotes more consistent sedation depth.

In both of these new trials, physician and nurse satisfaction scores were substantially higher with ketofol to a degree difficult to explain, given the similarity of most outcomes. In the second trial, these subjective ratings may have been biased by impaired blinding because, despite the use of sunglasses to obscure nystagmus, muscular hypertonicity was likely evident in the ketamine group. This was not an issue in the first trial because both groups received ketamine and the treating physicians were unable to guess group assignment at a rate greater than chance alone.\(^24\)
PRO ARGUMENT

There is ample evidence that ketofol is safe, effective, and positively regarded by ED staff. Adding ketamine to propofol promotes hemodynamic stability, an effect that is particularly reassuring in patients with known or potentially reduced cardiac function. The addition of ketamine reduces the quantity of propofol required, and the data from David and Shipp25 confirm previous evidence of synergism between the 2 drugs. Their data also indicate that ketofol provides smoother and less erratic sedation depth than propofol alone.

Despite equivocal evidence that adding ketamine to propofol reduces respiratory depression, it is known that the dose and rate of administration of propofol correlate with the incidence of adverse airway events.6,23 It therefore seems intuitive that a sedation regimen that achieves deep sedation with lower doses of propofol may be safer. Most clinicians administer opioids before propofol sedation for painful procedures despite their well-known potentiation of respiratory depression. The potent analgesia of ketamine precludes the need for, and thus potential risks of, coadministered opioids.5,27

Ketofol recovery time is, as expected, longer than that for propofol alone but shorter than that of ketamine alone.4 Clinicians can take advantage of this longer effect during procedures with more prolonged painful stimuli (eg, molding of a cast, incision and drainage of abscesses), without the limitations of the longer ketamine-alone recovery time and without the degree of repeated dosing that would be required for propofol monotherapy. Ketofol also exhibits less emesis and recovery agitation—a major concern in adults—compared with ketamine alone. Accordingly, the choice of ketofol allows the clinician to take advantage of the best features of both drugs.

CON ARGUMENT

Ketofol is a misleading concept and is nothing more than standard propofol sedation in which fentanyl analgesia is replaced with subdissociative ketamine. There is no compelling evidence that ketofol reduces respiratory depression or produces superior sedation to either ketamine or propofol alone. Promoting hemodynamic stability is clinically unimportant because propofol-induced

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Table 1. Previous ED ketofol case series.

<table>
<thead>
<tr>
<th>Study Characteristics</th>
<th>Willman, 20071</th>
<th>Sharieff, 20072</th>
<th>Andolfatto, 20103</th>
<th>Andolfatto, 20114</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>114 adults and children</td>
<td>20 children</td>
<td>219 children</td>
<td>728 adults</td>
</tr>
<tr>
<td>Procedures</td>
<td>Mostly fracture reduction</td>
<td>Fracture reduction</td>
<td>Mostly fracture reduction</td>
<td>Mostly fracture reduction</td>
</tr>
<tr>
<td>Dose</td>
<td>0.75 mg/kg of 1:1 mix in same syringe</td>
<td>Ketamine 0.5 mg/kg+propofol 1.0 mg/kg</td>
<td>0.8 mg/kg of 1:1 mix in same syringe</td>
<td>0.7 mg/kg of 1:1 mix in same syringe</td>
</tr>
<tr>
<td>Procedural success, %</td>
<td>97</td>
<td>95</td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td>Transient hypoxia/total number of subjects (%)</td>
<td>3/114 (3)</td>
<td>3/20 (15)</td>
<td>3/219 (1.4)</td>
<td>17/728 (2.3)</td>
</tr>
<tr>
<td>Median recovery, min</td>
<td>15</td>
<td>38</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>

Table 2. ED ketofol randomized controlled trials.

<table>
<thead>
<tr>
<th>Study Characteristics</th>
<th>Messenger, 20085</th>
<th>Shah, 201124</th>
<th>David, 201125</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>63 adults or teenagers</td>
<td>136 children</td>
<td>100 adults+93 children</td>
</tr>
<tr>
<td>Procedures</td>
<td>Mostly fracture reduction</td>
<td>Fracture reduction</td>
<td>Mostly fracture reduction</td>
</tr>
<tr>
<td>Ketofol arm</td>
<td>Ketamine 0.3 mg/kg, followed 2 min later by titrated propofol</td>
<td>Ketamine and propofol each 0.5 mg/kg, followed by propofol 0.5 mg/kg prn</td>
<td>Ketamine 0.5 mg/kg, followed by propofol 1 mg/kg, followed by propofol 0.5 mg/kg prn</td>
</tr>
<tr>
<td>Comparison arm</td>
<td>Titrated propofol (2 min after fentanyl 1.5 μg/kg)</td>
<td>Ketamine 1 mg/kg, followed by 0.25 mg/kg prn</td>
<td>Propofol 1 mg/kg, followed by 0.5 mg/kg prn</td>
</tr>
<tr>
<td>Procedural success, %</td>
<td>Ketofol 97, propofol 100</td>
<td>Ketofol 96, ketamine 100</td>
<td>100 in both groups</td>
</tr>
<tr>
<td>Transient hypoxia, %</td>
<td>Ketofol 38, propofol 77 (saturation &lt;92 at any time)</td>
<td>Ketofol 5, ketamine 3</td>
<td>Ketofol 7, propofol 12</td>
</tr>
<tr>
<td>Median recovery, min</td>
<td>Ketofol 28, propofol 37</td>
<td>Ketofol 10, ketamine 12</td>
<td>Not reported</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Fewer total sedation adverse events with ketofol, according to a composite outcome table</td>
<td>Total sedation time 3 min shorter with ketofol</td>
<td>Similar incidence of respiratory depression</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Similar satisfaction scores, more propofol required with ketofol</td>
<td>Ketofol versus ketamine demonstrated similar efficacy and incidence of respiratory adverse events; ketofol associated with less vomiting and greater provider and patient satisfaction</td>
<td>Ketofol versus propofol associated with greater provider satisfaction, less propofol administered, and a trend toward more consistent sedation quality</td>
</tr>
</tbody>
</table>
hypotension is essentially always transient and self-limited. Reducing the total propofol requirement is similarly insignificant because any “extra” propofol rapidly dissipates and does not meaningfully prolong recovery. If your clinical intent is deep sedation, then this can be readily and safely achieved with propofol alone. If your intent is instead dissociative sedation, then this is readily achieved with ketamine alone at dissociative doses.

Although the trial by David and Shipp25 appears to confirm synergy between propofol and subdissociative ketamine, does this translate into clinical gains? Why go to the added complexity of administering 2 drugs and having to anticipate the unique adverse effects of each when monotherapy works just as well and presents only 1 set of potential adverse events?

The higher staff satisfaction scores reported with ketofol must be regarded with suspicion because blinding is uneven in these trials and essentially all important efficacy and safety parameters are the same. To believe these data, we need evidence of the specific reasons supporting this preference, something still wholly unclear.

In some studies, emergency physicians administer ketamine and propofol together in the same syringe for loading and subsequent doses.1,3,4 Given that propofol is ultrashort acting and ketamine is not, such a strategy seems destined to result in disproportionate ketamine accumulation relative to that of propofol. If ketofol is used for a longer procedure, after administration of 3 or 4 doses, propofol has largely worn off in between doses, whereas ketamine has not. This does not seem to make good pharmacokinetic sense.

Before ketofol can be recommended, it needs to be established that the combination offers a tangible benefit over either agent alone, something not evident at this time.

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