Ketofol V: Risky or Revolutionary

Abstract

There is significant interest in ketofol as an agent for procedural sedation and analgesia. This is the last article in our series on ketofol, a combination of ketamine and propofol that can be mixed in the same syringe, or administered independently in two separate syringes. Ketofol can be administered as boluses or as a continuous infusion for longer procedures. Ketamine-propofol combinations in different ratios have been studied before. A delay in recovery times was found when higher doses of ketamine were used in the mixture. The optimal mixture and dosing of the ketofol combination has yet to be determined. It will probably depend on the level of sedation that is planned. It is advised to use as low as possible a dose of ketamine in the mixture. In clinical practice it looks as if a sub-dissociative dose of ketamine propofol (1:10) should give the least side effects with the most advantages.

Readers are reminded that a complete list of all references can be found at the end of this article.

Introduction

Ketofol mixtures/ratios

Wang et al investigated propofol-ketamine mixtures in ratios of 2:1, 3:1 and 4:1 comparing it with propofol administered alone, and with the combination of propofol-fentanyl[25]**.** This study showed ketofol to be as effective as the propofol-fentanyl combination for sedation and pain relief for abortions. All three concentrations were very effective for the procedure, with the 4:1 mixture the most effective for procedural sedation and analgesia (PSA).

The 3:1 and 4:1 mixtures of propofol and ketamine provided similar sedation, recovery, and discharge times, that were comparable to the propofol-fentanyl group, as well as the propofol only group. The 4:1 group (40 mg ketamine, 160 mg propofol in a 20 cc syringe) had a low incidence of respiratory depression and a relatively lower incidence of postoperative dizziness than the other ketofol groups. The sedation, recovery, and discharge times were also shorter than with the other ketofol groups, but they were slightly longer than the propofol and propofol-fentanyl groups. The propofol only group required significantly higher doses of propofol for PSA since no analgesic was used[25].

There were very few adverse events associated with the use of ketofol in this study; it is known that the combination of ketamine and propofol counteract the adverse haemodynamic effects of each other alone i.e., hypotension and respiratory depression.

The authors conclude that different ratios of the ketamine and propofol can be used depending on the type and duration of the surgery, and the dose can be adjusted accordingly. Their conclusion was that ketofol in the ratios 3:1 and 4:1 (propofol-ketamine) is as effective as the propofol-fentanyl group for abortions. The ketofol groups had few intraoperative events, but higher postoperative events, whereas the propofol-fentanyl group had high intraoperative events, but no postoperative events[25].

Daabis et al evaluated the effects of different mixtures of ketamine and propofol on the haemodynamic parameters, emergence phenomena, recovery times and occurrence of adverse events[34]. The combination provided effective sedation for spinal anaesthesia, gynaecology, ophthalmology and cardiovascular procedures in all age groups. Ketofol in a ratio of 1:1 was compared to ketofol in a ratio of 4:1.

The infusion rate needed in the 4:1 group was higher to reach the desired depth of sedation and to prevent pain. A higher incidence of clinically significant psychotomimetic effects was noted in the large-dose (1:1) ketamine group. The lower dose group had no emergence reactions, their mood in the recovery room was significantly better and their cognitive function recovered more rapidly.

Badrinath et al compared various mixtures of ketamine in a ketamine-propofol combination during monitored anaesthetic care and found an increase in post-operative nausea, vomiting, and psychomimetic effects, prolonged recovery and delay in discharge when increasing the dose of ketamine[11, 46].

Cillio suggested that a 10:1 propofol-ketamine mixture provides the greatest benefit for continuous intravenous sedation in adults undergoing dental surgery[23]. Better haemodynamic stability and faster recovery times will be achieved with this mixture. Lowering the ketamine concentration may also be associated with earlier discharge times[54].

Coulter et al[58] used ketofol in different ratios for general anaesthesia in children aiming to determine the optimum mixture ratio, and the best dosing regimen. It was a simulation study in which drug concentration (plasma and effect site) and anaesthesia profiles over time were estimated for racemic ketamine with propofol. They came to the conclusion that the addition of ketamine to a propofol infusion will prolong recovery unless infusion rates are decreased. They suggest an optimal ratio of racemic ketamine to propofol of 1 : 5 for 30-min anaesthesia, and 1 : 6.7 for 90-min anaesthesia.

It is probably reasonable to say that the efficacy and safety of ketofol as a sedative-analgesic agent are dependent on the dose used and the mixture of the ratio. There should be an ideal mixture where the benefits are maximized and the side effects are minimized.

Trying to find the perfect mixture might suggest that we will have to change to separate syringes to reach that goal. Whether bolus dosing according to individual patient needs will give us the required sedation consistency, remains to be seen. However, by administering the lowest possible dose of each drug, and combining the desired characteristics we need, we are aiming to keep the patient both safe and satisfied.

Independent dosing of ketamine and propofol is probably the way to go in children. In adults ketamine and propofol in the same syringe remain a safe option. The only issue that remains a concern is compatibility of the two drugs in the same syringe.

Conclusion

We live in an ever changing and demanding environment where the sedation practitioner is expected to provide a safe, pain-free and 'dream-like' patient with no side effects undergoing a variety of procedures. Ketofol should be considered as part of the armamentarium of the sedation practitioner in providing safe and effective PSA for procedures outside the operating room. It must however be administered by a trained sedation practitioner.

The question of “why not use one drug instead of two?” remains to be answered. There is no perfect drug at present, so we will need to find the perfect combination to achieve the perfect sedation.

Several factors are important in determining whether a sedative-analgesic combination is clinically acceptable. These include hemodynamic stability, effectiveness of the sedative-analgesic, the time required for surgery to start, recovery times, and the incidence of postoperative nausea and vomiting.

The ideal sedative-analgesic combination would provide a stable hemodynamic state, no respiratory depression, a rapid onset and recovery to baseline, and a low incidence of postoperative nausea and vomiting. Decreasing the incidence of postoperative nausea and vomiting is important because it significantly increase recovery time and is very upsetting to the patient. The ideal sedative-analgesic also will maintain a patient's hemodynamic status to as close to the pre-sedation state as possible[23].

More consideration should probably be given to a strategy to start PSA using ketofol, followed by propofol monotherapy. This is especially so in patients on psychotropic drugs and in young children. Bolus doses of ketofol in children should be carefully monitored for the level of consciousness.

Ketamine has a context-sensitive half-time. The implication of this is that the longer we give ketamine in an infusion the more the possibility of accumulation and slow recovery. The context-sensitive half-time of ketamine increases dramatically after 30 min of administration. Because of this substantially longer duration of effect of ketamine, it is maybe illogical to re-dose the ketamine component of ketofol near the end of a lengthy procedure when propofol alone would suffice.
Ketamine also appears to dissociate patients in a dichotomous manner, meaning that providing small additional boluses of the drug to already dissociated patients may provide very little clinical benefit. These concerns about the co-administration of the two agents have been suggested before, yet most emergency medicine investigations of ketofol nevertheless have studied the combined formulation[53].

Maybe independent dosing of these two drugs is superior to mixture dosing, but it may also be superior to propofol alone.

Andolfatto et al[10] suggest that ketamine may provide patients with an increased sedation consistency; without ketamine providers will probably have to rely solely on intermittent doses of propofol.

However, there exists a substantial body of prospective data demonstrating the effectiveness of the single-syringe combination. The recovery time with the single-syringe combination (8 minutes; range 7 to 10 minutes) is longer than that of propofol alone (6 minutes; range 2 to 8 minutes), as one would surmise, but only by a median of 2 minutes. This is probably of no clinical significance.

This longer duration of effect can be used to great advantage for those painful procedures that take a few extra minutes to perform i.e., incision and drainage of abscesses or fracture reduction with cast molding while still maintaining a recovery time similar to that with propofol alone, and with a consistency of sedation depth that lessens the need for repeated dosing of a sedative in response to patient agitation[53].

Another criticism has been the accumulation of metabolites and the different pharmacokinetics of the two agents. Propofol has been used extensively for sedation in intensive care units due to the fact that it is quickly redistributed and has little or no accumulation, although propofol infusion syndrome has caused complications at times with longer duration of the propofol infusion. On the opposite end ketamine's metabolite norketamine seems to have 20-30% the potency of the parent compound and can accumulate[6]**.** This has led some individuals to recommend using separate syringes or infusing propofol only after a set period of time i.e., one hour. One can appreciate that when given by an infusion, the initial dose of ketamine need not be maintained at the initial rate as the plasma concentration of ketamine does not redistribute as quickly as propofol dose.

It must also be kept in mind that this accumulation is dose-dependent and when infusing doses of 20-30mg/hour of ketamine, the accumulation of norketamine at these doses is probably not clinically significant.

Lovato criticized the Shah study[39] and suggested that ketofol might not be the answer to what we are looking for, the ideal agent for PSA[56].

In the clinical situation, we use a 10:1 mixture and a 2:1 mixture to bolus propofol: ketamine. With these low doses, we do not see the nausea and vomiting and the emergence reactions. However, we do see the sedation consistency and relatively short recovery times. We do see the safety and the reduced respiratory depression compared with the opiates. We do have the added benefit of using an infusion pump with a target-controlled infusion model, but the 20mg of ketamine added to 200mg of propofol rarely results in dosages above the recommended 1mg/kg ketamine per hour. In future one would like to see the perfect drug that will give us everything that we want for the perfect sedation, but in the meantime ketofol seems to be a cost-effective, safe way of having the hypnotic-analgesic combination that we need.

We agree with the work of Coulter et al[58] on the use of a 1 : 10 mixture of ketamine and propofol in the same syringe. They state that a “reduction in the infusion rate to maintain a probability of anesthesia >95% resulted in times of P_{50} of 16 – 24 min after 30-min exposure, and 40 – 60 min after 90-min exposure in all scenarios”.

Whether two syringes would give us more control and an ever better sedation is not known, but separate syringe titration might shorten the recovery time. It would be interesting to see whether it would result in fewer adverse events and whether the sedation consistency would stay the same[53].

When ketofol is used with higher concentrations of ketamine and propofol i.e., a 1:1 mixture, then there will be a higher incidence of adverse events. We as sedation practitioners have a responsibility to use these drugs in the lowest concentrations possible.

Maybe if we want to explore new horizons we can look at ketodex (a combination of ketamine and dexmeditomidine). The combination may be another option for PSA.

I want to acknowledge the contribution of a graduate of mine Mariki Durand.

As promised the references of all the articles on ketofol is included in this article.

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