Ketofol: risky or revolutionary: CPD article IV

Abstract

Ketofol, a sedative/analgesic combination of ketamine and propofol, which can be administered as a mixture in the same syringe or independently, is used for procedural sedation and analgesia (PSA) since the early 1990's. Sedation practitioners would like to have the ideal sedative/analgesic drug for PSA, it would even be nicer to have that in a single syringe. Some clinicians argue that ketofol can come close to the requirements of an ideal agent when mixed in the same syringe or administered as a combination independently. When we combine the sedative, analgesic, and amnestic effects of ketamine with the sedative, amnestic and anti-emetic effects of propofol we may be on the right track in finding the ideal agent. There are currently a significant number of publications on the use of ketofol for PSA; for more or less any medical and dental procedure that qualify for PSA. We need to look at the pros and cons of the articles to give sedation practitioners the opportunity to make a choice whether they want to use ketofol or not. The combination of ketamine and propofol (ketofol) for PSA shows promise as a formulation that minimize adverse effects of ketamine or propofol as single agents.

The risks of sedation using combination therapy with ketamine and propofol are probably those of the individual drugs, but the combination seems to decrease the adverse events of the two drugs.

Introduction

The search for the ideal sedative/analgesic drug that provides the perfect combination of desired effects needed for safe and effective outpatient sedation has been on going since the discovery of anaesthesia[23]**.** The question is, are we moving in the right direction with the introduction of ketofol. The simultaneous same-syringe

administration of two different drugs whose duration of action differ by an order of magnitude may be difficult to rationalise, or is it.[9]

Introduction

In this era of health care cost containment, it is important for us to use sedative/analgesic drugs for outpatient ambulatory surgery that have a rapid onset, a low incidence of side effects i.e., postoperative nausea and vomiting (PONV), adequate analgesia and a quick recovery. Local/regional anaesthesia with PSA is widely used for all kinds of operative procedures to provide analgesia where needed.

PSA is a technique where the use of combinations of sedative/analgesic/dissociative drugs induces a state of sedation and analgesia that allow the patient to tolerate unpleasant procedures while maintaining cardiorespiratory stability.
The drugs we use should provide an adequate level of sedation with no pain and anxiety, a low incidence of adverse drug-related events, amnesia, and stable cardiovascular and respiratory systems[18]. Unfortunately, at present, no single drug exists that has all the requirements of an ideal agent, so physicians often use combinations of different drugs to try and achieve the ideal agent status.

The effects of ketamine and propofol have been shown to be complementary[16]. The rationale behind combining them is that the cardiovascular and respiratory depressant effects of propofol can be attenuated by the addition of low doses of ketamine, a drug that does not depress respiration. Ketamine also provides the analgesic properties that propofol lacks[23]. This usually result in a stable haemodynamic status whilst ketamine compliments the sedative effect of propofol[7,23]. The combination of ketamine and propofol has also been successfully used in separate syringes (independent dosing) for a variety of procedures[15] like angiography, interventional radiology, sedation for spinal anaesthesia, gynaecological, dental and ophthalmology procedures[16,25].

The different mechanisms of actions of ketamine and propofol, the differences in duration of action of the two drugs and the different mixtures has called into question the reason for same-syringe titration of these two drugs. The sedative effect of propofol occurs in a dose-dependent way, whereas in contrast, ketamine displays a dissociative threshold usually in intravenous doses between 1-1,5 mg/kg[36]. Ketamine is also known to have a longer duration of action than propofol[37].

Despite these differences, combinations of ketamine and propofol have been shown to reliably produce safe and efficacious sedation with a low incidence of side effects. Previous case studies have shown that the differences in kinetics and the duration of action between ketamine and propofol do not compromise the effectiveness when using a titrated, same-syringe combination for sedation in children and adults[23].

The combination of ketamine and propofol appears to provide sedation and analgesia with fewer side effects than either drug alone, and with fewer adverse events than a combination of propofol and fentanyl[10]. This is most likely due to the reduction in dose of both drugs when administered together[11]. For the same quality of sedation one needs a smaller dose of each drug, with ketamine often used in sub-dissociative doses[16,36]. This will most probably lead to a lower incidence of side-effects.

Ketofol in various studies has consistently produced sedation with a rapid onset, and with a reliable and reproducible quality of sedation. Adding the ketamine to propofol results in faster onset of sedation with a smaller bolus dose administered, thus decreasing the possibility of respiratory and cardiovascular compromise[11,25].

Shorter recovery times have also been reported after administration of ketofol for PSA when compared to using ketamine alone. Ketofol is also associated with a lower incidence of emergence reactions than ketamine alone[7]. The incidence may however depend on the dose of ketamine used.

Using ketamine and propofol together in one syringe is a concern for some clinicians. Physical compatibility and chemical stability were however proven in a study when a 1:1 mixture of ketamine and propofol was evaluated in capped polypropylene syringes. The combination was physically and chemically stable for at least 3 hours when stored at room temperature with exposure to light. There were no significant changes in the pH after 1 or 3 hours of storage; pH of the 1:1 mixture was 4.98, and that of the 3:7 mixture (30% ketamine and 70% propofol) 5,16. There were no visible signs of separating or cracking of the emulsion and no apparent change in the white milky colour, and no evidence of gas formation after three hours[15]. There are similar studies available that support these findings.

In our search for the ideal sedative/analgesic combination, ketofol has been compared to other combinations of drugs used for PSA i.e., propofol-fentanyl, propofol-remifentanil, and midazolam-fentanyl. Propofol is associated with a dose-dependent risk of respiratory depression that is heightened with the concomitant use of opiates. This can be problematic for the clinician wishing to provide analgesia with opiates as propofol has no intrinsic analgesic properties. It is claimed that when we combine ketamine and propofol (ketofol) we need less propofol and then a lower incidence of respiratory-related adverse events. Compared to the propofol-fentanyl combination, ketofol administration seems safer with less adverse respiratory events[7].

Ketofol versus Ketamine

Abdoelahab et al showed that ketofol administration leads to a quick onset of sedation with haemodynamic stability and a lower incidence of adverse events[44]. The BIS readings (level of consciousness) in the ketofol group were on average 70 (conscious sedation), propofol group 45 (anaesthesia), and ketamine group 94 (conscious sedation) two minutes after administration of the drugs.

Shah et al compared the total sedation times, time to recovery, adverse events and efficacy[39] when using ketofol and ketamine. The ketofol group produced faster recoveries, less PONV and higher satisfaction scores. The combination of ketamine and propofol showed less adverse events than ketamine alone, most likely due to the lower dose of ketamine used in the mixture.

Ketofol versus Propofol

Propofol in the hands of the trained sedation practitioner is a safe and reliable hypnotic/sedative drug for PSA and is often used alone for painless procedures or where the patient receives local/regional anaesthesia for analgesia. It can be administered as boluses or as a continuous infusion using TIVA or TCI.

Mortero et al compared ketofol and propofol in patients undergoing elective ambulatory surgery[31]**.** They demonstrated a significant increase in end-expiratory pCO_2 in the propofol only group. This could indicate hypoventilation related to the dose administered and the effect of propofol on the respiratory system. Normal ventilation and significantly improved post-operative analgesia were reported after the addition of low-dose ketamine to propofol.

Akin et al evaluated the effects of propofol and ketofol in children for cardiology procedures. They reported better haemodynamic stability, without prolonged recovery in the ketamine-propofol group, compared to the propofol monotherapy group[45]**.** The patients in Akin's study received ketamine in sub-dissociative doses and propofol in doses far less than those usually required for deep sedation in children.

PSA in children using intravenous ketamine alone is reliably achieved with a dose of 1.5mg⁄kg, while lower doses frequently require repeat doses. It is believed that by combining ketamine with propofol, clinicians have the ability to provide deep sedation using lower doses of ketamine, which may allow for more rapid recovery.

As expected, the median recovery time of 14 minutes documented in this series was longer than most recovery times reported for propofol alone, and shorter than those reported for intravenous ketamine.

Aydogan et al reported the haemodynamic data to be more or less similar when using propofol and ketofol; the mean recovery times of ketofol were shorter than with propofol alone[24]. The data suggest that the use of ketamine and propofol in combination might be beneficial for haemodynamic stability and recovery times when reducing the total amount of propofol used. They concluded that the propofol/ketamine 3:1 mixture is associated with shorter recovery times than propofol alone, with similar haemodynamic stability and without any significant side effects[24].

Frey et al compared propofol and ketofol for PSA in patients who had retrobulbar blocks that can be uncomfortable. None of the patients in the ketofol group required airway assistance and patients had a significantly faster onset of acceptable sedation levels[42]. They concluded that the addition of ketamine improved the quality of sedation without prolonging sedation recovery.

In 2007 Andolfatto et al compared ketofol to propofol alone for emergency department PSA sedation[35]. They concluded that ketofol is safe for use in PSA[35]. They also published studies in 2010 and 2011 that showed that ketofol sedation is safe and effective for use in children and adults for PSA[36,37]. Recovery times with ketofol are quick and the incidence of adverse events low. Sedation efficacy was found to be similar in both the propofol only and ketofol groups.

The 2012 study of Andofatto et al[10] shows that there is reason for caution when deep sedation is targeted for PSA emergency department PSA sedation[10]. With a mixture of 1:1 of ketamine and propofol, forty-three (30%) of patients experienced an adverse respiratory event in the ketofol group, compared with 46 (32%) in the propofol group. In this study of Andofatto et al[10] three ketofol patients and 1 propofol patient received bag-valve-mask ventilation. It must be noted that more than 50% of

patients were more than 50 years old, and that a significant percentage was above 70 years of age. Some of the patients were classified as ASA 111.

It is the author's view that high doses of ketamine and propofol should not be routinely used for sedation outside the operating theatre. It is not advised for sedation practitioners targeting "conscious sedation". If used patients must be monitored carefully preferably using capnography.

Shipp et al reported that the combination of ketamine and propofol (ketofol) when compared with propofol for PSA did not reduce the incidence of respiratory depression. Ketofol did produce greater provider satisfaction, less propofol administration and perhaps better sedation quality[33]. Again deep sedation was targeted as in the previous study with a higher incidence of adverse events.

From all the studies quoted we can say that there are potential advantages when ketofol is used and where moderate sedation and analgesia is targeted;

- Lower doses of propofol can be used thus limiting propofol-induced respiratory depression.
- Provision of analgesia by ketamine without respiratory depression that is often seen with opiate administration.
- Possible shorter recovery times and a lower incidence of PONV

and emergence phenomena depending on the ratios of ketamine and propofol used in the mixture.

It is clear from many studies published on the use of ketofol for PSA that there is a place for the use of ketofol. It is a very useful combination but our patients need to be monitored carefully. The ratios of the mixtures must be selected carefully. A decision has to be made whether the ratios for induction, bolus administration and continuous infusion should be the same.

In literature different ratios are described for ketamine and propofol; 1:2, 1:3, 1:4, 1:5, and 3:7. We use a mixture of 1:10 (20mg of ketamine and 200 mg of propofol) for continuous infusions using either TIVA or TCI and do not seen respiratory depression or PONV when used for PSA outside the operating theatre.

Ketofol versus a propofol-opiate combination

Some sedation practitioners are still resistant to the use of ketamine, for various reasons. They often combine propofol with a short-acting opiate to provide analgesia and sedation. Sedative effects of the opiates are a secondary effect but there is the risk of respiratory depression that is dose-related. The most commonly used opiates include fentanyl, remifentanil, tramadol and alfentanil.

The author uses a mixture of tramadol and propofol as an infusion technique for almost all cases undergoing PSA; 100 mg of Tramadol is mixed with 200 mg of propofol in the same syringe. Either a TCI (starting at 1mcg/ml) or TIVA technique (2 – 4 mg/kg/hr of the mixture) is used. The infusion is titrated to response. Infusion of the tramadol-propofol mixture is followed by a 1:10 ketamine-propofol mixture (starting at 1mcg/ml, and titrated to response). We do not see any respiratory depression or PONV with this technique. An additional benefit that we see is is the analgesia provided by both tramadol and ketamine.

Fentanyl is a popular analgesic for PSA. When administered intravenously it has an onset of action of 3 – 5 minutes, a redistribution half-life of 2,5 minutes and a terminal half-life of 3,7 hours. Respiratory depression is dose-related and not seen with the doses we use for PSA. The peak respiratory depressant effect of a single intravenous dose of fentanyl is seen 5 to 15 minutes following injection depending on the dose administered. The dose of fentanyl is between 0.5 – 1mcg/kg titrated when administered as boluses and part of a PSA technique.

Remifentanil is an ultra short-acting opiate with a rapid onset of action and a biological half-life of 3-5 minutes. It is probably an ideal analgesic for PSA but a very potent respiratory depressant and should not be used outside the operating theater. The terminal half-life of the unchanged drug Is 10 to 20 minutes[14]. Remifentanil is often combined with propofol in the same syringe for PSA in the hospital setting.

Alfentanil has become a very popular short-acting analgesic for use for PSA. The onset of action of alfentanil is more rapid than that of fentanyl. A peak effect is reached 1 to 2 minutes after an intravenous bolus dose (2-3 min after starting an intravenous infusion). The time to onset of analgesia is 55.7 (range 15 -120) seconds for alfentanil, compared to 103.8 (range 30 -120) seconds for fentanyl.

The duration of action of alfentanil is shorter than that of fentanyl, and is dose-related. Alfentanil elimination is rapid with a terminal elimination half-life of 90 - 111 minutes (range 50 - 150 minutes), which is significantly quicker than compared with fentanyl.

Alfentanil in combination with propofol in the same syringe provide excellent sedative and analgesic effects for PSA. The author uses a mixture of 1 mg of alfentanil and 200 mg of propofol in the same syringe for continuous infusion using either a TIVA or TCI technique. When using TIVA the mixture is infused at 2 – 4 mg/kg/hr; with TCI the starting dose is 0.8mcg/ml. The patient must be monitored carefully for respiratory depression. This mixture of 50µg per cc of alfentanil can also be used for bolus administration. It has a rapid onset of action.

In 2008, Messenger et al reported on the safety and efficacy of a sub-dissociative dose of ketamine (0,3mg/kg) compared with a mixture of fentanyl and propofol for emergency department PSA[9]. Their primary outcomes were frequency and severity of adverse cardiorespiratory events and interventions. They concluded that ketamine was safer than fentanyl and propofol and the quality of sedation was similar.

Ketofol was reported as superior to a mixture of propofol-fentanyl for changing dressings of burn victims in the ICU[50]. Published data suggest that the use of ketofol may allow clinicians to take advantage of the haemodynamic stability and analgesia of ketamine, while minimizing the recovery time by reducing the total amount of ketamine required for adequate sedation. Lower doses of propofol may be associated with lower incidences of hypoxia and apnoea. Recovery agitation, a common effect with the use of high doses of ketamine alone in adults, and PONV appear to be blunted by the sedative and anti-emetic actions of propofol.

Kramer et al compared ketofol to a propofol–remifentanil mixture[1] that is a very popular mixture for anaesthesia. In his study it was evident that the remifentanil had a significant effect on the respiratory rate; it decreased whilst it was increased in the ketamine group. Continuous infusions of propofol-remifentanil and ketofol provided remarkably comparable deep sedation, with the ketofol group demonstrating significantly longer recovery times. The ketofol group had a clinically significant increase in mean heart rates. There were no differences in the incidence of PONV, and patients and surgeons were both satisfied with the levels of sedation.

Hasanein et al did a very interesting study on the use of drugs in obese patients for PSA. We as sedation practitioners need to take note of this as we often see obese patients for sedation. They compared ketofol and propofol-fentanyl for obese patients undergoing ERCP[30]. Patients with a high body-mass index (BMI) are at higher risk for hypoxaemia/hypoventilation during sedation (usually a BMI of above 32). The ketofol combination consisted of 400mg propofol and 100mg ketamine. A higher incidence of hypotension, bradycardia, apnoea and desaturation was observed in the fentanyl-propofol group.

The dose of propofol needed to achieve deep sedation in the patients undergoing ERCP was lower in the ketofol group. This probably contributed to the lower incidence of adverse effects. The recovery times and time to discharge were shorter in the fentanyl group, probably because of slower clearance of ketamine in

comparison to fentanyl. A higher incidence of emergence agitation and PONV was observed in the ketofol group but the incidence was still lower than when compared to ketamine alone. The conclusion was that the ketamine-propofol combination provided better sedation quality than a fentanyl-propofol combination, with less haemodynamic and respiratory effects.

Singh et al conducted a randomized, double blind study to compare the combination of fentanyl and propofol, with ketofol in patients undergoing outpatient laparoscopic tubal ligation. They evaluated the haemodynamic effects, postoperative recovery characteristics, duration of hospital stay, adverse events, patient comfort and acceptability of technique[47]. The study showed postoperative recovery to be better, the duration of hospital stay was also shorter in the fentanyl–propofol group, as compared to the ketamine–propofol group. Discharge was delayed because of adverse effects like PONV in the ketofol group. Recovery time in the fentanyl group was shorter than that in the ketamine group. The patients were more comfortable and satisfied with the propofol–fentanyl combination as compared to ketofol because of a lower incidence of PONV.

Heart rates were comparable, the blood pressures were consistently higher in the ketofol group, probably due to the sympathomimetic activity of ketamine[47]**.** The conclusion was that the combination of fentanyl (1.5 µg/kg) and propofol (2 mg/kg) leads to faster recovery, earlier discharge, and better patient acceptability than the combination of ketamine (0.5 mg/kg) and propofol (2 mg/kg) for PSA in patients undergoing laparoscopic tubal ligation[47]**.**

Akin et al compared a combination of propofol and fentanyl with ketofol in 40 adult patients undergoing endometrial biopsy[48]**.** They observed no differences in the recovery times, but the discharge of patients was delayed in the ketofol group. The longer discharge time with ketofol was caused by the higher frequency of vertigo, nausea, and visual disturbances. With regard to patient satisfaction, the propofol–fentanyl group was superior.

Badrinath et al investigated the combination of propofol with ketamine at various doses in patients undergoing breast biopsy with local anesthesia[46]. They added 2,5µg of sufentanil when patients complained of discomfort and pain. They also noted an increased incidence of PONV and visual disturbances in the ketofol group with a prolonged time to discharge.

Jakobsson et al used four different drug combinations in patients undergoing termination of pregnancy and reported that the ketofol combination led to the highest frequency of postoperative pain, psychomimetic side effects, and emesis. Although ketofol did not delay discharge, they concluded that propofol–fentanyl was the most suitable combination[51]. Despite these adverse events, ketofol still provided good sedation-analgesia and decreased the incidence of hypotension compared to the fentanyl-propofol combination during PSA. Low-dose ketamine–propofol infusion was found to be a more effective and a safer sedative-analgesia mixture than a propofol–fentanyl infusion in paediatric emergency short surgical procedures.

Low-dose ketamine–propofol infusions were found to be a more effective and a safer sedative-analgesia regimen than a propofol–fentanyl infusion in short paediatric emergency surgical procedures. Haemodynamic stability was maintained and a lower incidence of apnoea was reported[43]. There was a higher rate of emergence reactions and PONV in the ketofol group. This study showed that the amount of propofol needed to achieve a deep sedation level was lower in the ketamine–propofol group than in the fentanyl–propofol group, which probably contributed to the lower incidence of hypotension and apnoea[43].

Conclusion

What can we say after all the information regarding ketofol. Well, the studies are all evidence-based studies. They can be accessed and studied in detail. It gives us direction as to doses, and the incidence of adverse events.

Based on all the studies reviewed it is difficult to say whether ketofol meets all the requirements of an ideal sedative/analgesic drug. There are pros and cons. Some studies report ketofol as the ideal agent others say it is not ideal.

If we look at some of the reported studies we need to understand that deeper levels of sedation may lead to a higher incidence of adverse events.

In literature however we also find studies suggesting that ketofol might not be the most suitable combination. The context-sensitive half-life of ketamine is known to increase dramatically after 30 min. Infusion rates should be reduced as the proportion of ketamine is increased for the longer duration infusions and patients may have longer recovery times.

The side effects of the opiates are more serious with respiratory depression complicating sedation maybe more than post-operative nausea or diplopia. Titration still remains the most effective way of administration of drugs during sedation.

Respiratory depression is always a serious adverse event but more so in small children. Ketamine is definitely a better option in children as a sedative-analgesic drug with no respiratory depression when injected slowly intravenously or as part of a continuous infusion.

There are some concerns i.e., sterility when mixing drugs, and the possibility of incompatibility with other drugs. The issue can easily be resolved by not mixing ketamine and propofol in the same syringe. Based on the pharmacokinetics of the two drugs ketamine can be administered first, followed by propofol as needed for PSA.

Ketofol we can say is a useful addition to the armamentarium of the sedation practitioner. It has created a tremendous interest in drugs for PSA. It can be used safely where clinically indicated but safety must be ensured by monitoring the patient. Titration of drugs to effect remains an important concept in PSA.

We use a ketamine:propofol mixture of 1:10 for continuous infusions and for bolus administration in adults and children. We have not seen any serious adverse events leading to an escalation in care. One needs to be extremely careful with bolus administration of ketofol in small children as cardiorespiratory depression can be a real possibility.

All references related to ketamine, propofol, and ketofol will appear in the last article.