Systematic Review Article

Ketofol (ketamine/propofol) as a superior sedative agent to mitigate cardiorespiratory effects and alleviate pain when used for procedural sedation and analgesia: A review

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ABSTRACT

Ketofol (ketamine/propofol) as a superior sedative agent to mitigate cardiorespiratory effects and alleviate pain when used for procedural sedation and analgesia: A review

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Procedural sedation and analgesia (PSA) is often necessary in order to deal with anxiety, pain and stress that may accompany patients at the hospital during invasive, unpleasant and/or painful procedures. The literature has not presented firm conclusions regarding ideal sedative agents in terms of efficacy and safety in PSA or even present firm data regarding superiority of specific drugs over others which are considered the "gold-standard" in sedation (i.e. propofol). Ketofol is a combination of ketamine and propofol and is considered by many health-care professionals to cause less respiratory suppression and haemodynamic instability, ensuring better analgesia and often amnesia, and possibly improved patient satisfaction.

We reviewed the existing evidence regarding superiority of ketofol in mitigating cardiorespiratory effects when administered as a main agent for PSA in comparison to other drugs administered for such purposes underlying the safety and efficacy profile of this cocktail medication. We conducted

three times an advanced Pubmed research using the following terms: “ketofol” or “ketamine and propofol” and “sedati*” and “analgesia or pain” in “Title/Abstract” of articles using filters, such as “clinical study”, “clinical trial”, “controlled clinical trial”, “meta-analysis”, “multicentre study”, “randomised controlled trial”, “review”, “systematic review”, “comparative study”, “observational study” in English language and in population of “Adult: 19+ years”. We found 46 articles appropriate to be included in this review.

We found limited evidence to support superiority of ketofol compared to other agents, specifically to propofol, the “gold-standard” drug in sedation; undoubtedly, propofol frequently leads to respiratory suppression, hypotension and bradycardia. It seems that the addition of ketamine to propofol in sub-dissociative doses is associated with less respiratory and haemodynamic complications during PSA, while achieving adequate analgesia and deeper sedation, possibly more amnesia and consequently high satisfaction in both patients and health-care professionals. Frequent side-effects of ketofol, such as increased psychomimetic complications, nausea and vomiting and perhaps more prolonged recovery do not outweigh its potential benefits during PSA. Therefore, we consider that it represents a good choice for PSA, especially in specific populations. Further research with large, well designed, randomised clinical trials is necessary to extract firm conclusions regarding superiority of ketofol against other agents used for PSA.

Keywords: ketofol, ketamine-propofol, ketamine/propofol mixture, sedation, analgesia, procedural sedation and analgesia (PSA).

INTRODUCTION

Alleviation of anxiety, pain and stress is often necessary in patients who undergo invasive procedures which are unpleasant and sometimes painful as well. The medical term “procedural sedation and analgesia” (PSA) refers to the administration of sedative, anxiolytic and analgesic drugs to people experiencing these stressful and painful procedures at the hospital under controlled conditions by well trained-health care professionals who monitor the patient and also deal with any complications that may occur during the procedure. It may also be required to provide amnesia and adequate operating conditions to minimize movement at specific time points. This need often becomes necessary only because of patients’ age[1]. An appropriate medication for PSA should provide rapid, deep, and consistent sedation with minimum adverse effects and complications. It should be associated with minimization of anxiety, maximization of amnesia and analgesia while maintaining haemodynamic stability, and also brief recovery time. Ideally, it should have an antidote and the property of being given orally which is especially important in children[2]. There is no perfect agent as most medi-

cations used nowadays combine different sedative, analgesic, amnestic and dissociative properties. Untreated pain and improper sedation may result in psychological distress such as post-traumatic stress disorder, major depression or delirium. For the alleviation of these symptoms fast-acting opioids can be combined with ketamine, propofol, dexmedetomidine or benzodiazepines, intravenously. Adjuvant drugs such as clonidine or non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol (acetaminophen) may also help[3].

Propofol is one of the most popular agents mainly because of good efficacy, relative safety and rapid recovery, despite the risk of respiratory depression, apnoea, hypoxemia and hypotension[4]. Propofol exhibits antiemetic, anticonvulsant and amnestic properties[5]. It has no analgesic actions and therefore, it is usually combined with opioids for painful procedures.

Ketamine is a dissociative sedative agent with analgesic and amnestic properties, which does not cause significant respiratory suppression; patients receiving ketamine usually maintain spontaneous breathing[6]. This is an important beneficial feature of the drug, especially for patients who are continuously turned during wound dressing procedures and where analgosedation is often performed by practitioners who are not specialists in anaesthesiology[7]. The main disadvantages of ketamine are its psychomimetic effects and the development of post-operative dysphoria. In addition, it increases the risk for nausea and vomiting and can prolong recovery of patients. It is also important to note that ketamine has sympathomimetic effects; therefore it can increase the cardiac workload[8].

Propofol has been combined with low dose ketamine to produce a mixture named “ketofol” in order to counteract the side effects of each medication when given alone, thus maintaining cardiovascular and respiratory stability[9,10]. The use of lower doses of each drug, along with their synergistic effect reduces the adverse effects while achieving optimal PSA conditions[11,12]. Various mixture strengths (mg: mg ratios) have been used ranging from 1:1 up to 1:10 ketamine-to-propofol ratios, but the optimal combination still remains unclear[12].

Regarding the properties of the specific agents in ketofol mixture, ketamine provides analgesia and usually maintains respiratory stability with intact airway reflexes. This is very important since propofol frequently leads to loss of airway reflexes and causes significant respiratory suppression. On the other hand, ketamine causes nausea and vomiting, whereas propofol acts as an antiemetic. Additionally, ketamine causes sympathetic stimulation with tachycardia and hypertension while propofol causes hypotension and usually bradycardia. Finally, analgesia offered by ketamine has an opioid sparing action, therefore less opioid-associated side-effects[13].

Despite the abovementioned advantages of ketofol, there are studies which showed that the addition of ketamine to propofol presents no benefits so ever. In fact, adding ketamine might just complicate things; while in addition, ketamine may prolong recovery and cause agitation. Thus, a number of investigators suggest that there is no reason to use the combination since propofol is just as safe and efficient[14].

In this review, we present the data from current literature that answer the question whether ketofol is superior to propofol or other sedative/analgesic agents used for PSA regarding cardio-respiratory effects in adult patients. Also, we present the existing data that suggest the ideal analogy of ketamine/ propofol in the ketofol mixture.

METHODS

We collected and analysed data relevant to the question about ketofol superiority over other sedatives used in PSA in terms of oxygenation, ventilation and cardiovascular stability (i.e. safety profile). We also analysed data regarding the efficacy profile of ketofol in terms of providing satisfactory sedation, analgesia and amnesia.

We performed three times an "advanced research" in Pubmed database using the keywords: "ketofol" OR "propofol/ketamine" OR "ketamine AND propofol" AND "sedati*" AND "analgesia" OR "pain" to be screened in "Title/Abstract" using filters such as "books and documents", "clinical study", "clinical trial", "clinical trial, phase I", "clinical trial, phase II", "clinical trial, phase III", "clinical trial, phase IV", "comparative study", "controlled clinical trial", "meta-analysis", "multicentre study", "observational study", "pragmatic clinical trial", "randomised controlled trial", "review" and "systematic review". Additional filters we used were: "English language" and "adult: 19+ years" population". Articles published up to January 23rd 2023 were retrieved. Of the 237 articles identified, 98 were duplicates and were excluded. Therefore, 139 articles were screened in relevance to the subject to end up including 46 articles in the present review. Of these 46 studies, 3 were "Reviews and Meta-analyses", 5 were "Reviews", 34 were "Randomised Controlled Trials" (RCTs) and 4 were "Comparative Studies" (Fig.1).

The primary outcome in most studies was respiratory suppression. Secondary outcomes included haemodynamic stability [blood pressure (BP) and heart rate (HR) compared to baseline values], recovery time, procedure time, total dosage of propofol required, depth and consistency of sedation, time to reach desired level of sedation, satisfaction score of patients and health-care professionals, nausea and vomiting rate, emergence reactions and any other side-effects rate, Visual Analogue Scale (VAS) score, amnesia rate and discharge time.

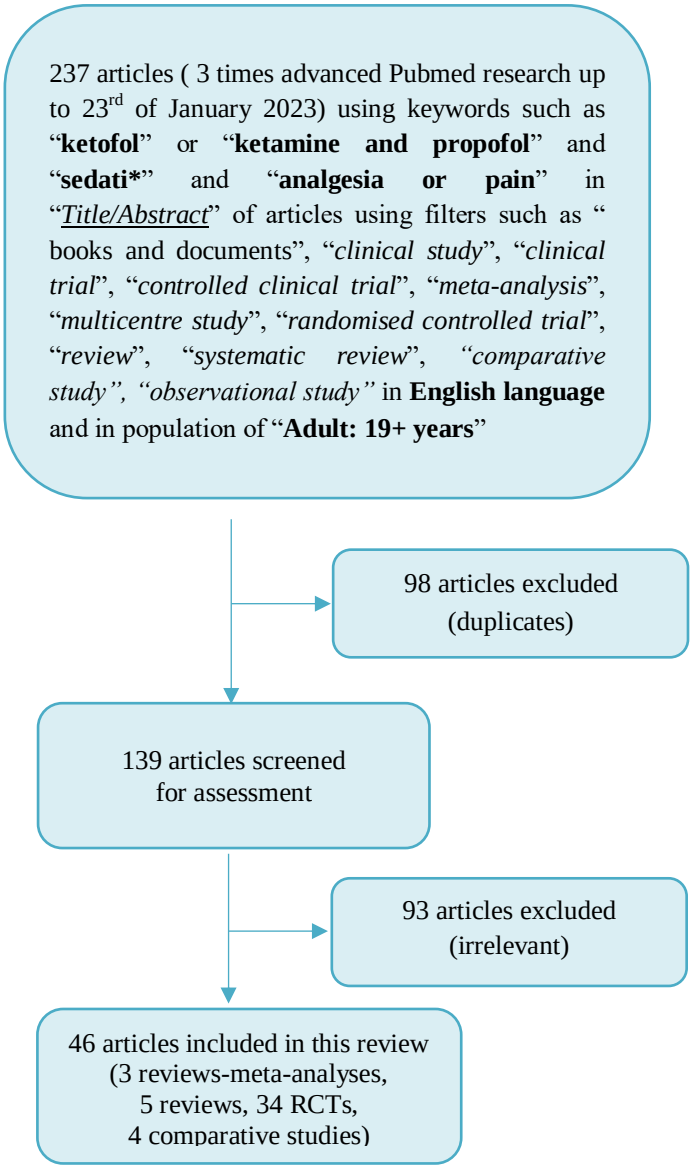

Figure 1. Flow diagram for "ketofol" review.

RESULTS

Studies comparing ketofol with propofol

One of the most important meta-analyses regarding comparison of ketofol to propofol belongs to Jalili et al. and was published in 2016 (Table 1).

This study was based on 18 trials. According to their results, the risk of respiratory complications appeared decreased in the case of ketofol around 70% compared to propofol (RR=0.31 in 14 trials, p=0.001).

The same applied for cardiovascular complications. Hypotension was less likely to occur with ketofol, up to 90% reduction (RR=0.11 in 9 trials, p=0.04), whereas risk for bradycardia presented 50% reduced with ketofol compared to propofol (RR=0.47 in 8 trials, p=0.008). Nevertheless, psychomimetic complications were more frequent with ketofol (RR=1.95 in 13 trials, p=0.15), so as nausea and vomiting rates (RR=1.23 in 12 trials, p=0.72)[15].

Authors/ Type of study	Trial Studies/ pts (n)	Groups	Main findings
Jalili M et al[15] 2016 Review and meta-analysis	18 trials	K/P vs P	1. *Respiratory complications*: significantly reduced in K/P group. 2. *Cardiovascular complications:* hypotension, bradycardia significantly less in K/P group. 3. *Psychomimetic complications:* non significantly increased in K/P group. 4. *Muscle rigidity:* non significantly less in the same group. 5. *Nausea and vomiting*: non significantly more frequent in K/P group.
Ghojazadeh M et al[16] 2019 Review and meta-analysis	5 Studies / 1250	K/P vs P	*1.* *Sedation:* K/P group shown better quality compared to P group in two studies. The other three showed no statistically significant difference between the two groups. 2. *Respiratory adverse effects:* less in pts of K/P group. 3. *Haemodynamic profile:* similar between two groups.
Hany ZA et al[31] 2022 Review and meta-analysis	6 studies	K/P vs K	1. *Desaturation:* no significant difference between the two groups. 2. *Nausea-Vomiting:* K/P significantly less compared to K group. 3. *Clinician's satisfaction:* K/P no impact compared to K group. 4. *Respiratory adverse effects:* in K/P were not reduced compared to K group. 5. *Recovery time:* K/P significantly shorter compared to K group 6. *Level of sedation and the BIS values:* K/P and K group similar associations between the above parameters. 7. *Other SEs:* no significant difference between the two groups
Loh G et al[17] 2007 Review	No data available	K/P vs P	1. *Discharge time:* not different in case K/P group for PSA. 2. *Haemodynamic-respiratory compromise*: K/P group required less active interventions in comparison to P group but this finding was not significantly different between groups. 3. *Nausea, vomiting, emergence reactions:* Patients with higher dosage of K experienced more. *Few studies included satisfaction scores and the effect of adding ketamine to propofol on the discharge time was inconclusive.*
Thomas MC et al[18] 2011 Review	10 trials	K/P (1:1) vs P vs K	1. *Respiratory complications – Hypotension:* Patients who are at great risk for developing the above on PSA are great candidates for the K/P combination group compared to either drug given as solo agent.
Sih K et al[32]. 2011 Review	6 studies	K (supplementary) for PSA and RSI	1. *Adequate sedation, high patient satisfaction and lack of pain and procedural recall* were reported in the majority of studies as a result of the use of K for PSA. There is no evidence to support the superiority of a combination of K/P in comparison to P alone for PSA in adults. 2. *Recovery agitation*: common with K use (minimised with premedication with midazolam) (NNT=6).

continued			*Although not a first line agent for RSI, ketamine can be safely used for such purpose.*
Wakai A et al[1] 2015 Review	10 studies/ 813	P to other drugs	1. *Comparative effects, alternative interventions on AEs, participant satisfaction:* No firm conclusions can be drawn in pts using P with or without adjunctive analgesic agents. 2. *Limitations:* no two studies employed the same comparator interventions, small number of participants in most of the studies included (<100).
Barends C et al[19] 2018 Review	No data available	Commonly used and new drugs for PSA	*The properties that would constitute an ideal sedative have not yet combined in one drug.* *The selection of the drugs for ambulatory sedation depends on the procedure type, patient's characteristics and the expectations of patient and health-care provider.* *The literature cannot yet provide a definitive answer as to which drug is best selected in a specific situation.*

AEs: Adverse Events, BIS: Bi-spectral index, K: ketamine, K/P: ketamine-propofol (ketofol), n: number, NNT: Number Needed to Treat, P: propofol, PSA: Procedural Sedation and Analgesia, pts: patients, RSI: Rapid Sequence Induction, SEs: Side effects.

Table 1. Meta-analyses and reviews comparing ketofol with propofol and ketamine.

This study was based on 18 trials. According to their results, the risk of respiratory complications appeared decreased in the case of ketofol around 70% compared to propofol (RR=0.31 in 14 trials, p=0.001). The same applied for cardiovascular complications. Hypotension was less likely to occur with ketofol, up to 90% reduction (RR=0.11 in 9 trials, p=0.04), whereas risk for bradycardia presented 50% reduced with ketofol compared to propofol (RR=0.47 in 8 trials, p=0.008). Nevertheless, psychomimetic complications were more frequent with ketofol (RR=1.95 in 13 trials, p=0.15), so as nausea and vomiting rates (RR=1.23 in 12 trials, p=0.72)[15].

Ghojazadeh et al. published more recently a meta-analysis based on 5 studies (n=1250 pts). According to their results, the respiratory adverse effects were decreased when ketofol was used instead of propofol for PSA. Additionally, ketofol produced better sedation, whereas the haemodynamic profile was similar between the comparators[16]. Another, older review had presented similar results regarding decreased respiratory effects of ketofol compared to propofol, but this finding was not significantly different between the groups[17]. In agreement with the above, Thomas et al. suggested that patients at high risk of developing respiratory complications and hypotension on PSA are good candidates for the ketamine/propofol combination compared to either drug alone[18].

On the other hand, Wakai and colleagues suggested that no firm conclusions could be drawn regarding efficacy, adverse events (AEs) and participants' satisfaction when administering propofol with or without adjunctive analgesic agents. The researchers however mentioned limitations associated with the comparator and sample size of studies included in their review[1]. Another important

truth in the field came in light in 2018 by Barends et al., who declared that the properties of an ideal sedative have not yet been combined in one drug and that the selection of the drugs for ambulatory sedation depends on many factors such as procedure type, patient characteristics and expectations of both patients and health-care providers[19].

The findings of the RCTs we identified are presented in Table 2.

Authors/ Year/ Type of study	pts (n)	pts characteristics/ Surgery/ Anaesthesia	Groups	Main findings
Frizelle HP et al[20] 1997 RCT	40	pts ASA I-II/ urologic or orthopaedic surgery/ spinal anaesthesia	K/P vs P	1. *Sedation scores, total P requirements:* similar between groups. 2. *MAP:* significantly lower in P group for the first 25 min. 3. *Respiratory complications:* no difference between groups. 4. *Administration of fluids, vasopressors, emergence and recovery phenomena:* similar between the groups.
Frey K et al[21] 1999 RCT	70	Elderly pts / undergoing cataract surgery/ general anaesthesia	K/P vs P	1. *Onset of sedation:* K/P group faster and significantly less supplemented sedation compared to group P 2. Assisted bag mask ventilation: Two patients in P group, none in the K/P group. *The addition of ketamine to propofol improved the quality of sedation and time to acceptable depth of sedation whereas it did not prolong recovery.*
Mortero F et al[28] 2001 RCT	39	ASA I-III/ / elective ambulatory surgery/ general anaesthesia	K/P vs P	1. *End-expiratory pCO_2*: lower in group K/P compared to group P. 2. *Mood and MMSE scores:* higher in group K/P. 3. *Pain and analgesic consumption after discharge*: less in case of K/P group. *Addition of small-dose ketamine on propofol may mitigate hypoventilation caused by propofol producing positive effects on mood without perceptual changes post-surgery and may provide earlier recovery of cognition.*
Phillips W et al[22] 2010 RCT	28	pts at ED requiring PSA for fracture manipulation	K/P vs P	1. *Hypotension:* less in the K/P group compared to P group. 2. *BIS score at goal sedation*: more increased in K/P combination compared to P group. 3. *Difference between goal sedation and baseline*: less in K/P group compared to P group. 4. *Propofol dosage*: less in K/P group compared to P group. *No patient in either group experienced respiratory depression or required any intervention.*
David H et al [23]. 2011 RCT	220	pts requiring PSA at the ED to undergo painful procedures	K/P vs P/Pl	1. *Respiratory depression*: similar between the groups. 2. *Personnel satisfaction*: more satisfied in K/P pts because of a trend towards better sedation quality.

continued				3. *Propofol dosage*: less in the K/P group compared to P/Pl group.
Andolfatto G et al[24] 2012 RCT	284	pts ASA I-III requiring PSA at ED to undergo painful procedures	K/P (1:1) vs P	1. *Respiratory AEs outcome*: K/P group did not result in reduced compared to P group, when given as an agent for PSA. 2. *Sedation depth* (*requiring repeated medication dose)*: more consistent in the case of K/P group compared to P group. 3. *Induction time, efficacy and sedation time* : similar between groups 4. *Satisfaction rates*: high for both agents.
Yalcin S et al [29] 2012 RCT	90	pts with major depressive disorder requiring sedation to undergo ECT sessions	K/P (1:1) vs P vs K	1. *Motor seizure:* significantly decreased in P group compared to others. 2. *Spontaneous breathing*: statistically increased in K group compared to the other two groups. 3. *Eye opening time, obeying command time*: significantly longer in K group. 4. *HR at induction and on the 3rd minute*: significantly higher with the following descending order: group K, K/P and P. *Ketofol (1:1) is associated with longer mean seizure time compared to propofol and shorter recovery time compared to ketamine with better haemodynamic stability without any important SEs in ECT anaesthesia.*
Wang X et al[30]. 2012 RCT	48	pts with major depressive disorder requiring sedation to undergo ECT sessions	K/P vs P vs K	1. *HDRS scores:* improved earlier in groups K and P/K. *Decreases in HDRS scores*: significantly greater in groups K and P/K compared to group P. 2. *AEs*: less in group P/K compared to group K. 3. *Seizure energy index and seizure duration*: greater in groups K and P/K compared to group P during ECT. *Propofol and ketamine combination might be a first line agent for PSA in patients with major depressive disorder who undergo ECT.*
Ferguson I et al[25] 2016 RCT	573	pts > 18 years old requiring deep sedation to undergo painful procedures at the ED	K/P (1:1) vs P	1. *Respiratory complications, need for intervention:* similar between the two groups. 2. *Depth of sedation:* similar in both groups 3. *Hypotension:* more likely to happen in P group. 4. *Patient satisfaction*: similarly high in the two groups. 5. *Emergence delirium:* more frequently observed in the K/P group.
Baykal TZ et al[26] 2016 RCT	95	pts requiring PSA to undergo colonoscopy	K/P vs P	1. *Time to reach deep sedation level, recovery time*: Group K/P exhibited shorter time to reach deep sedation level but longer recovery time. 2. *HR, MAP*: significantly lower compared to initial values in the case of P group. 3. *Respiratory depression, hypotension, nausea/vomiting:* more frequently observed in the P group compared to K/P' .

continued **Lemoel F. et al[33]** **2017** **RCT**	152	pts > 18 years old, ASA I-II / orthopaedic injuries requiring PSA to undergo painful procedures	K/P (1:1) vs K	1. *The incidence of recovery reactions, pharmacological and clinical interventions:* less in the K/P group compared to group K. 2. *Satisfaction scores:* similar between the groups. 3. *Emesis:* reduced in the K/P group compared to ketamine group (threefold reduction in incidence). 4. *Frequency of AEs regarding respiratory effects and hypotensive episodes:* similar between the two groups.
Tian L et al[27] **2020** **RCT**	200	pts requiring sedation to undergo colonoscopy	K/P vs P	1. *Cognitive functions*: more impaired when ketamine was added to propofol for PSA. *2. MAP:* the K/P group had better values at 5 min 3. *Respiratory depression, hypotension*: less in K/P patients 4. *OAA/S scores, BIS, MAP, complications, recovery times and endoscopist and patient satisfaction scores*: similar between the groups.

AEs: Adverse Events, ASA: American Society of Anaesthesiology, BIS: bi-spectral index, ECT: Electroconvulsive Therapy, ED: Emergency Department, HDRS: Hamilton Depression Rating Scale, HR: Heart Rate, K: ketamine, K/P: ketamine-propofol (ketofol), MAP: Mean Arterial Pressure, MMSE: Mini Mental State Exam, n: number,NNT: Number Needed to Treat, OAA/S scores: Observer Assessment of Alertness/ Sedation Scale scores, P: propofol, P/Pl: propofol-placebo, PSA: Procedural Sedation and Analgesia, pts: patients, RCT: Randomised Controlled Trial, SEs: Side-effects.

Table 2. Studies (RCTs and comparative studies) comparing ketofol with propofol and ketamine.

A few studies showed no significant differences between ketofol and propofol regarding respiratory effects[20-25]. It should be noted though, that a number of these studies employed a very small number of participants. However, most of the researchers who conducted these trials seemed to agree that the addition of ketamine to propofol reduced the likelihood for hypotension.

Interestingly, some of the studies claimed that sedation depth was more consistent in the case of ketofol compared to propofol[24], whereas the difference between targeted and baseline sedation was less for ketofol rather than propofol[22]. In fact, ketofol exhibited shorter time to reach deep sedation compared to propofol, but at the cost of longer recovery[26]. In general, sedation of better quality was achieved with ketamine/propofol combination compared to propofol alone. This was one of the main reasons why some health-care professionals reported to be more satisfied with ketofol rather than propofol[23].

Cognitive functions were more impaired when ketamine was added to propofol for PSA according to a RCT with 200 patients who received sedation for colonoscopy[27]. Meanwhile, ketofol was shown in some studies to improve mood in the long-term possibly due to the antidepressant effects of ketamine[28]. This finding was confirmed by two RCTs that compared ketofol versus propofol and ketamine when

used for sedation in patients with major depressive disorder scheduled for electroconvulsive treatment (ECT) sessions. Apparently, ketofol was associated with longer mean seizure time and seizure energy index compared to propofol and shorter recovery time and less side-effects compared to ketamine. In addition, the Hamilton Depression Rating Scale (HDRS) scores gave earlier and better results in the case of presence of ketamine. The researchers concluded that ketofol might be a first line agent for PSA in patients undergoing ECT as treatment for major depressive disorder[29,30].

Satisfaction was rated high by patients and providers in the majority of the studies regarding both ketofol and propofol, without significant differences between the two agents. However, emergence delirium was more strongly associated with ketofol compared to propofol (3% difference in a study of 573 patients who underwent painful procedures at the Emergency Department)[25]. Paradoxically, one study showed that nausea and vomiting were more frequent with propofol use compared to ketofol (17% vs 4.2%, p=0.041), possibly due to an increased consumption of opioid analgesics[26].

Studies comparing ketofol with ketamine

Hany et al. published recently a meta-analysis of 6 studies comparing the effects of ketofol versus ketamine[31]. They found no significant differences in desaturation rates (p=0.1) and other respiratory effects between the groups. Ketofol showed less nausea and vomiting compared to ketamine (p<0.05). The nature and extent of other side-effects (SEs) were found similar between the two agents except nausea (Table 1). Clinicians' satisfaction was not influenced by the agent, although ketofol appeared to have significantly shorter recovery time compared to ketamine. Interestingly, in both ketofol and ketamine groups the levels of sedation corresponded to the bi-spectral index (BIS) values.

Kendra Sih et al. included 6 studies in their review investigating ketamine when used as a supplement for PSA and rapid sequence induction (RSI) purposes. Adequate sedation, high patient satisfaction and lack of pain and procedural recall were reported in the majority of studies as a result of the use of ketamine for PSA. Recovery agitation was common but could be minimised with premedication midazolam. Lastly, they concluded that there was not enough evidence to support the superiority of a combination of ketamine and propofol over propofol alone for adult patients and that ketamine can be safely used for PSA and RSI, although not a first line agent for the latter[32].

Lemoel et al. published the results of a RCT which included 152 adult patients with orthopaedic injuries who required PSA to undergo invasive and painful procedures (Table 2). They randomly allocated patients in two groups: ketamine (K) and ketofol [K/P (1:1)]. One of their results was the reduction of recovery reactions with the use of ketofol [22% less

in K/P (1:1) compared to K group, p<0.01]. The risk for emesis was three-fold decreased in the case of ketofol compared to ketamine, whereas satisfaction scores, respiratory effects, hypotensive episodes and other AEs did not have significant differences between the two agents[33].

Studies comparing ketofol with other sedative agents and opioids

Most studies that compare the effects of opioids versus ketofol underlie the improved analgesia provided by opioids at the cost of increased risk of respiratory compromise. Specifically, a study in 2008 showed that patients who received fentanyl had a 5.1 times the odd of having a more serious intrasedation event compared to those who had ketamine as an addition to propofol[34] (Table 3).

Authors/ Year/ Type of study	pts (n)	pts characteristics/ Surgery/ Anaesthesia	Groups	Main findings
Akin A et al[41] 2005 RCT	40	Female pts requiring PSA to undergo endometrial biopsy	K/P vs P/F	1. *Respiratory depression:* observed in five and one patient from groups P/F and K/P respectively with no statistical significance 2. *Nausea, vertigo and visual disturbances:* more often seen in group K/P (p<0.05). 3. *Time to reach MAS:* similar between the groups. 4. *Discharge time:* significantly longer in group K/P compared to group P/F. 5. *Patient satisfaction:* more frequent in group PF compared to group K/P.
Hwang J et al[42]. 2005 RCT	276	pts requiring PSA to undergo fiberoptic bronchoscopy	K/P vs A/P	1. *Total dosage of propofol:* not significantly different between the groups. 2. *Haemodynamic stability:* achieved more successfully during sedation with K/P. *Decrease of HR and SAP:* shown in the case of A/P whereas no intervention for hypotension was required. 3. *HR:* increased after initiation of FOB compared to prior values in both groups. 4. *SaO_2:* fell in both groups with no statistical significance between both groups. 5. *Amnesia, patients' satisfaction:* significant higher percentage in K/P patients compared to A/P group.
Messenger D et al[34] 2008 RCT	63	pts ASA I-II, 14-65 years old, requiring PSA for orthopaedic reduction or abscess drainage	K/P vs P/F	1. *Intrasedation event:* presented in 83.9% and 46.9 in groups P/F and K/P respectively. Those events were moderate to severe in 51.6% and 21.9% in groups P/F and K/P respectively. P/F group had 5.1 times the odd of having a more serious intrasedation event compared to those in K/P group. 2. *Propofol total requirements:* higher in the

continued				K/P group.
Nejati A et al[43] **2011** **RCT**	62	pts requiring PSA to undergo repair of deep traumatic lacerations and reduction of bone fractures	K/P (1:1) vs M/F	1. *Satisfactory sedation and analgesia:* better in K/P group. 2. *Desaturation:* less in K/P group compared to M/*F. Apnoea:* observed in one patient of the K/P group. One patient from each group required bag-mask ventilation while neither was intubated. 3. *Sedation time:* no differences in the between the groups. 4. *Physician satisfaction scores:* no significant differences in the between the groups. 5. *Pain:* less in K/P group compared to M/F group.
Kramer KJ et al[44] **2012** **RCT**	37	pts requiring deep sedation for surgical extraction of all 4 third molars	K/P vs P/R	1. *Respiratory and haemodynamic stability:* similar between the groups 2. *Prolonged emergence and recovery:* significantly greater in K/P vs P/R group 3. *Satisfaction scores of patients and surgeons:* similarly high for both groups. 4. *PONV:* non statistical or clinical significant difference between the groups. *Ketamine failed to show any pre-emptive analgesic effect in this study.*
Fabbri LP et al[40] **2012** **RCT**	322	pts ASA I-III, 18-85 years old requiring PSA to undergo ERCP	P/R vs P/R/K	1. *Respiratory depression:* observed in 25 P/R patients versus 9 in P/R/K group (p=0.0035). 2. *Mean saturation:* significantly lower in P/R group at all times compared to P/R/K. 3. *Total propofol dose:* no difference between groups. 4. *Cardiovascular parameters:* no difference between groups. 5. *Discharge time:* greater in P/R opposed to P/R/K patients. 6. *Nausea and vomiting, (delaying ward transfer):* significantly greater in P/R vs P/R/K pts. 7. *Interruption of ERCP:* 9 cases of P/R vs no cases in P/R/*K.* 8. *Quality of intraoperative conditions*: highly satisfactory in 92% of P/R/K vs 67% of P/R patients.
Türk H et al[46] **2014** **RCT**	70	pts ASA I-II requiring PSA to undergo elective colonoscopy	K/P vs A/P	1. *Haemodynamic stability, quality of sedation:* better in K/P compared to A/P group 2. *Propofol dose:* less in K/P group 3. *Discharge time:* longer in K/P compared to A/P group
Kilic E et al[47] **2016** **RCT**	52	Obese pts requiring PSA to undergo upper gastrointestinal system endoscopy	K/P vs A/P	1. *Sedation onset time, duration of sedation:* shorter in group A/P compared to K/P. 2. *Time to reach MAS:* shorter at 5 min in group A/P but not significantly different at 10 min time between the groups 3. *Total propofol consumption*: significantly greater in group K/P. 4. *Hypotension, bradycardia:* more

continued				frequently observed in group A/P with no statistical significance. 5. *Nausea and vomiting:* more frequent in group K/P with no statistical significance. 6. *Patient and physician satisfaction:* no statistically significant differences between groups.
Akhondzadeh R et al[35] 2016 CS	98	pts > 18 years old requiring deep sedation to undergo painful procedures at the ED	K/P vs P	1. *Haemodynamic variables:* similar between two groups. 2. *Pain at the end of the procedure and 1 hr after:* less in K/P group with no statistical significance. 3. *RSS:* similar between the two groups. 4. *Total propofol requirements:* similar between the two groups. 5. *Apnoea rate:* 32% in K/P vs 63% in P/F group.
Oncul S et al[39] 2016 CS	60	Female pts ASA I-II requiring PSA to undergo hysteroscopy in combination with paracervical block	K/P vs R	1. *Time to recovery:* significantly greater in the K/P group compared to remifentanil group. 2. *PONV rate:* more increased in the R group compared to K/P. 3. *Hypotension or hypertension rate, bradycardia rate:* not statistically significant between groups. 4. *Tachycardia:* more frequently observed in the R group (16.6% vs 3.3%, p=0.08). 5. *Respiratory depression:* most frequently shown in the R group compared to K/P . 6. *Satisfaction of participants:* similar between groups.
Fruchter O et al[45] 2017 RCT	80	pts requiring sedation to undergo flexible fiberoptic bronchoscopy	K/P/M vs F/P/M	1. *Minimal TcpCO2 during the procedure and saturation:* did not differ significantly between groups. 2. *Respiratory and haemodynamic parameters:* not significantly different between groups. 3. *Satisfaction of patients and operators:* similar between groups. *Ketamine is as effective as fentanyl providing adequate analgesia for FFB, a potent bronchodilator achieving respiratory and haemodynamic stability.*
Aminiahidashti H et al[36] 2018 RCT	136	pts with trauma requiring PSA at the ED to undergo invasive and painful procedures	K/P vs P/F	1. *Pain scores:* significantly lower in the P/F group *Analgesia:* fentanyl was significantly better compared to ketamine. 2. *Sedation:* deeper in P/F group compared to K/P. 3. *Respiratory and cardiovascular events:* more observed in P/F group (desaturation and bradycardia episodes) compared to K/P with no clinical importance.
Seleem WM et al[37] 2020 CS	150	pts requiring PSA to undergo colonoscopy	K/P vs P/F	1. *Haemodynamic stability:* achieved better in K/P compared to P/F group. 2. *Significant decrease in HR* more common in female patients of the P/F group. 3. *Recovery time:* shorter in P/F group compared to K/P group.

continued				4. *Nausea, vomiting and hypoxia:* more common in P/F group. 5. *Hallucinations:* more frequently observed in K/P group. *Sedation with propofol and ketamine during colonoscopy was found to be safe and efficacious.*
Bahreini M et al[38] 2021 RCT	96	pts requiring PSA to undergo invasive and painful procedures at the ED	K/P vs T/F	1. *Patient satisfaction, provider's satisfaction:* better in K/P group compared to T/F group. 2. *Recalling of the events:* significantly higher in T/F group compared to K/P group. 3. *Transient hypoxia, airway intervention:* significantly higher in T/F group compared to K/P group, without the need for intubation or any admission.

AEs: Adverse Events, A/P: Alfentanil-propofol, ASA: American Society of Anaesthesiology, BIS: bi-spectral index, CS: comparative study, ED: Emergency Department, ERCP: Endoscopic Retrograde Cholangiopancreatography, FFB: Flexible Fiberoptic Bronchoscopy, FOB: Fiberoptic Bronchoscopy, F/P/M: fentanyl-propofol-midazolam, HR: Heart Rate, K: ketamine, K/P: ketamine-propofol (ketofol), K/P/M: ketamine-propofol-midazolam, MAS: Modified Aldrete Score, MAP: Mean Arterial Pressure, M/F: midazolam-fentanyl, n: number, P: propofol, P/F: propofol-fentanyl, PONV: Post-operative Nausea and Vomiting, P/R: propofol-remifentanil, P/R/K: propofol-remifentanil-ketamine, PSA: Procedural Sedation and Analgesia, pts: patients, R: remifentanil, RCT: Randomised Controlled Trial, RSS: Ramsey Sedation Score, SaO2: Saturation of haemoglobin in oxygen, SAP: Systolic Arterial Pressure, TcpCO2/pCO2= end-tidal carbon dioxide, T/F: thiopental-fentanyl, VAS: Visual Analogue Scale.

Table 3. Studies comparing ketofol with opioid combinations (and other agents).

Similarly, there are studies which report that the rate of respiratory complications was significantly increased when opioid was added to the sedative regimen[34-38]. When remifentanil was compared to ketofol, the respiratory depression risk increased almost five times more. The same risk increase applied regarding tachycardia rate in remifentanil compared to ketofol[39]. Interestingly, there was an RCT which showed that only the presence of ketamine in the combination can actually help to mitigate the risk of respiratory effects of the sedative regimens. Specifically, when remifentanil/propofol was compared to ketofol/remifentanil for sedation purposes, the risk for respiratory complications was significantly reduced when ketamine was present in the regimen[40]. Nevertheless, there were studies which showed no significant differences between the opioid combination and ketofol groups or the samples were too small to extrapolate safe conclusions regarding this effect[41-45]. Of course, the intervention performed so as the status and the comorbidities of the patient play a major role to this.

Maintenance of haemodynamic stability favours ketofol over opioid/sedative combination[36,37,42,46,47]. It has to be noted though, that some of these findings were not statistically significant. Furthermore, there were many researchers also who reported that the episodes of haemodynamic change were not clinically important in the majority of the cases[36,42]. Other studies reported that the haemodynamic var-

iables did not present significant differences between the groups[35,39,44,45] but none in favour of an opioid and a sedative combination compared to ketofol regarding this outcome.

It is generally accepted that the analgesia provided by opioids is superior to the analgesia provided by ketamine despite the many side-effects of opioids[36]. Nevertheless, this was not verified by some of the studies which mentioned that analgesia caused by ketamine was as efficient as analgesia caused by opioids and the intervention was managed to be successfully completed in all cases[35,43,45]. It depends however on the level of pain caused by the intervention. Interestingly, there was a study which showed that pain was less in the ketamine/propofol group compared to the midazolam/fentanyl group[43]. A RCT with adult patients who required deep sedation for endoscopic retrograde cholangiopancreatography (ERCP) showed that the addition of ketamine to the propofol and remifentanil combination not only was related to less SEs during or after the procedure but could also create better conditions for the intervention to be successfully completed[40]. Nevertheless, quite often healthcare professionals realized that pain could not be dealt enough with ketamine ending up administrating opioids. Indeed, opioids were used in a lot of the studies mentioned in this review, regardless of the agents being compared.

Amnesia was also greatly achieved in the case of ketofol, probably being improved compared to the opioid combination[42]. The same applied regarding sedation depth which was more consistent with ketofol. Nevertheless, there were studies with contrary findings[36]. Patient satisfaction was rated high in the majority of the studies, both in the ketofol and the opioid regimen groups[39,42,44,45,47]. One study however showed that the satisfaction rate of the patients was better in the case of opioid use[41]. Satisfaction rates for health care professionals were also rated high, without significant differences between the groups[42-45,47]. Time to recovery and discharge seemed to appear longer in the case of ketofol[37,39,41,44,46]. The same applied regarding nausea and vomiting[41] and hallucination rates[37]. Nevertheless, there were studies which showed that post-operative nausea and vomiting was similar between the comparators[44] or even being strongly associated with the use of opioids compared to the ketofol group[37].

Studies comparing ketofol with dexmedetomidine

When dexmedetomidine was compared to ketofol no significant differences were found regarding respiratory suppression rates[48] (Table 4).

This finding underlies the safety profile of ketofol regarding respiratory effects, since dexmedetomidine is not strongly associated with respiratory depression. Differences in desaturation and hypoxia episodes were more evident when propofol became “player” of the “com-

parison game"[49,50].

Authors/ Year/ Type of study	pts (n)	pts characteristics/ Surgery/ Anaesthesia	Groups	Main findings
Mogahd M et al[53] 2017 CS	70	pts receiving PSA post CABG surgery	K/P vs K/D	1. *Weaning and extubation times:* significant shorter in K/D group compared to group K/P. 2. *Fentanyl consumption:* significantly less in the case of K/D compared to K/P. 3. *Haemodynamics and length of ICU stay:* similar between the groups.
Sruthi S et al[48] 2018 RCT	50	Adult pts,18-60 years old, with atrial septal defect and rheumatic valvular heart disease requiring PSA to undergo TOE	K/P vs D	1. *Time to RSS ≥ 3:* significant less for K/P compared to D group. 2. *HR:* significant decrease in D group, with no significant change from baseline in the K/P group. 3. *Total procedure time and recovery time*: no significant differences between groups. 4. *Respiratory, haemodynamic or any other complications:* no significant differences between groups. 5. *Patient satisfaction score:* comparable between groups. 6. *Cardiologist's satisfaction score:* more satisfied in the case of K/P compared to D.
Yin S et al[51] 2019 RCT	120	Elderly pts requiring PSA to undergo GI endoscopy	K/P vs P/Sa vs P/Su vs P/D	1. *HR (AUC):* lowest in the P/D. 2. *SaO_2 (AUC):* higher in the P/D and K/P groups compared to the other two groups. 3. *Incidence of bradycardia and hypotension:* P/D group had the highest episodes. 4. *Hypoxia:* highest rate in P/Sa (control) group. 5. *Propofol consumption:* greater in control group (P/Sa) and lowest in the K/P group. *The combination of K/P succeeded the most haemodynamic and respiratory stability in elderly pts requiring PSA compared to the other agents used in the study.*
Tekeli AE et al[54] 2020 RCT	60	pts ASA I-II, 18-60 years old, requiring PSA to undergo upper GI system endoscopy	K/P vs P/D	1. *Sedation depth:* P/D superior compared to K/P group. 2. *Early recovery:* K/P group superior compared to P/D. *P/D and K/P in upper GI endoscopy may Be appropriate and safe with minimal AEs.*
Elkalla RS et al[49] 2020 RCT	60	Adult OSA pts requiring PSA to undergo drug induced sleep endoscopy	K/P vs P vs D	1. *Oxygen desaturation (<90%):* more evident in group P as compared to groups D and K/P. 2. *Time to reach sufficient sedation level, prolonged recovery time:* Dexmedetomidine required significantly longer

continued				times and required more rescue propofol compared to the other groups. 3. *HR:* lower in group D after the loading dose until 30 mins post bolus in comparison to the other groups. BP: lower in both groups P and D throughout the whole procedure and reaching recovery compared to K/P group. 4. *Psychomimetic effects*: two patients in group K/P. 5. *Other AEs, patients' and endoscopists' satisfaction levels:* no significant differences between groups.
El Mourad MB et al[50] 2021 RCT	75	pts with left to right shunt requiring PSA to undergo diagnostic TOE interventions	K/P vs P vs D	1. *The time onset and offset of sedation, duration of TOE procedure and the need for rescue propofol:* less in P and K/P groups compared to group D. 2. *MAP, HR, CO:* significantly decreased in groups P and D compared to baseline and group K/P. 3. *Hypoxia:* more frequently observed in group P. 4. *Cardiologist's satisfaction:* higher in group K/P compared to the other groups.
Azizkhani R et al[52] 2021 RCT	93	pts older than 18 years old requiring PSA to undergo invasive and painful procedures at the ED	K/P vs K/D vs K	1. *The incidence of recovery agitation:* 26% in the K/D group, 29% in the K/P group and 58% in the K group. 2. *Severe agitation:* mostly observed in the K group.

AEs: Adverse Events, ASA: American Society of Anaesthesiology, AUC: Area Under the Curve, BP: blood pressure, CABG: coronary artery by-pass graft, CO: Cardiac Output, CS: comparative study, D: dexmedetomidine, ED: Emergency Department, GI: Gastrointestinal, HR: Heart Rate, K: ketamine, K/D: ketamine-dexmedetomidine, K/P: ketamine-propofol (ketofol), MAP: Mean Arterial Pressure, n: number, OSA: obstructive sleep apnoea, P: propofol, P/D: propofol-dexmedetomidine, PSA: Procedural Sedation and Analgesia, P/Sa: propofol-saline, P/Su: propofol-sufentanil, pts: patients, RCT: Randomised Controlled Trial, RSS: Ramsey Sedation Score, TOE: trans-oesophageal echo.

Table 4. Studies comparing ketofol with dexmedetomidine (and other agents).

Dexmedetomidine was associated with longer time to reach sufficient sedation level, prolonged recovery time and increased requirements of rescue propofol compared to ketofol to reach the goal sedation level[48]. Similarly, there are studies which showed that bradycardia and hypotension episodes were frequent in patients who received dexmedetomidine for sedation[48-51]. This is not a finding though which has been confirmed by all researchers. In fact, these haemodynamic changes were not clinically important in most of the cases.

Ketofol was the only drug which was able to achieve haemodynamic stability by maintaining (and perhaps increasing) blood pressure (BP), heart rate (HR) and cardiac output (CO) during sedation when it was compared with propofol and dexmedetomidine[49,50]. Providers' satisfaction levels seemed to rank higher in the case of ketofol, possibly due to that reason. Nevertheless, psychomimetic complications were more frequent when ketamine was pre-

sent in the mixture[49]. The same applied regarding agitation which presented strongly associated to the use of ketamine, whereas the incidence of agitation was lower when dexmedetomidine or propofol was added to ketamine for comparison[52].

Interestingly, the combination of ketamine and dexmedetomidine (K/D) has been compared to ketofol when administered for sedation in patients after cardiac surgery [coronary artery bypass graft (CABG)]. Group K/D exhibited reduced time of weaning and extubation compared to ketofol group, whereas fentanyl consumption was significantly less with K/D compared to ketofol. Both these findings were statistically significant. Haemodynamics and length of stay in the Intensive Care Unit (ICU) were comparable between the groups in this study[53]. Similarly, the combination of dexmedetomidine and propofol (D/P) has been compared to ketofol. This was a small study performed in patients who required sedation to undergo upper gastrointestinal endoscopy. Their findings were that D/P and ketofol are appropriate and safe sedatives with minimal AEs when used for such purposes. Nevertheless, D/P appeared superior to ketofol in terms of sedation depth, while ketofol proved superior in terms of early recovery[54].

Another RCT compared all possible combinations. It was performed in 120 elderly patients who required sedation to undergo gastrointestinal endoscopy. The comparators were propofol/saline (P/Sa, control group), propofol /sufentanil (P/Su), propofol/ dexmedetomidine (P/D) and ketofol. The area under the curve (AUC) for HR was lowest in the P/D group, whereas the AUC for saturation (SaO_2) was higher in groups P/D and ketofol. The P/D group exhibited the highest incidence of bradycardia and hypotension whereas the control group presented the highest rate of hypoxia episodes. Propofol consumption was lowest in the ketofol group. Apparently, the ketofol group succeeded the most haemodynamic and respiratory stability in elderly patients as shown by this study[51].

Studies comparing different ratios of ketofol (and other agents)

Different ratios of ketamine/propofol combination were compared in various studies but the ideal analogy to the mixture still remains undetermined. Most studies in this domain were performed in children, possibly because ketamine is more frequently used to children compared to the adult population for sedation. We identified 5 studies which compared different ratios of ketofol in adult populations (Table 5).

As expected, the higher the dosage of ketamine, thus less propofol in the mixture, the more reduced the risk of respiratory suppression and haemodynamic compromise. On the other hand, the increased dose of ketamine is associated with more nausea and vomiting, psychomimetic complications, agitation and prolonged recovery[55]. In most studies, the need

for opioid rescue appeared inversely analogous to the ketamine dose; meaning that higher doses of ketamine in the mixture were associated with less need for opioids[56,57].

Authors/ Year/ Type of study	pts (n)	pts characteristics/ Surgery/ Anaesthesia	Groups	Main findings
Badrinath S et al[56] 2000- RCT	100	Adult female pts undergoing breast biopsy procedures under local anaesthesia	P/Pl vs K/P1 vs K/P2 vs K/P3	1. *Requirement for opioid rescue*: less in ketamine groups in a dose depended manner contributing to analgesia and minimizing the need for supplemental opioids. 2. *Nausea, vomiting and psychomimetic effects:* more frequent as more ketamine was added to the mixture leading to more delayed discharge times. *The combination of propofol and subanaesthetic dose of ketamine is a safe sedative/analgesic mixture during monitored anaesthesia care whereas ketamine may be a useful adjuvant to propofol sedation especially where procedures are expected to be painful.*
Erden IA et al[59] 2010 RCT	72	pts ASA I-III undergoing interventional radiological procedures under sedation	K/P (1:1) vs K/P (1:2)	1. *Demographics, duration of the procedure, haemodynamic values, oxygen saturation, side effects:* no significant differences between groups. 2. *Mean propofol dose, number of oversedated pts, additional propofol requirements*: higher in group K/P (1:2). 3. *Mean recovery time:* not significantly different between groups.
Miner JR et al[58] 2015 RCT	271	Adult pts ASA I-III undergoing interventional radiological procedures under sedation	P vs K/P (1:1) vs K/P (1:4)	1. *Airway and respiratory AEs:* similar between the groups. 2. *Recovery agitation: more frequently observed in K/P groups.* 3. *Efficacy, sedation depth and time, reported pain, recall and satisfaction:* similar between the groups.
Sanatkar M et al[57] 2015 RCT	80	pts requiring PSA to undergo plastic and reconstructive surgery	K/P (1:2) vs K/P (1:4)	1. *Anaesthesia induction:* similar between groups. 2. *Oversedation:* more frequent in group (1:4) but not statistically significant. 3. *Sedation efficacy:* similar between groups. 4. *Haemodynamic changes:* greater in group (1:4) compared to group (1:2). 5. *Respiratory depression:* less prominent in group (1:2).

continued				6. *Recovery time, other AEs:* similar between groups. 7. *The mean pain score, opioid administration:* lower in group (1:2) compared to group (1:4).
Ayatollahi V et al[55] 2016 RCT	100	pts requiring PSA to undergo closed reduction of nasal fractures	K/P (1:1) vs K/P (1:3)	1. *Haemodynamic profile:* similar between groups. 2. *Hallucination, vomiting rate and recovery duration:* reduction in K/P (1:3) group compared to the (1:1) agent [higher concentration of ketamine on the mixture (1:1)].

AEs: Adverse Events, ASA: American Society of Anaesthesiology, K: ketamine, K/P: ketamine-propofol (ketofol), K/P1: propofol-ketamine 0.94 mg/ml, K/P2: propofol- ketamine 1.88 mg/ml, K/P3: propofol-ketamine 2.83 mg/ml, n: number, P: propofol, P/Pl: propofol-placebo, PSA: Procedural Sedation and Analgesia, pts: patients, RCT: Randomised Controlled Trial.

Table 5. Studies comparing different ketofol ratios.

In a large RCT performed in patients ASA I-III undergoing interventional radiological procedures under sedation, the groups of propofol, ketofol (1:1) and ketofol (1:4) were used. Paradoxically, the airway and respiratory AEs did not appear to have significant differences between the groups. The same applied regarding other outcomes, including efficacy, time and depth of sedation, reported pain, recall and general satisfaction[58]. On the contrary, when ketofol (1:2) was compared to ketofol (1:4) in another study, the haemodynamic change was more pronounced as the dose of propofol increased in the mixture, meaning it was greater in group (1:4) compared to the (1:2) group. In the same way, respiratory depression was less evident for group (1:2). Nevertheless, it is important to mention that in this study the doses of ketamine and propofol in the ratio (1:4) were 2.25 mg/ml and 9 mg/ml respectively. The doses became 4.5 mg/ml and 9 mg/ml for the ratio (1:2) respectively[57]. Therefore, we can easily realise that there is great discrepancy even regarding the doses in the mixture between the studies, regardless of the ratios of the two drugs present.

Interestingly, a study comparing the ratios (1:1) and (1:2) showed that the number of over-sedated patients increased as the dosage of ketamine decreased in the mixture, because these patients required more extra propofol (rescue) to complete the intervention[59].

DISCUSSION

Most of the researchers agree that the combination of ketamine and propofol is associated with a reduced risk of respiratory and haemodynamic compromise in comparison to propofol[15,18,26,27]. The addition of subanaesthetic doses of ketamine provides not only sufficient analgesia with preservation of a patent airway, breathing and reflexes but is also associated with reduced dose of propofol in the mixture, therefore less risk of developing apnoea, hypotension and bradycardia[14]. Regard-

ing side effects, many researchers seem to agree that the addition of ketamine leads to increased risk of nausea and vomiting, psychomimetic effects, recovery agitation and emergence phenomena and finally prolonged recovery time[15,17]. Nevertheless, premedication with midazolam can mitigate the latter phenomena[32].

There are a few studies which showed no difference between ketofol and propofol regarding respiratory[20-25] and haemodynamic complications[16]. The same applied for other side-effects, time of sedation, recovery time and satisfaction of patients and health-care professionals[24,27].

In relation to other sedative agents, ketofol seems to present both advantages and disadvantages. Apparently, the analgesia provided by ketamine in the mixture of ketofol is not sufficient in comparison to opioid analgesia[36]. Nevertheless, it is considered a successful opioid sparing option, which is especially important in cases where administration of many opioids should be avoided. It is well known that opioids present synergistic effects with other sedatives and can lead to increased risk of respiratory and haemodynamic compromise, especially in opioid naive patients.

Regarding benzodiazepines, the use of midazolam may lead to prolongation of awakening. Also, titration to optimal sedation with midazolam is neither so versatile nor predictable. Respiratory effects are also frequent with this drug. Administration of midazolam can end up extremely problematic in specific populations, such as geriatric patients where prolongation of recovery and delirium are frequent and obese or sleep apnoea patients where respiratory effects, mainly hypoventilation, hypercapnia, apnoea and easy loss of airway consist issues of extreme clinical significance[60].

Similarly to dexmedetomidine, ketofol is also not frequently associated with respiratory suppression. Though a very useful and advantageous agent, dexmedetomidine appears to have some drawbacks. Bradycardia, hypotension and even hypertension can occur during its use[61]. Additionally, dexmedetomidine requires some time to reach target sedation level and frequently needs boluses of propofol to achieve that. On the contrary, ketofol seems to require less propofol rescue while at the same time it can achieve sedation of higher quality and in less time than dexmedetomidine[48]. Furthermore, ketofol was the only sedative in some studies which was able to succeed cardiovascular stability during its' use for sedation purposes while maintaining and perhaps increasing arterial pressure, heart rate and cardiac output[49,50]. Nevertheless, the dosage of ketamine should be taken into consideration during its use since there are many cases where increase of cardiac workload is not desirable nor expected, especially in people with non stable coronary artery disease.

Several limitations exist in the majority of the

studies which were included in the present review. Specifically, the sample size was small in several studies, while in addition, the comparator variables were not the same. Additionally, the types of the procedures were frequently different, the demographic data of the patients and their status also; even the dosages of the drugs were different among ketofol mixtures, regardless of the ratios present. Therefore, caution is needed for the extrapolation of safe conclusions and generalization of the findings to different populations and procedures. It is well known that the selection of drugs for PSA depends on many factors, such as the procedure type, patient characteristics, expectations of both patients and the health-care providers[19]. Unfortunately, all properties that would constitute an ideal sedative have not yet been combined in one drug[19]. There is no golden recipe and drug combinations should be tailored to each individual case.

Nevertheless, literature agrees that ketofol is associated with less respiratory and haemodynamic suppression in comparison to propofol which is considered the "gold-standard" in sedation[15]. Therefore, patients at risk of respiratory or haemodynamic compromise during sedation with propofol are good candidates to receive ketofol instead[18], especially where the intervention is expected to be painful. This is suggested only when ketamine is not contraindicated; known contraindications of ketamine are history of schizophrenia or other psychotic behaviour or epilepsy, reduced level of consciousness, recent trauma or intracranial bleeding, raised intracranial pressure, uncontrolled hypertension (>190/110 mmHg) or high risk coronary artery disease, moderate or severe hepatic dysfunction, history of heart failure or recent myocardial infarction or stroke (last 6 months), pregnancy or known hypersensitivity, raised intraocular pressure and history of thyrotoxicosis[62].

Finally, the literature has not provided an answer regarding the optimal ratio of ketamine: propofol in the ketofol mixture in order to maintain respiratory and haemodynamic stability while providing adequate sedation and analgesia, but without prolonging recovery. Most studies designed to answer that question have been performed in children. The most relevant study belongs to Coulter et al. and involved patients in good health, aged between 2 and 20 years who received ketofol (ratios from 1:1 up to 1:10) for PSA. The investigators concluded that the optimal ratio of ketamine: propofol is 1:3 for intermittent doses and 1:4 for a continuous infusion[63]. It is possible that the same ratios may apply to adult population as well, but perhaps not to elderly or fragile patients with significant co-morbidities.

CONCLUSIONS

There is no strong evidence in the literature to support the superiority of ketofol compared to other available agents, and specifically propofol which is considered the "gold-

standard" in sedation. The literature is also inconclusive regarding the ideal ratio of ketamine: propofol in terms of ketofol optimal efficacy and safety. It seems that the addition of ketamine in sub-dissociative doses to propofol is associated with less respiratory and haemodynamic effects during sedation, better analgesia, deeper and more consistent sedation, perhaps more amnesia in patients and also high satisfaction in both patients and health care providers. Frequent side-effects of ketofol such as increased psychomimetic effects, agitation, nausea and vomiting and perhaps prolongation of recovery may not outweigh its potential benefits during PSA. Therefore, we consider that ketofol use should be encouraged in cases where there are no contraindications for ketamine, especially when interventions are expected to be painful and when the risk of respiratory depression is high. Definitely, more large well-designed randomised clinical trials are necessary to extract robust conclusions regarding superiority of ketofol against other agents during PSA.

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