Efficacy of Sedation Medications for Procedural Sedation

Hayley R. Stromberg

University of Wyoming

PICOT: In adult patients undergoing procedural sedation, how does the administration of Ketofol compared with Propofol alone affect adverse respiratory effects within the perioperative period?
Procedural Sedation and Medications

Coming to the hospital in any fashion can be an anxiety-ridden and potentially painful experience for our patients. The most common reasons for Emergency Department and hospital visits for adults ages 18-85+ were open wounds of the head, neck, trunk, and extremities, chest pain and cardiac issues, asthma exacerbations, and sprains and strains, in which most instances, these cases resulted in discharge after treatment (Weiss, Wier, Stocks, & Blanchard, 2006). There are many uncomfortable and unpleasant procedures that can take place within the hospital whether you are in the emergency department, intensive care units, or even general medicine floors. Some of these procedures can include cardioversion, orthopedic injury reduction, and even a bronchoscopy (Adams, Dervay, Alexander, & Susla, 2012). With the thought of having a procedure done, this can cause anxiety, pain, and agitation for the patient and as a care provider, the goal is to minimize these behaviors that patients exhibit and experience. Currently, one of the best ways to accomplish this goal is by acting with procedural sedation. Procedural sedation, which was previously known as conscious sedation, is defined as “a technique of administering sedatives or dissociative agents with or without analgesics to induce a state that allows patients to tolerate unpleasant procedures while maintaining cardiorespiratory function” (Adams et al., 2012).

With the variety of different medications available to be used in the procedural sedation and analgesia (PSA) setting, there are multiple adverse effects, pharmacological distinctions, and functions that can be of use to the provider. When it comes to what makes a great PSA pharmacological agent, there a few considerations. The agent must allow the patient to be subject to minimal anxiety, pain, and discomfort while experiencing maximal amnesia during the procedure. To maximize procedural timeliness, procedural sedation and analgesia agents should
have a rapid onset of action, short duration of action, and an ease of administration (Deady, Smith, & Kuhn, 2007). The most commonly used agents include propofol, benzodiazepines, ketamine, opioids, and etomidate. The varying onset and action times is what helps to determine which medication will be used. Most importantly, the sedative, analgesic, and dissociative effects such as hemodynamic changes and respiratory depression should be closely monitored (Adams et al., 2012). With the objective of identifying whether Ketofol or propofol alone creates more adverse respiratory effects for those undergoing procedural sedation, it is imperative to examine and understand the inner workings of these medications and their characteristics.

**Anesthetics- Receptors and Neurotransmitters**

Anesthesia refers to the practice of blocking the feeling of pain to allow medical and surgical procedures to be undertaken without pain. Before anesthesia methods were discovered, opium and alcohol were regularly used to produce insensibility, both of which had a number of negative side effects and did not dull the pain completely (History of Anesthesia, n.d.). Patients were often held or tied down, and few procedures were possible as speed was the main determinant of a successful surgeon. Due to the lack of sedation and their painful nature, surgeries or procedures were an absolute last resort.

With the creation and findings of vapors, gases, and medications, we are now able to perform these procedures with more ease than was experienced hundreds of years ago. We are now able to provide a better procedural experience for the patient; doctors are allotted more time during surgery to complete their refined and complex skills.

As of recently, we have been able to figure out how anesthetics work. Scientists are now able to study how drugs affect specific molecules within cells. It has been discovered that these
drugs target proteins in the membranes around nerve cells (Anesthesia, 2020). Some of the available agents used for procedural sedation mimic the activity of gamma-aminobutyric acid (GABA), which is an inhibitory neurotransmitter (Adams et al., 2012). Since GABA acts in the central nervous system, it functions to reduce the activity of the neurons it binds. It essentially inhibits nerve transmission in the brain, which calms nervous activity (Zanetti, n.d.). Within the GABA receptors, there are two types known as GABA-A and GABA-B. General anesthetics and benzodiazepines typically act on GABA-A, as it is associated with a chloride ion channel. By activating these receptors, this causes hyperpolarization of the neuron, which results in sedation, anxiolysis, and hypnosis (Adams et al., 2012).

However, not all anesthetics function on the GABA receptors and neurons. Some agents, one being ketamine, works by inhibiting N-methyl-D-aspartate (NMDA) receptors that are found throughout the central nervous system as well. When these receptors are activated by excitatory neurotransmitters, such as glutamate, an influx of calcium enters the neuron resulting in excitation. By inhibiting these receptors, this prevents the excitation and results in a sedative and dissociative effect (Adams et al., 2012).

**Ketamine**

While ketamine has been around for quite some time, it is just now making an appearance to the forefront of procedural sedation and analgesia. When referring to its neurotransmitters and receptors, ketamine is very effective. Ketamine is an NMDA receptor blocker that inhibits the binding of glutamate (Adams et al., 2012). Ketamine is an agent that provides excellent anesthetic induction and maintenance. It causes a dissociation between the cortical and limbic systems and prevents patients from perceiving sensory stimuli (Ghojazadeh, Sanaie, Paknezhad, Faghih, & Soleimanpour, 2019). While it is a great amnestic and analgesic agent, it helps to
preserve airway reflexes, cardiovascular and respiratory stimulation, and analgesia. Ketamine has a rapid onset of action but has a longer half-life compared to other sedative agents (Adams et al., 2012). However, the use of ketamine alone is limited due to longer recovery time, and the potential side effects of agitation and vomiting (Andolfatto & Willman, 2011). It is important to note, that ketamine could be a good analgesic for a patient who is hypotensive, as a dose of ketamine is shown to increase heart rate and blood pressure, but not affect respiratory function (Adams et al., 2012). Ketamine is a great agent to combine with other sedative medications as most sedatives do tend to lower the heart rate and blood pressure on their own.

**Propofol**

As a long standing and well known sedation agent, propofol is a consistent procedural sedation agent that many providers and personnel will turn to due to its effects and characteristics. Looking at its receptors and chemical make-up, propofol is a short acting alkylphenol that is used to induce and maintain anesthesia while also sedating patients for procedure. Due to the discovery of propofol in 1975, the use has now been more common and has benefitted the medical world immensely. From the chemical model of this agent, we can see how efficiently it works due to its agonist properties on the GABA and NMDA receptors which causes a huge pain reduction (Ghojazadeh et al., 2019). Propofol also suppresses sympathetic activity and inhibits the baroreceptor reflex, which is what could cause a drop in blood pressure and heart rate (Kanaya, Hirata, Kurosawa, Nakayama, & Namiki, 2003). While propofol does facilitate a sedation and amnesia effect, the lack of an analgesic property makes this agent one that works better when in combination with another medication that can make up for the missing pieces. Due to the fast onset of action and short duration of action, this is an ideal agent for short procedures and a quicker recovery time (Adams et al., 2012). However, propofol does include a
few adverse effects, some of which include respiratory depression and hypotension. Since there is that potential of negative effects, the dosing of propofol is typically given slower so that less hemodynamic changes are observed.

**Ketofol**

Since medicine is lacking a drug that provides all benefits of a great procedural sedation analgesic, a combination of dissociative, sedative, and analgesic agents are used together to create the desired effects. When the combination of ketamine and propofol are used in conjunction to create Ketofol, they are mixed into a single syringe which reduces the required doses of each individual agent. The use of both agents potentially mitigates the risk of adverse respiratory events compared to propofol alone or in combination with opioids. By adding ketamine to propofol, the potential for hemodynamic instability is reduced while still providing deep sedation and analgesia to patients (Yan, Mcleod, & Iansavitchene, 2015). While ketamine may bring on feelings of nausea, vomiting, and agitation after a procedure, propofol has antiemetic and anxiolytic properties to combat the side effects of ketamine (Smith, Monk, White, & Ding, 1994). It has also been noted these two agents are physically compatible and chemically stable when mixed in syringes and stored at room temperature with light exposure (Andolfatto et al., 2011). In an effort to balance the hemodynamic adverse effects, the combination is usually dosed at a 1:1 ratio.

**Acquisition of External Evidence**

As the world of medicine and the use of anesthetics are constantly evolving, it seems pertinent to discuss the data pertaining to this topic of the use of Ketofol versus Propofol for adults undergoing procedural sedation. Having met with a librarian for a previous paper, I was
able to apply the same ideals and principles for solidifying my topic by using searches that would return the most reflective and applicable data available to my research. To find the necessary data, I utilized databases such as PUBMED, National Center for Biotechnology Information (NCBI), the American Journal of Emergency Medicine, Society for Academic Emergency Medicine, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). These databases provided me with health science relevant sources from a multitude of different disciplines. Key terms that were utilized included: “propofol, ketamine, Ketofol, procedural sedation, conscious sedation, respiratory.” In conjunction with key terms, I used key phrases which included: “propofol and ketamine, Ketofol and propofol, Ketofol and procedural sedation, Ketofol and conscious sedation, propofol versus Ketofol, and propofol and procedural sedation.” I was then able to narrow down the search criteria to compare these medication uses in a procedural sedation setting to give me focused articles.

From these results, the PICOT question was refined in order to reflect the current and available data to create a well-rounded evidence based recommendation. I did some further evaluation of all internal and external factors of the sources including sample size, selection criteria, length, and any potential confounding variables. There was also a higher precedence to use systematic reviews and meta-analyses as they helped to ensure high standards of evaluating the study at hand.

**Summary of External Evidence**

There were various sources that were used to gather data on which sedation medications were more effective at producing less adverse respiratory effects for adults undergoing procedural sedation. A systematic review done by Yan et al. (2015) utilized six different randomized control trials that had a primary objective of determining if Ketofol has a lower
frequency of adverse respiratory effects in patients undergoing PSA than propofol alone. This systematic review presents high levels of evidence, a large sample size (932 total patients reported on: 520 given Ketofol, 412 given propofol), and the results of each study were reported clearly with the use of tables and charts. Additionally, in all of the studies, there was reported times for sedation, procedure, and recovery. However, only five of the six RCTs reported on adverse events, but out of the five that did, they were able to see what events were reported as the same. Some weaknesses or limitations included that not all six of the RCTs were limited to just adults, some trials had different methods that were used (i.e., randomized, blind), and there was some heterogeneity with the doses and ratios of Ketofol used. The systematic review did conclude that Ketofol had a lower incidence of adverse respiratory events when compared to propofol alone (29% vs. 35.4%), which shows statistical significance.

A clinical trial performed by Miner et al. (2014) compared the frequency of airway and respiratory adverse events leading to an intervention between propofol with a 1:1 ratio and a 1:1 propofol: ketamine or 4:1 mixture of propofol: ketamine in a randomized, double blind experiment. This experiment went from October 2010 to February 2013 in which there were 271 patients randomized to three groups: Propofol only had 90 patients, 1:1 Ketofol had 85 patients, and 4:1 Ketofol had 96 patients. All three groups received an initial sedative bolus of 0.1mL/kg. Additionally, this experiment did a great job in the areas of randomization, providing a large sample size, and enrolling only adults. Individuals who had a hypersensitivity to either medication, who were pregnant, showed signs of intoxication, or had an American Society of Anesthesiologists physical status greater than two were disqualified. The main weakness/limitation of this trial was that many patients had clinical interventions but not an airway or respiratory adverse event, indicating that clinicians responded to a subtle cue to
intervene before an adverse event happened, which could make it hard to detect these factors between the groups. Additionally, all the individuals in this trial were sampled from one facility. The study concluded that their primary outcome was similar between groups and they did not detect a difference in the frequency of adverse airway or respiratory events leading to intervention between a 1:1 (19%) or 4:1 (32%) combination of propofol and ketamine relative to propofol alone (29%). Therefore, this study deems each combination of medication to appear similarly safe and effective by resulting in a $p$ value of $p = 0.21$.

A systematic review done by Jalili et al. (2015) used the data and information from 18 randomized control trials to meet their objective of evaluating the analgesic and side effects of the ketamine-propofol combination (Ketofol) in comparison to propofol in procedural sedation and analgesia (PSA). This study sufficiently outlined did a great job of outlining their criteria while sorting through a large amount of articles. A strength of this review was that they used the Jadad quality score, in which all articles used had a score of at least 3. The score came from a combination of randomization, blinding, and dropouts to which it was given a score on whether or not it was present or described appropriately. However, the main weakness identified in this review was the heterogeneity that was present in each individual review as there was variance between the procedures being performed, settings, and doses of Ketofol that were used. To combat the heterogeneity that was calculated, the random effect was applied for risk ratio calculations. With the risk ratio in effect, this yielded a statistically significant result for Ketofol being a more effective choice than propofol for reducing respiratory adverse events. This was presented in a clearly laid out table showing that out of all the RCTs used, Ketofol had 6% of patients experience an incidence, while propofol had 11% of the patients experience an incident. In conjunction of applying the random effect, it was shown that Ketofol lowered the incidence of
cardiovascular issues such as hypotension and bradycardia as well. Overall, the study supports the use of ketamine-propofol as an effective combination in reducing many complications, and the authors recommend Ketofol as an appropriate substitution for propofol.

Ferguson et al. (2016) put out a successful great randomized double-blinded clinical trial whose primary outcome was to determine whether physicians providing deep sedation with 1:1 Ketofol versus propofol results in fewer adverse respiratory events requiring physician intervention when used for procedural sedation and analgesia. A major strength is the sample size and those they chose to enroll in this study. They enrolled patients aged 18 years or older, who required deep procedural sedation. Patients were excluded if they were unable to provide consent, were pregnant, allergic to the medications, had uncontrolled hypertension, or a reduced level of consciousness. These parameters allow researchers to base each individual from the same baseline. I also think the fact that this was a randomized double-blind clinical trial speaks volumes to the mechanics of this study. However, while their study was rather large (573 patients), they did have some limitations. There may have been some selection bias as they had recruited a convenience sample and there were definite staffing limitations. Due to the required staff and mandated ER physician for the procedure, they could not recruit as many people for this study which could have affected them at times when the ER was very busy. There could have also been some confounding variables in the study since they did not control preprocedural opiate use or prophylactic oxygen delivery. In terms of primary outcomes, they were looking at the occurrence of a respiratory event, defined as hypoxia (SpO2 < 93%), hypoventilation (RR < 8 breaths/min), apnea, aspiration, and the occurrence of a rescue intervention (increased O2 flow, airway repositioning). When comparing the two groups, the occurrence was similar, with the exception of the propofol group more frequently needing bag-valve-mask ventilation. In
conclusion, the authors stated that while propofol had a slightly higher incidence of causing hypotension, that procedural sedation using Ketofol versus propofol alone results in similar frequency of adverse respiratory events requiring intervention.

**Clinical Practice Recommendations**

As a nurse, there are many different roles involving patient care, one of which includes being an advocate for patient safety and satisfaction. Even though nurses are not the ones to perform the procedural sedation procedure, they are typically there during the procedure and can suggest the use of different medications as an appropriate alternative to the more commonly used ones. Procedural sedations are used frequently for a variety of procedures, some of which could include burn debridement, endoscopy, orthopedic injury reductions, and imaging scans. With a common goal of minimizing pain, anxiety, and trauma to the patient, the interdisciplinary team’s job is to increase the safety of the procedure for the physicians and the patient for it to be successful.

Nurses are a critical component in directing patient care due to our increased interactions with our patients. Nurses are a secondhand to the doctors as sometimes they are more in tune with the feelings, thoughts, and wishes of our patients. With the working relationship between nurses and physicians, this provides a great space to emphasize the importance of pain control while minimizing potential harmful effects involving both the respiratory and cardiovascular system alike. Nurses should encourage the implementation and relay the information of systematic reviews, meta-analyses, and the most current up to date evidence there is to best suit our patients. A meta-analysis would be pivotal in being able to assess not only the benefits of ketofol versus propofol, but patient satisfaction between the two, and the occurrence of these potentially fatal outcomes that may need required interventions. From there, nurses can then
advocate for their patients based on the interpretation of the data that is being presented with the knowledge in mind of the best evidence based practices.

**Conclusion of Evidence**

Overall, while there was great evidence, clinical trials, and systematic reviews to look over, there is still a good amount of research left to be done in the realm of procedural sedation and analgesia. While the goal of this evidence was to identify which of these anesthetic options best reduces respiratory complications, other factors were also assessed. The respiratory outcome was the primary determinant for which anesthetic would be most ideal for procedural sedation, but studies also took a look at cardiovascular complications, recovery time, patient satisfaction, and nausea and vomiting. There were some gaps and potential confounding variables when it came to all of the evidence. Some patients were administered a pre-procedural medication and prophylactic oxygen which could have contributed to a different overall effect when patients were administered ketofol or propofol. It was also difficult to find studies that just included adults ages 18 and over, as some focused on younger kids or teenagers.

When comparing the data collected from the clinical trials, meta-analyses, and systematic reviews, Miner et al. and Ferguson et al. found that there was no statistical difference in the adverse respiratory events between propofol and ketofol groups alike. However, in the reviews of Yan et al. and Jalili et al., these teams of researchers did find evidence to be statistically significant of ketofol having a lower number of adverse respiratory events. While all of these studies show a high level of understanding and provide quality evidence, there is no consistent evidence to show that propofol or ketofol is better than the other for procedural sedation. While both of these anesthetics have benefits and negative side effects, procedural sedation and anesthesia usually requires combinations of multiple agents to reach desired effects of analgesia
plus anxiolysis (Deady et al., 2007), which is why I think the benefits of the combined effects of ketamine and propofol outweighs the effects of propofol alone.

By following the acronym SOAPME (suction, oxygen, airway, pharmacy, monitors, and equipment), this method can be implemented and encouraged by nurses and physicians alike to ensure patient monitoring and quality care is followed entirely (Deady et al., 2007). In combination with physicians, nurses are crucial in implementing the best and most helpful pain management and anxiety helpful options for care whether it is during an emergency visit, a longer stay, or more importantly during procedural sedation.

While the choice of the medications used is ultimately left up to the physicians and anesthesiologists, it is crucial to look at an individual’s health history to choose the anesthetic drug that will offer the best health outcome and surgical experience while combating any potential negative side effects. Patient care is of the utmost importance in any situation, especially during an event requiring anesthesia. With the help of a great interdisciplinary team and the best evidence based practices, we can help our patients experience successful outcomes throughout their procedure and on the road to recovery.
References


Review and Meta-analysis. Retrieved from


http://www.chm.bris.ac.uk/motm/gaba/gabajm.htm