Research: Comparison of Sedatives in Intubated ICU Patients

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Abstract

Differences in popular sedatives used in intubated ICU patients have been a topic of interest for many nurses and healthcare providers. This question arises due to different options available to use with these types of patients. The sedatives compared are propofol, midazolam, and dexmedetomidine. The differences examined include the sedatives efficacy, patient satisfaction, hemodynamic complications, and incidences of delirium. The choice of sedative does consider all of these factors, but it usually comes down to the sedative's efficacy most of the time (Lacoske, 2015). This research analyzes these factors to help determine which sedative is preferred in this setting. The study will be conducted as a literature review focused on the factors mentioned above. Its goal is to help determine if there is a preferred sedative when looking at the sedative's efficacy, patient satisfaction, hemodynamic complications and incidences of delirium. Current studies point to propofol as the preferred sedative, but other sedatives may be just as effective.

Patients in the intensive care unit (ICU) are often intubated for a variety of reasons. This involves a complex care regimen that addresses both physiologic and psychological needs (Lacoske, 2015). Patients requiring an endotracheal tube for mechanical ventilation are intubated and this is often difficult to manage. Patients may also be sedated for their overall safety and comfort. There have been multiple studies published by the *Journal of Clinical Nursing, Australian Critical Care* and many more that compared different sedatives to determine if there is one particular sedative that works best (Lacoske, 2015). Many different sedatives are seen in these studies but in this literature review the focus will be on propofol, midazolam and dexmedetomidine; three very popular and widely used sedatives in intensive care units (Selaraj, 2017). The choice of which sedative is best for patients in an intensive care setting is always an important question (Selaraj, 2017). Throughout this review three popular sedatives are going to be compared based of their efficacy, patient satisfaction, hemodynamic complications and delirium.

Propofol

Propofol is a very potent sedative, which has a poorly understood mechanism of action. It is believed this drug has sedative and hypnotic effects attributed to its action on GABAA receptors in the central nervous system (Lacoske, 2015). Other effects of this drug are anxiolytic, amnestic, antiemetic, and anticonvulsant. One possible downside of propofol is its highly lipid-soluble composition that can cause propofol infusion syndrome (PRIS), a rare but serious syndrome caused by long term use of propofol. The lipid composition allows it to rapidly cross the blood brain barrier and into peripheral tissues. This gives it an onset time of 40 seconds to 3 minutes (Lacoske, 2015).

One major downfall of using propofol for long-term infusions is propofol infusion syndrome. This syndrome is usually seen with a rate greater than 70 ug/kg/min (Lacoske, 2015). Signs and symptoms of PRIS are hypertriglyceridemia, worsening metabolic acidosis, hypotension, and arrhythmias (Lacoske, 2015). Other problems associated with this syndrome include acute kidney failure, hyperkalemia, rhabdomyolysis, and liver dysfunction. Other problems that can occur from long-term use of propofol include acute pancreatitis and myoclonus (Lacoske, 2015).

Propofol can cause respiratory depression and hypotension secondary to vasodilation. Rapid IV push can cause rapid apnea and hypotension and should not be given IV push by anyone that is not a trained anesthesia provider when an endotracheal tube is not in place (Lacoske, 2015).

Dexmedetomidine

Dexmedetomidine is a highly selective alpha2-adrenergic agonist with sedative properties (Lacoske, 2015). Dexmedetomidine is often indicated for sedation of intubated and mechanically ventilated patients in an intensive care setting. One drawback of this drug is that it is not recommended to be used longer than 24 hours on a continuous infusion (Lacoske, 2015). Side effects and long-term problems with dexmedetomidine are less than propofol, but there are still some side effects attached to this drug (Lacoske, 2015). These side effects include hypotension, bradycardia, sinus arrest, transient hypertension, dry mouth, nausea, and atrial fibrillation (Lacoske, 2015).

Midazolam

Midazolam is a short acting benzodiazepine. The drug has amnestic, anxiolytic, sedative, and hypnotic effects. Benzodiazepines in general have anticonvulsant effects. Sedation is achieved within 3-5 minutes of IV injection. This drug acts on the y-aminobutyric acid A receptors of the central nervous system (Lacoske, 2015). Midazolam can cross the placenta into fetal circulation, which can cause an increased risk of congenital malformations in early stages of pregnancy if used in pregnant women (Lacoske, 2015). It is also advised not to use this drug with patients with narrow angle glaucoma.

Hypoventilation and airway obstruction can occur after administration. If these two complications occur and go untreated it can lead to cardiac arrest. Side effects include headache, nausea, drowsiness, vomiting, hiccups, coughing, agitation, confusion, and seizures (Lacoske, 2015).

Efficacy

One study that compared these three drugs was conducted in Europe from 2007 to 2010. This study was a two phase, multicenter, randomized, and double blind respectively. It compared dexmedetomidine with midazolam (MIDEX trial) and propofol with dexmedetomidine (PRODEX trial) (Jakob et al., 2012). The first efficacy endpoint was the proportion of time in target sedation range. The scale used for this was the Richmond Agitation-Sedation Scale (RASS) with a range of +4 to -5. The RASS scale is a validated and reliable method to assess a patient's level of sedation (see table 2 on page 8). Each study had 500 participants who were intubated ICU patients. There were 249 participants in the dexmedetomidine group and 251 patients in the midazolam group in the MIDEX trial. In the PRODEX trial there were 251 patients in the dexmedetomidine group and 247 patients

in the propofol group. In the MIDEX trial 53 midazolam patients and 68 dexmedetomidine patients died between randomization and at day 45 of follow up. In the PRODEX trial 48 propofol patients and 43 dexmedetomidine patients died during this period as well (Jakob et al., 2012).

After the study was conducted it was concluded that dexmedetomidine was not inferior to midazolam or propofol for long-term sedation in intubated ICU patients (Jakob et al., 2012). This study also confirmed that dexmedetomidine was not suitable for deep sedation due to the lack of efficacy in approximately 1 in every 8 to 10 patients determined by the RASS score (Jakob et al., 2012). Dexmedetomidine did reduce the duration of mechanical ventilation compared to the other two sedatives, but there were more adverse effects with dexmedetomidine as compared with midazolam, and propofol (Jakob et al., 2012).

A study comparing the effects of protocol-directed sedation with propofol versus midazolam by nurses in intensive care units looked at these two drugs efficacy, hemodynamic stability and patient satisfaction (Huey-Ling, Chun-Che, Jen-Jen, Shau-Ting, Hsing-I, 2008). This was a randomized, prospective cohort study collected in 2003. The subjects were put into two groups, 32 propofol and 28 into midazolam. Efficacy of sedation, hemodynamic stability, pulse oximetry saturation, weaning time, duration, length of stay at the intensive care unit, sedative drug costs and patient satisfaction were measured by Huey-Ling et al. (2008). In (table 1 on page 7) is the Ramsay Sedation Scale (RSS), which was used in this study to score the level of sedation the subject was in.

Response	Level
Awake and anxious, agitated, or restless	1
Awake, cooperative, accepting ventilation, oriented, or tranquil	2
Awake, responds only to commands	3
Asleep, brisk response to light, glabella tap, or loud noise	4
Asleep, sluggish response to light, glabella tap, or loud noise	5
Asleep, no response to light, glabella tap, or loud noise	6

Table 1
https://www.researchgate.net/figure/Ramsay-Sedation-Scale_tbl3_261884216

The study concluded that the nursing staff was able to maintain patients on the RSS 3-4 during the sedation period (Huey-Ling et al., 2008). The efficacy of sedation for propofol was 74.2% and for midazolam it was 66.9% (Huey-Ling et al., 2008). Based off of this data, patients that received propofol were sedated at a more desirable level than those being sedated with midazolam.

Since the FDA approval of dexmedetomidine in 1999 there has been many studies conducted to determine its sedation efficacy in intensive care settings by (Huey-Ling et al. (2008), Selaraj (2017), and Lacoske (2015)). According to Selvaraj (2017), many randomized controlled trials have taken place to assess the efficacy of dexmedetomidine. These have either been done with a placebo or typical sedative drugs like propofol or midazolam. Physicians' orders allow nursing staff to titrate dexmedetomidine to achieve desired sedation but many of the times it requires increased dosage of dexmedetomidine and even additional sedatives in order to achieve the desired amount of sedation on either

the RAS or RASS scales (Selaraj, 2017) In a phase 2 prospective study conducted by Venn, Newmans, Grounds (2003), a maximum loading dose and maintenance dose of 0.7mcg/kg/hour was not sufficient enough to keep that patient sedated on the RSS at a level of 3-4. Other medication was needed to achieve a score of 2 or more on the RSS even at doses up to 2.5mcg/kg/hr.

In another study conducted by Ruokonen, Parviainen, Jackob (2009), a phase 2 multicenter, randomized control study used twice the recommended dose to compare the efficacy of high-dose dexmedetomidine with standard protocol sedation such as propofol or midazolam. They concluded that the patients' time at the target sedation level using the Richmond Agitation-Sedation Scale to score between 0 and -3 were all very similar between the groups (Selaraj, 2017).

Richmond Agitation and Sedation Scale (RASS)		
+4	Combative	violent, immediate danger to staff
+3	Very Agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious, apprehensive but movements not aggressive or vigorous
0	Alert & calm	
-1	Drowsy	Not fully alert, but has sustained awakening to *voice* (eye opening & contact ≥ 10 sec)
-2	Light sedation	Briefly awakens to *voice* (eye opening & contact < 10 sec)
-3	Moderate sedation	Movement or eye-opening to *voice* (but no eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to *physical* stimulation
-5	Unarousable	No response to *voice or physical* stimulation

Table 2
https://www.researchgate.net/figure/Richmond-Agitation-and-Sedation-Scale-RASS-Sessier-et-al-2002-Reprinted-with_fig2_26766428

In conclusion the research shows that dexmedetomidine is not suitable for deep sedation but may be better used for light to moderate sedation Therefore, using just dexmedetomidine for deep sedation in intensive care units without an adjunct agent may be questionable (Selaraj, 2017).

Patient Satisfaction

Patient satisfaction was one of the variables measured in a study by Huey-Ling, et al. (2008). Questionnaires were given to patients verbally after extubation. The scale used was a three-point Likert scale (1=disagree strongly to 3= agree); the total score was 12 (Huey-Ling et al., 2008). High scores meant the patient perceived more satisfaction during the sedation phase. The questionnaire was validated before this study by interviewing ten coronary artery bypass graft patients in ICUs (Huey-Ling et al., 2008). One trained interviewer conducted all the questionnaires during the trial period and with the subjects in this study (Huey-Ling et al., 2008). This was done to maintain consistency with all questions and in-patient responses (Huey-Ling et al., 2008).

The first aspect that was measured was overall satisfaction of sedation regardless of which sedative was used. The results are as follows: 55 patients felt sedated in the ICU, 52 patients felt comfortable in the ICU, 46 patients could tolerate intubation all the time in the ICU and 52 patients agreed nurses understood what they need during intubation (Huey-Ling et al., 2008). In both groups there were no mortality or reintubation. There also was no report of any complications based off of the protocol-based sedative care (Huey-Ling et al., 2008).

Based off this research, overall patient satisfaction is very similar between propofol and midazolam. These can draw the conclusion that one sedative is not clearly better than

the other based just off of patient satisfaction (Huey-Ling et al., 2008). There are many more aspects to these sedatives that may help conclude which sedative is clearly better to use for sedation in an intensive care setting.

Hemodynamic Complications

According to Magarey (2001) there can be many hemodynamic complications in sedatives used in intensive care units. In the study they measured the incidence of hemodynamic complications (Magarey, 2001). These complications include changes in mean arterial pressure (MAP), diastolic blood pressure (DBP), systolic blood pressure (SBP) and heart rate (HR) (Magarey, 2001). One study by Huey-Ling et al. (2008), also reported incidences of adverse events such as hypertension and hypotension. One study performed showed that propofol was more likely to cause a decrease in heart rate versus midazolam (Magarey, 2001). Cardiac depression between the two sedatives was not clinically significant (Magarey, 2001). Another study concluded that propofol caused a greater decrease in mean arterial pressure and systolic blood pressure as well (Magarey, 2001).

In a study by Roekaerts, Huygen, Delange (1993) on patients in a post-cardiac unit they demonstrated that propofol might be more likely to cause hypotension and decreased heart rate. It was also seen that midazolam can cause hypotension during the induction of sedation and increase in heart rate during the maintenance phase. In this situation it did not cause change in the type of sedative that was being used, but changing in doses did occur (Roekaerts et al., 1993).

There was a study conducted by Roekaerts et al. (1993) on medical and surgical patients and adjustments to infusion rates related to hypotension were needed more for

patients receiving propofol than patients receiving midazolam. This also supports that propofol causes hypotension more so than midazolam. Based off these studies, it is seen that propofol has a higher incidence rate of hypotension and a decreased heart rate (Roekaerts et al., 1993).

As with dexmedetomidine the most common side effect associated with it is bradycardia and hypotension. The bradycardiac effect is most commonly dose-dependent and often occurs during the loading dose (Magarey, 2001).

Propofol Infusion Syndrome

As mentioned earlier, one downfall of propofol is a serious side effect called propofol infusion syndrome. This syndrome is seen in patients that undergo long-term treatment with propofol with high dosages. This syndrome can lead to cardiac failure, rhabdomyolysis, metabolic acidosis and kidney failure. This syndrome is often fatal (Kam, Cardone, 2007)

This syndrome is seen after the rate is greater than 70ug/kb/min (Lacoske, 2015). In most ICUs there is a titration limit that is set by the physician. If the nursing staff needs to go above that limit the physician needs to write an order that justifies why that amount of sedation is needed to achieve the desired amount of sedation on either of the sedation scales.

Delirium

Delirium is a short-term brain illness that involves changes in consciousness, attention, cognition, and perception. According to Djaiani et al. (2016) the incidence of postoperative delirium in patients that undergo cardiac surgery is 20% to 50%. Elderly patients are at greatest risk. Delirium can be distressing to both patients and their families.

Delirium has been associated with higher rates of morbidity, mortality, prolonged hospital stays, and increased hospital costs (Djaiani et al., 2016). However there is evidence that shows that the type of sedation can play a factor with the risk of delirium (Djaiani et al., 2016). Postoperative delirium can be one serious complication patients may experience after surgery, but particularly in postoperative cardiac surgery. Recent studies show that the use of dexmedetomidine is controversial (Djaiani et al., 2016).

In a study measuring delirium for patients past cardiac surgery which was a single blinded, prospective, randomized controlled trail that was conducted on 60 year old or older patients (Djaiani et al., 2016). If the patient had a history of a serious mental illness, delirium or had severe dementia, they were excluded from the study. Before the patients arrived to the ICU they were even given dexmedetomidine or propofol that was given according to a computer-generated randomized code in blocks of four (Djaiani et al., 2016). Assessment of the patients was performed with the confusion assessment method in the ICU and/or confusion assessment method after the patient was discharged from the ICU. This assessment was performed at 12-hour intervals during the 5 postoperative days (Djaiani et al., 2016). The goal of this study was to determine the incidence of postoperative delirium.

Post-operative delirium was present in 16 of 91 patients in the dexmedetomidine group and 29 of 92 patients in the propofol group (Djaiani et al., 2016). The information shows that delirium was seen more in the propofol group rather than in the dexmedetomidine group (Djaiani et al., 2016). Based on this it can be seen that dexmedetomidine is less likely to cause delirium in patients based off of this study. Another variable was measured though, the mean onset of postoperative delirium. The median

onset was postoperative day number two for dexmedetomidine and postoperative day number 1 for propofol (Djaiani et al., 2016). The average duration for postoperative delirium lasted two days in the dexmedetomidine group and 3 days in the propofol group (Djaiani et al., 2016).

When these two sedatives were compared side to side to determine which sedative had a lower rate of postoperative delirium in patients after cardiac surgery it can be clearly interpreted that postoperative delirium is less likely to occur when dexmedetomidine is used. This can be a great benefit to patients that need to be sedated because delirium is often seen in patients in intensive care units (Djaiani et al., 2016). If dexmedetomidine is used more often, the incidences of delirium seen in intensive care units may be reduced (Djaiani et al., 2016).

In 2008 a study was conducted in Honolulu that compared midazolam and dexmedetomidine (Hitt, 2008). In this study the researchers measured the efficacy and incidence of delirium between these two sedatives. Patients were treated for 30 days or until extubation (Hitt, 2008). This study concluded that delirium was decreased or prevented when dexmedetomidine was used (Hitt, 2008). From days 1 to 8 there was a significantly higher rate of delirium seen in patients that were sedated with midazolam rather than dexmedetomidine (Hitt, 2008). Patients that had baseline delirium also showed a significantly reduced rate of delirium over the 8 days as well (Hitt, 2008). Overall, patients receiving dexmedetomidine had delirium for about 1.4 days and patients sedated with propofol had delirium on average for 2.7 days (Hitt, 2008).

Whether the choice of sedative is propofol, midazolam or dexmedetomidine it can be concluded off of these studies that there is a lower rate of delirium when

dexmedetomidine was used regardless of baseline delirium (Hitt, 2008). Many may think delirium is not a huge issue, but delirium can have many negative effects for patient outcomes. Some of these complications include prolonged altered mental status and hospital readmissions (Hitt, 2008).

Conclusion

In conclusion, there will always be controversy over which sedative is preferred for sedation of intubated ICU patients. The current research that I analyzed throughout this literature reviewed favored propofol due to the excellent efficacy in most patients. Dexmedetomidine in the future may be used more often because of its reduced incidences of delirium, but as of now it's still less preferred based on the lack of efficacy seen in current research. Midazolam is still used in many ICU's, but due to its lower efficacy, propofol is still preferred. Common hemodynamic complications were seen in all three sedatives. Patient satisfaction was similar between the sedatives.

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