COMPARING KETOFOL VS OTHER INDUCTION AGENTS FOR PROCEDURAL SEDATION AT PORTAGE HOSPITAL

By: Jarrett Best

Home For The Summer Program – June to July, 2017

Portage la Prairie, Manitoba

Supervisor: Dr. Alan K. Macklem

Abstract

This project looked at procedural sedation & analgesia induction agents used at the Portage la Prairie hospital and aimed to compare both adverse event frequency and recovery time after administration induction agents. More specifically, the goal was to compare the 'ketofol' cocktail, which uses a mixture of ketamine and propofol against other medication combinations containing propofol, opioids (fentanyl) and benzodiazepines (midazolam). Data was collected from 20 procedures, 9 using the ketofol mixture and 11 using alternatives. This local data at Portage Hospital showed that the ketofol cocktail had shorter recovery times (22 minutes) and less adverse events (11%) compared to the alternatives (26 minutes & 64%, respectively). Additionally, physicians at Portage Hospital verbally stated their higher preference for ketofol over other concoctions due to these reasons. However, it should be noted that this is a very small sample size with many variables (pt. age, dosing, comorbidities, etc.) present and interestingly, larger studies similar in nature have shown no significant clinical difference between ketofol and propofol alone (as well as other mixtures) during procedural sedation.[1,2]

Introduction

Previously (and inappropriately) described as conscious sedation, procedural sedation & analgesia refers to medically providing sedatives & analgesics (which alter consciousness) to accomplish a therapeutic or diagnostic procedure. PSA's are beneficial in decreasing use of healthcare resources such as operating room loads, health-care personnel, costs, patient wait & recovery time by performing these procedures in monitored environment outside the operating room. Ideal characteristics of proper sedation include alleviation of anxiety, minimizing pain, side effects, recovery & discharge time, maximizing amnesia while regulating patient behavior & movement during the procedure.[3]

The various levels of sedation are outlined by definitions as per the American Society of Anesthesiologists[4]:

Levels of Sedation/Analgesia

- Minimal Sedation (Anxiolysis) is a drug-induced state during which an individual responds normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected.
- Moderate Sedation / Analgesia ("Conscious Sedation") is a drug-induced depression of consciousness during which an individual responds purposefully* to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.

- Deep Sedation / Analgesia is a drug-induced depression of consciousness during which an individual cannot be easily aroused but responds purposefully* following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. The individual may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.
- Dissociative sedation – Dissociative sedation is a trance-like cataleptic state in which the patient experiences profound analgesia and amnesia but retains airway protective reflexes, spontaneous respirations, and cardiopulmonary stability. Ketamine is the pharmacologic agent used for procedural sedation that produces this state[2].

* Reflex withdrawal from a painful stimulus is NOT considered a purposeful response.

To prevent unwanted side effects only the level of sedation required to adequately carry out the procedure should be induced.

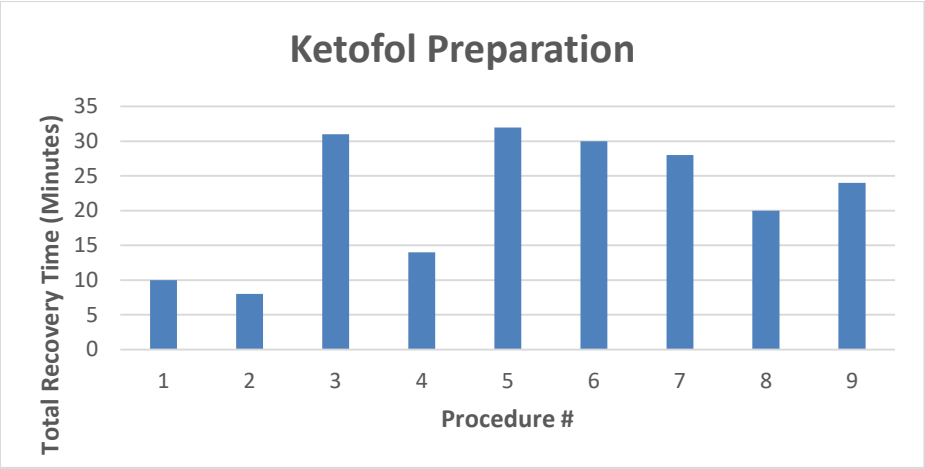
Report

This report looked at 20 procedures requiring PSA in Portage la Prairie Hospital completed by a variety of physicians with a variety of different levels of training (eg: surgeons, family physicians, +1 anesthesia, etc). The procedures being carried out were either electrical cardioversions or closed bone reductions and the patients ages varied from 6 to 86 years old. As such the dosages of the medications given also varied.

Group 1 contained individuals given a ketofol preparation - that is propofol & ketamine mixed together. The ratio of the mixtures varied from 1:1 to 10:1 propofol to ketamine. The literature shows varying ideal ratios dependent on age and weight[5]. Group 2 were given alternative agents which involved 1 or more of the following in various ratios: propofol, fentanyl or midazolam. The results below show two factors:

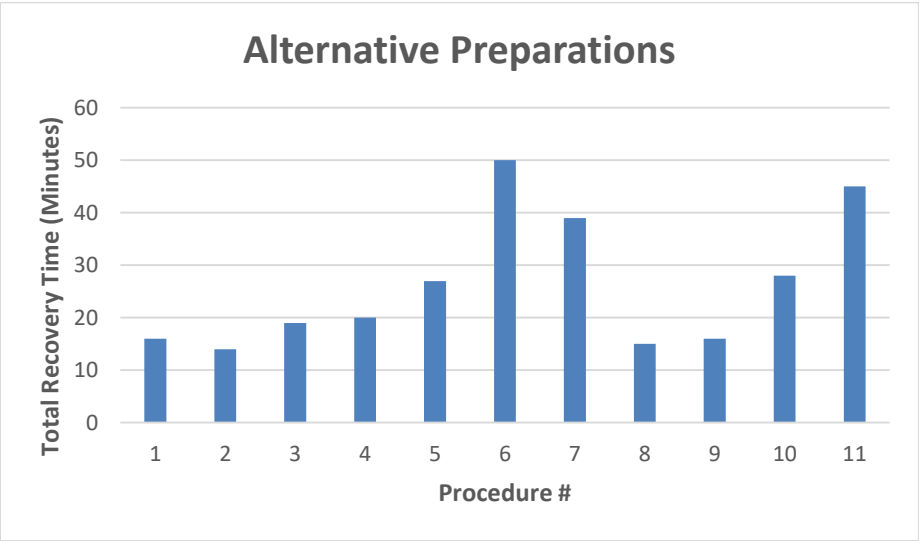
1) Complete Recovery Time – this is defined as the moment the first induction agent is given until the patient is talking and coherent
2) Adverse Reactions – these include even mild transient adverse events such as inability to maintain own airway without oral adjunct or brief O2 desaturations.

Figure #1: Total recovery times in procedures using ketofol induction agent



Average = 22 minutes

Figure #2: Total recovery times in procedures using ketofol induction agent



Average = 26 minutes

Table #1: Adverse reactions in PSA for both ketofol and alternative medication mixtures

Procedure & #	Drug & Dosages	Adverse Events
1 - Cardioversion	40mg Ketamine / 40mg Propofol	None
2 - Forearm Reduction	10mg Ketamine / 50mg Propofol	None
3 - Wrist Reduction	10mg Ketamine / 80mg Propofol	None
4 - Wrist Reduction	10mg Ketamine / 70mg Propofol	None
5 - Wrist Reduction	20mg Ketamine / 150mg Propofol	Mild confusion upon prior to discharge
6 - Wrist Reduction	5mg Ketamine / 50mg Propofol	None
7 - Wrist Reduction	80mg Ketamine / 100mg Propofol	None
8 - Wrist Reduction	30mg Ketamine / 50mg Propofol	None
9 - Wrist Reduction	6mg Ketamine / 60mg Propofol	None
10 - Cardioversion	2mg Midazolam / 30mg Propofol	
11 - Cardioversion	1mg Midazolam / 50mg Propofol	
12 - Cardioversion	2mg Midazolam / 20mg Propofol	
13 - Cardioversion	2mg Midazolam / 90 mg Propofol	Jaw-thrust required to maintain a/w
14 - Cardioversion	140 mg Propofol	
15 - Cardioversion	100mcg Fentanyl / 3 Midazolam / 30mg Propofol	Oral adjunct required to maintain a/w
16 - Cardioversion	200 mcg Fentanyl / 2mg Midazolam	Oral adjunct required to maintain a/w
17 - Cardioversion	50mg Propofol	Transient hypotension (20 mmHg systolic drop)
18 - Cardioversion	1mg Midazolam / 50 mg Propofol	Hypotension - 132/77 to 87/62 - NS given W/O
19 - Cardioversion	100 mcg Fentanyl / 200mg Propofol	Desaturation (98% to 89%) - treated with supplemental O2
20 - Wrist Reduction	200 mcg Fentanyl / 2mg Midazolam / 40 mg Propofol	Jaw thrust & oral adjunct required to maintain a/w

Note that only 1 of the 9 procedures in Group #1 were subject to an adverse reaction (11%) while 7 of the 11 procedures in Group #2 were (64%).

Discussion

The data here shows an average of 4 fewer minutes to recover from sedation using ketofol vs the benzodiazepine and opioid counterparts and drastically less adverse events (by definition) – 11% vs 64%. It should be observed that the majority of Group #1 procedures were orthopedic in nature (reductions) whereas the majority of Group #2 procedures were cardioversions. As ketamine is known to cause transient increases in heart rate and blood pressure which would be unfavorable, even in the short term for a patient requiring cardioversion this could be the line of reasoning behind the drugs chosen. The shorter recovery of Group #1 times make sense when looking at the pharmaceutical properties of the drugs involved (see Appendix 1).

While anesthesia literature (see Appendix 1) shows vomiting to be the most common side effect of ketamine we don't see any in Group #1's data. This may be due to the beneficial anti-emetic properties that propofol has. Larger sample sizes would be helpful to discern this more clearly.

The data here further shows that the patient falls is likely falling into a comparatively deeper sedation state when under the influence of midazolam or fentanyl thus why they tend to experience impairment of maintaining their airway. While these effects were treated without issue it should still be noted that they may give rise to more serious complications if not monitored or rectified appropriately by keen and qualified practitioners. As patients in the ketofol group enter a different sedation state (dissociative) this allows them to maintain their airway while still receiving adequate levels of analgesia preventing the chance of unnecessary complications.

In summation, the data shows that ketofol preparations have slightly faster recovery times and less adverse events than the non-ketofol combinations shown here. Additionally, Portage Hospital physicians seem to prefer ketofol preparations when dealing with orthopedic-related sedations and non-ketofol agents when carrying out cardioversions. When observing the various different combinations of agents given for these procedures one might conclude that the physician performing the particular sedation gives the medications that they personally feel most comfortable with based on previous experience.

References

1) Annals of Emergency Medicine, 2007-01-01, Volume 49, Issue 1, Pages 31-36, Copyright © 2007 American College of Emergency Physicians
2) Robert L Frank. Procedural sedation in adults outside the operating room. In: Post T, ed. UpToDate. Waltham, Mass.: UpToDate; 2017. www.uptodate.com. Accessed Aug 1, 2017.
3) Fowler A. " Ketofol " for Procedural Sedation and Analgesia in the Emergency Is the Juice Worth the Squeeze ? 2014:1-20.
4) American Society of Anesthesiologists. (2004, October). Continuum of depth of sedation: Definition of general anesthesia and levels of sedation / analgesia. Retrieved January 7, 2005 from http://www.asahq.org/publicationsAndServices/standards/20.pdf
5) Ketofol Dosing Simulations for Procedural Sedation. Coulter, Finn L.S. MBBS, DTM&H *; Hannam, Jacqueline A. BSc (Hon) +; Anderson, Brian J. PhD, FANZCA + [Article] Pediatric Emergency Care. 30(9):621-630, September 2014

Appendix A

Common PSA Agents & Properties [2]

- Propofol (IV) – sedative & amnesic (no analgesia)
    - Phenol derivative – highly lipophilic (crosses BBB easily)
    - Onset within 40 seconds
    - Duration ~6 minutes
    - Slow Push - Initial loading dose of 0.5 to 1 mg/kg IV, followed by doses of 0.5 mg/kg IV every three to five minutes as necessary
    - Unchanged pharmacokinetics regardless of liver or kidney function but higher plasma levels in elderly pt's (recommendation is 20% dosage reduction in pt's over 55 as well was slower injection)
    - Propofol formulation contains egg lecithin & soybean oil there contraindicated in pt's with allergies/sensitivities to these
    - Side Effects
        - Hypotension due to myocardial depression / respiratory depression
            - Both brief
            - Respiratory depression seen in form of O2 desaturation & easily treated/prevented w/ oxygen
    - Note no analgesia thus propofol injection can be painful so methods to decrease should be used
    - If no pain is felt by patient analgesics are not always necessary to adjunct with propofol
- Etomidate
    - Imidazole derivative
    - PSA dose IV over 30 to 60 seconds in doses of 0.1 to 0.15 mg/kg
    - Onset ~ immediate w/ 5-15 min duration
    - More potent in hepatic/renal impairment & elderly
    - Benefit – maintains cardiovascular stability
    - No analgesic properties (similar to propofol)
    - Common side effect – myoclonus (making some procedures like suture repair or lumbar puncture more difficult or even dangerous) & less common - respiratory depression
        - Also dose-dependent adrenal suppression
- Benzodiazepines (Midazolam)
    - Produce amnesia & anxiolysis but no analgesia
    - Onset 2-5 minutes w/ 30-60 min duration

  - Prolonged sedation in obese/elderly/renal & hepatic disease
    - Accumulates in adipose tissue
  - Adequate dosage for sedation highly variable (eg: tolerance, age, size, comorbidities, etc)
- Fentanyl
  - Short acting analgesic
  - Onset in 2-3 minutes w/ 30-60 min duration
  - No amnestic properties
  - Primary side effect is respiratory depression w/ more serious effects in elderly & hepatic/renal disease
- Ketamine
  - Phencyclidine derivative that acts as a dissociative sedative
    - Dissociative sedation is a trance-like cataleptic state in which the patient experiences profound analgesia and amnesia but retains airway protective reflexes, spontaneous respirations, and cardiopulmonary stability
  - Provides sedation, analgesia & amnesia while preserving upper airway tone
  - Onset ~immediate w/ 10-20 min duration
  - Side effects
    - Most prevalent → Nausea/Vomiting & Emergence reactions (rx's after the procedure is over) including hallucinations & agitation
      - Pre-treatment w/ Anti emetics helpful
    - Tachycardia & hypertension (mild & transient)
    - Hypersalivation
    - Increased intraocular & intracranial pressure (transient)
- Ketofol
  - Synergistic effects allow lower doses of each drug reducing risk for side effects
  - Counteracting qualities between propofol associated hypotension & ketamine associated HTN which forms a nice medium
    - Also anti-emetic propofol w/ emetic ketamine
  - More consistent sedation & less agitation than propofol alone with lower doses required
    - Note opposite during recovery (more agitation with ketofol vs propofol)

Appendix B

Ketofol Group

Procedure & #	Time of induction	Recovery Time	Discharge Time (D/T)	Total Recovery Time (min)	PSA to D/T	Drugs & Dosages	Adverse Events
1- Cardioversion	9:30 AM	9:40 AM	10:40 AM	10	70	40mg Ketamine / 40mg Prop	
2 - Forearm Reduction	1:32 PM	1:40 PM	2:15 PM	8	43	10mg Ketamine / 50mg Prop	
3 - Wrist Reduction	7:59 AM	8:30 AM	9:15 AM	31	76	10mg Ketamine / 80mg Prop	
4 - Wrist Reduction	9:41 AM	9:55 AM	10:45 AM	14	64	10mg Ketamine / 70mg Prop	
5 - Wrist Reduction	12:38 PM	1:10 PM	1:40 AM	32	62	20mg Ketamine / 150mg Prop	Mild confusion upon prior to discharge
6 - Wrist Reduction	7:55 PM	8:25 PM	10:10 PM	30	135	5mg Ketamine / 50mg Prop	
7 - Wrist Reduction	8:07 PM	8:35 PM	9:10 PM	28	63	80mg Ketamine / 100mg Prop	
8 - Wrist Reduction	9:20 AM	9:40 AM	10:50 AM	20	90	30mg Ketamine / 50mg Prop	
9 - Wrist Reduction	7:21 PM	7:45 PM	9:00 PM	24	99	6mg Ketamine / 60mg Prop	
				197	702		
Average				**21.9**	**78**		

Alternative Group

Procedure #	Time of Induction	Recovery Time	Discharge Time	Total Recovery Time (min)	PSA to D/T	Drugs & Dosages	Adverse Events
1 - Cardioversion	8:44 AM	9:00 PM	10:40 PM	16	116	2mg Midaz / 30mg Prop	
2 - Cardioversion	8:01 AM	8:15 AM	8:37 AM	14	36	1mg Midaz / 50mg Prop	
3 - Cardioversion	9:26 AM	9:45 AM	10:30 PM	19	64	2mg Midaz / 20mg Prop	
4 - Cardioversion	8:30 AM	8:50 AM	9:15 PM	20	45	2mg Midaz / 90 mg Prop	Jaw-thrust required to maintain a/w
5 - Cardioversion	8:33 AM	9:00 AM	9:20 AM	27	47	140 mg Propofol	
6 - Cardioversion	9:34 AM	10:24 AM	11:50 AM	50	136	100mcg Fent / 3 Midaz / 30mg Prop	Oral adjunct required to maintain a/w
7 - Cardioversion	8:41 AM	9:20 AM	9:50 AM	39	69	200 mcg Fent / 2mg Midaz	oral adjunct required to maintain a/w
8 - Cardioversion	10:20 AM	10:35 AM	10:45 AM	15	25	50mg Propofol	Transient hypotension (20 mmHg systolic drop)
9 - Cardioversion	8:04 AM	8:20 AM	10:10 AM	16	126	1mg Midaz / 50 mg Prop	Hypotension - 132/77 to 87/62 - NS given W/O
10 - Cardioversion	9:22 AM	9:50 AM	11:45 AM	28	143	100 mcg Fent / 200mg Prop	Desat (98 to 89) - treated with supp O2
11 - Wrist Reduction	3:15 PM	4:00 PM	5:20 PM	45	125	200 mcg Fent / 2mg Midaz / 40 mg Prop	Jaw thrust & oral adjunct required to maintain a/w
				289	932		
Average				**26.3**	**84.7**		