Sedation and analgesia in intensive medicine

Style, Charles David

UNIVERSITY OF ZAGREB

SCHOOL OF MEDICINE

Charles David Style

Sedation and Analgesia in Intensive Medicine

Sedacija I Analgezija u Intenzivnoj Medicini

GRADUATION PAPER

Zagreb, 2020

Zagreb, 2010

This graduation paper was made at Zagreb School of Medicine, Anaesthetics department under supervision of Prof. Dr. Sc. Dinko Tonković, MD and it was submitted for evaluation in the academic year 2019/2020

Graduation paper was made at the Anaesthetics Depaartment of University of Zagreb School of Medicine

Mentor: prof. dr. sc. Professor Dinko Tonković

Sedation and Analgesia in Intensive Medicine

Introduction

Sedation and analgesia are incredibly important and frequently used aspects of hospital practice and even out of hospital life. Sedation refers to the administration of a sedative hypnotic agent with the hopes of reducing the patient's awareness or level of consciousness. Analgesia refers to administration of an analgesic drug to prevent or stop pain.

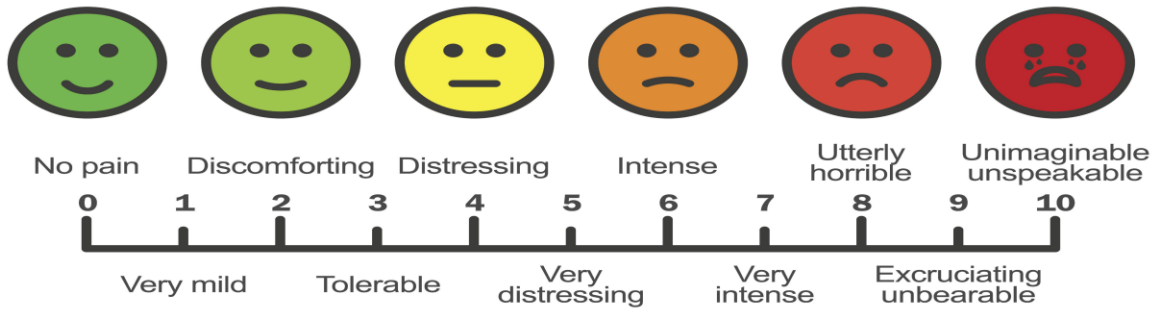
It is very important to provide the right balance between sedation and normal physiology with the use of sedatives and analgesics keeping in mind side effects that go with these drugs. In the intensive care we often have patients that require sedation and analgesia for whatever reason, and these procedures often come hand in hand in a practice called Procedural Sedation Analgesia (PSA)[1].

In this thesis I am going to discuss the variety of methods of sedation and analgesia in the ICU. This includes the different drugs we can use to achieve the desired outcome, as well as the procedures and interventions we can use to achieve the same.

Methods of Assessment

To assess the variety of sedative and analgesic drugs available, along with analgesic procedures and interventions, we need a way of comparing the effectiveness and use a variety of scales to know what level we are at in this.

Pain is a very subjective sensation. Some people have much higher pain tolerances than others, and so it is very difficult for healthcare workers to gauge the amount of pain a patient is in. Also, it can be difficult for patient to accurately label how much pain they are in. As a result, a variety of visual face and numerical scales have been produced in order to get a better example of this and help treat patients more accurately. Here was can ask the patient "on a scale of 1 to ten, 1 being no pain, and 10 being the worst pain you have ever felt, where would you rate your pain?". Or with children, we can ask them to point at the face that most displays how they feel.



One problem specific to ICU patients is most of them are mechanically ventilated, sedated, or for some other reason have an impaired ability to verbalize or communicate, and so they cannot self-report their pain to the healthcare professional working with them. In this case it is totally up to the healthcare professional to use a combination of his judgment and methods like the Behavioral Pain Scale shown below to guide therapy and treatment [4].

.

Facial Expressions	Relaxed	1
	Partially tightened	2
	Fully tight	3
	Grimacing	4
Upper Limbs	No movements	1
	Partially bent	2
	Fully bent with fingers flexion	3
	Permanently retracted	4
Compliance with mechanical ventilation	Tolerating movements	1
	Coughing but tolerating ventilation most of the time	2

	Fighting with the ventilator	3
	Unable to control the ventilation	4

When it comes to gauging levels of sedation, there are many different stages we might want to reach, depending on the procedure in question. For example, with an irritable child who is very scared of receiving an injection, we might want to give a very small amount of benzodiazepine, to provide a light level of anxiolytic and sedation. On the other end of the scale is for a procedure like intubation we require the patient to be unconscious. The levels of sedation can be gauged by factors such as; Response to stimuli, Airway, Spontaneous Ventilation, and Cardiovascular function. An example of this such scale is given below [2].

Level of Sedation	**Responses to Stimuli**	**Airway**	**Spontaneous Ventilation**	**Cardiovascular Function**
Minimal	Normal response to verbal stimuli	unaffected	unaffected	unaffected
Moderate	Response to verbal or tactile stimulation	No intervention required	Adequate	Usually maintained
Deep	Response to painful stimulation	Intervention may be required	May be adequate	Usually maintained
General Anesthesia	Unarousable	Intervention often required	Frequently inadequate	May be impaired

There are also a variety of scales such as The Ramsey Sedation Scale, The Michigan Sedation Scale, and the Richmond Agitation Sedation Scale; all of which can be used to describe the level of sedation of a patient in terms of behavior of the patient. An example of such scales is the Ramsay Sedation Scale given below.

Score	Level of Sedation
1	Patient is anxious and agitated, or restless, or both
2	Patient is co-operative, oriented, and tranquil
3	Patient responds to commands only

4	Patient exhibits a brisk response to light tactile stimuli or loud auditory stimulus
5	Patient exhibits a sluggish response to light tactile stimuli or loud auditory stimulus
6	Patient exhibits no response

The Richmond Agitation-Sedation scale is shown below:

Points	**Classification**	**Description**
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior towards staff
+2	Agitated	Frequent non-purposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert, but has sustained (>10 s) awakening, with eye contact, to voice
−2	Light sedation	Briefly (<10 s) awakens with eye contact to voice
−3	Moderate sedation	Any movement (but no eye contact) to voice
−4	Deep sedation	No response to voice, but any movement to physical stimulation
−5	Unrousable	No response to voice or physical stimulation

Physiology of Sleep

When we talk about the physiology of natural sleep, we need to discuss two main points; sleep cycles, and circadian rhythms.

Sleep cycles are the stages of sleep we call go through, as defined by characteristics we see on electroencephalography (EEG) monitoring. There are 4 main stages of the sleep cycle, 3 of which we classify as Non-Rapid Eye Movement sleep, and the other we call Rapid Eye Movement sleep (REM). Rapid eye movement sleep is defined by having, firstly, rapid eye movements, secondly muscle atonia (paralysis), and lastly EEG desynchronization. The major specifics of each of the stages of sleep I will highlight in the table below:

Stage of Sleep	Characteristic EEG Findings	Characteristics in the stage
N1	Theta wave activity	Hypnogenic hallucinations, Hypnic Jerks Easily woken up
N2	Theta wave activity, with K-complex's, and Sleep Spindles	Less easily aroused
N3	Delta Waves	Sleepwalking/ sleeptalking stage
REM	Complex activity	Paradoxical- active mind on EEG but a paralyzed body

When we go through a natural sleep, our body will go through all the above cycles in durations of about 90 minutes each, however these durations depend largely on the person and so can vary. What we do know is the order of stages tends to follow; N1 through to N2, through to N3, then back to N2, and finally onto REM sleep. To have a good night's sleep and allow the body to fully recover, we must allow our body to go through all stages of sleep.

Briefly put, the circadian rhythm is what we call out “body clock”, and this tells us when we wake up and when to go back to sleep. Although the details of this are beyond the scope of this thesis, it is largely controlled by both environmental factors such as light, and hormonal factors such as the endogenously released hormone Melatonin.

Pathophysiology of Sleep: Sleep Disorders

There are three major classes of sleep disorders which we must be familiar with. These include Parasomnias, Dyssomnias, and Disorders of the Circadian Rhythm [13].

Parasomnias can be broadly described as a sleep disorder "that involves abnormal movements, behaviors, emotions, perceptions, and dreams that occur while falling asleep, sleeping, between sleep stages, or during arousal from sleep" [13]. Within the class of parasomnias, we can break it down into three further subcategories, each containing many different disorders, as shown in the table below:

Parasomnias		
Disorders of arousal from non-REM sleep	**Disorders of arousal from REM sleep**	**Other Parasomnias**
Sleepwalking	REM Behavior Disorder	Sleep enuresis
Sleeptalking	Recurrent isolated sleep paralysis	Parasomnias due to drugs or toxins
Sleep terrors	Nightmare disorder	Exploding head Syndrome
Confusional arousals		Parasomnias due to a medical condition

Dyssomnias can be broadly described as a sleep disorder involved with difficult falling asleep, staying asleep or excessive sleepiness [13]. The table below lists some of the more common Dyssomnias:

Dyssomnias	
Idiopathic hypersomnia	Narcolepsy
Restless leg syndrome	Alcohol dependent sleep disorder
Obstructive Sleep apnea	Post traumatic hypersomnia

Finally, those sleep disorders involving the circadian rhythm are common, for example Jetlag is something most people who travel intercontinentally will experience. Or Shift Work

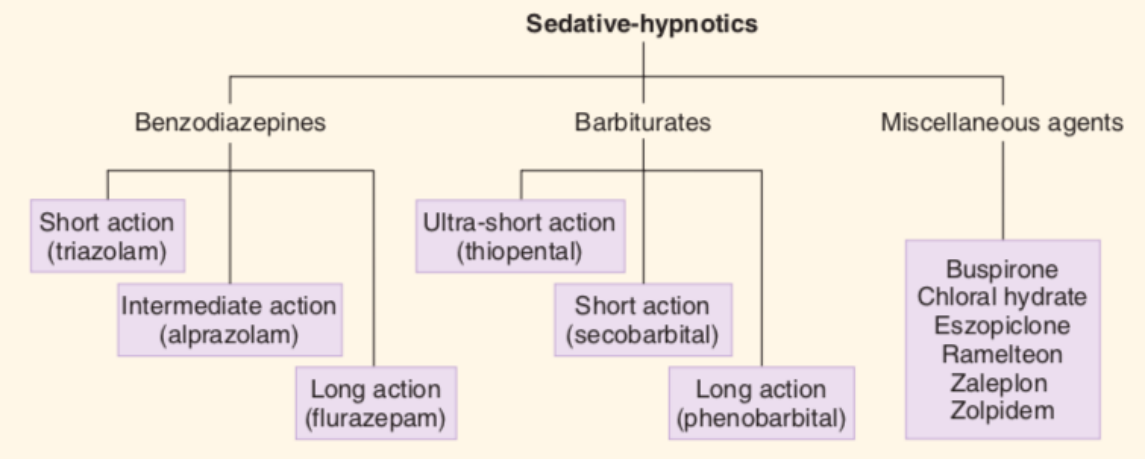
Sleep Disorder is that commonly seen in people who routinely have to change between working in the day and night, such as healthcare professionals [13].

It is important for us to be aware that drugs we use to induce sedation in patients do not provide a "natural" sleep. Benzodiazepines for example have been proved to result in less REM [14] and so despite the fact the patient will be asleep, they will not be properly rested. This leads to problems down the line such as delirium that we will discuss later.

Pharmacology

There are many drugs available for doctors to use, in a variety of preparations, including drugs to be taken orally (PO), by injection (IV, IM, SC), rectally, intranasally, or even transdermally for some. The choice and route of drug chosen depends on desired effects, duration of action, and keep in mind the side effects associated with all drugs. In this section I will discuss some of the main drugs available to physicians at this time, the main ones used, the mechanism of action, pharmacokinetic/dynamics, and my conclusions as to benefits and drawbacks.

Sedative Hypnotics



[3]

There are a variety of sedative drugs used today. The main drugs are those of the benzodiazepines class. These drugs are all available in oral and intravenous preparations. The drugs target the benzodiazepine receptor (BZ Receptors), which form part of the $GABA_A$ chloride ion channel. Benzodiazepines bind this receptor specifically at α1, α2, and α5 subunits. The binding of benzodiazepines to this receptor increase the frequency of opening of the channel, which in turn causes the effect of the drug.

All benzodiazepines have similar effects, including sedation, hypnosis, anesthesia at high dose, anticonvulsant actions, muscle relaxation, and some can produce medullary depression as high dosages. Benzodiazepines possess the ability to induce significant amnesia, specifically anterograde amnesia. Meaning after administration of the drug at sufficient dosage, a patient is unable to remember the subsequent events. This can be useful for stressful times or painful procedure.

One important thing to note about benzodiazepines is the ability for their action to be antagonized by the drug Flumazenil. This is useful in cases of excessive sedation or coma caused by excessive or inappropriate use of the drugs, or accidents like overdosages. One problem with the use of Flumazenil however is the ability to trigger seizures in those with high tolerance or dependence to benzodiazepines, and so its use is limited.

Drug Name	**How Supplied**	**Dosage Range [5]**
Diazepam	Inj; 5mg/ml Tab; 2-10mg Supp; 5-10mg	2–10 mg IM/IV q 3–4 hrs prn Max 30 mg
Midazolam	Inj; 1-5mg/ml	1–2.5 mg IV over 2 mins prn anxiety; titrate to effect q 2 mins

		Max 5 mg total dose
Lorazepam	Inj; 2-4mg/ml Tab; 0.5-2mg	0.05 mg/kg IM (2 hrs preoperative) 0.02 mg or 0.04 mg/kg (whichever is smaller) IV prn (for anxiety) Max 4 mg/d IM or IV
Flumazenil	Inj; 0.2mg/ml	0.2-0.3 mg IV, titrated until desired effect Max 3mg /hr

Drugs like diazepam have lots of uses ranging from muscle relaxation for back pain in low dosages, to anxiety relief in social anxiety and pre preprocedural anxiety situations, and is considered a milder long acting benzodiazepine. Midazolam on the other hand is able to be used in the operating room to induce general anesthesia. Benzodiazepines have a relatively large therapeutic window and so their use out of acute treatment settings is safer. As a result, they are often prescribed to patients to take home for use as sleep aids.

Due to the tolerance building and addictive nature of benzodiazepines, alternative agents have been made which have less of these issues. The so called “Z Class” drugs are useful for helping patients who have problems with sleep, but less of the muscle relaxing anti-anxiety properties. These drugs also interact with benzodiazepine receptors, classified as BZ1 or ω1 in a similar way to benzodiazepines.

Drug Name	**How Supplied**	**Dosage Range [5]**
Eszopiclone	Tab; 1-3mg	1-3mg PO

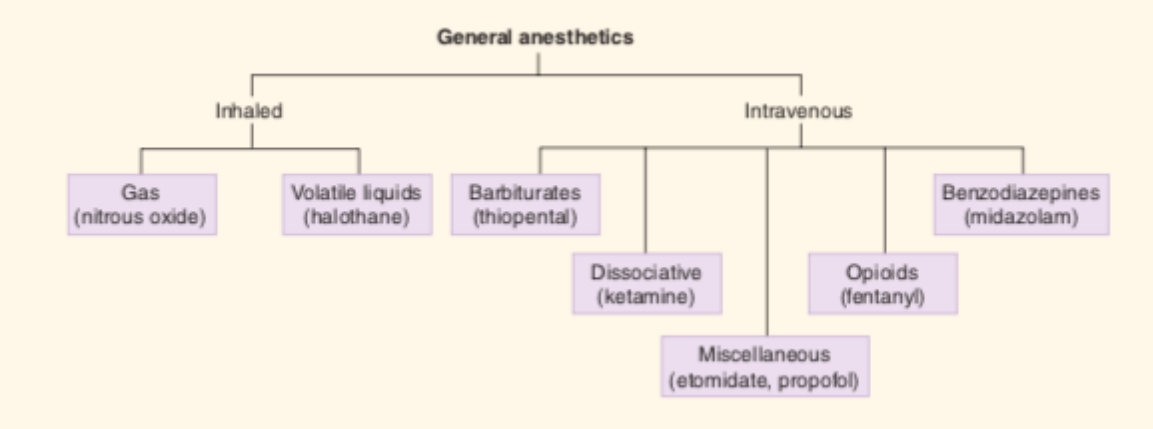
		Max 3mg/day
Zolpidem	Tab; 1.75-10mg	5-10mg PO Max 10mg/day
Zaleplon	Tab; 5-10mg	5-10mg PO Max 20mg/day

Finally, in this class we can talk about the barbiturate class of drugs. These are older generations to benzodiazepines and unlike benzodiazepines are not able to be antagonized by Flumazenil. Barbiturates bind to the GABAa receptor, at a different location to Benzodiazepines, and their mechanism of action is to increase the duration of opening of the GABAa channel, and also block the excitatory transmitter glutamic acid, and, at high concentration, sodium channels.

Barbiturates are much more able to cause anesthesia than conventional benzodiazepines, and cause much greater levels of medullary depression. This coupled with a relatively narrow therapeutic window causes them to be relatively more difficult to use safely as there is a very real possibility to stop the patient breathing. As a result, their use tends to be limited to places like the operating room and ICU where airway can be controlled and used safely.

Drug Name	**How Supplied**	**Dosage Range [5]**
Thiopental	Inj; 500-1000mg vial	3-4mg/kg for anaesthesia 75-150mg for seizures
Secobarbital	Tab; 100mg Inj; 50mg/ml	100-300mg PO qHS
Phenobarbital	Tab; 15-60mg Inj/ 65mg/ml	15-18 mg/kg IV loading dose infused at 25-60 mg/min.

General Anesthetics



[3]

These are drugs that are able to induce a state of unconsciousness, skeletal muscle relaxation, analgesia, amnesia, and loss of reflexes.

As previously mentioned in sedatives and hypnotics; Midazolam, a benzodiazepine and all Barbiturates fall into this category as they are able to induce similar levels of CNS depression and so can be used for this purpose. There are a variety of other agents able to induce a similar level of CNS depression that is commonly used in the ICU.

Of limited use in the ICU but worth a mention are the inhaled anesthetics, consisting of the gas Nitrous oxide, and volatile halogenated ethers such as Sevoflurane, Isoflurane, and Desflurane. Whilst the mechanism of action of these agents is rather unclear, they are often used to induce or maintain anesthesia in the operating room. Nitrous oxide has a rather special property of also being an analgesic agent, and is used often in the prehospital environment for this property, or in hospital in combination with other agents for its synergistic effect. Due to their limited use in the ICU I will not mention any more on these anesthetics.

The other general anesthetics are all used in the ICU for maintaining a patient in a comatose state, for example when the patient is on a respirator, or when anesthesia is desirable.

Drug Name	How Supplied	Dosage Range [5]
Propofol	Inj; 10-20mg/ml (1-2% formulation)	40 mg IVP q10sec until onset (2-2.5 mg/kg IV for induction) 0.1-0.2 mg/kg/min IV for maintenance (or 25-50mg boluses)
Ketamine	Inj; 10-100mg/ml	1-4.5 mg/kg slow IV once (for induction) 0.1-0.5 mg/min IV continuous infusion (for maintenance) 2.5-15mcg/kg/min (for analgesia)
Etomidate	Inj; 2m5/ml	0.3-0.6 mg/kg IVP over 30-60 sec (for induction) 0.1 mg/kg IV bolus x1-3 doses (for sedation)
Dexmedetomidine	Inj; 80mcg/20mL (4mcg/mL) 200mcg/50mL (4mcg/mL) 200mcg/2mL (100mcg/mL)	Load: 1 mcg/kg IV over 10 minutes Maintenance 0.2-0.7 mcg/kg/hr continuous IV infusion; not to exceed 24 hr (for ICU sedation)

Now although we have a large number of drugs available to use for use in sedation in the ICU, each drug has its own very unique properties and consequently its own strengths and

weaknesses for use, for example with regards to haemodynamic effects, duration of action, effect on the intracranial pressure, amongst others. As a result, I will briefly talk about each of these drugs and go over these traits.

Propofol, also known as Milk of Amnesia due to its appearance, is available as a 1% or 2% emulsion of the active ingredient, 2,6-diisopropylphenol in both an aqueous base and soybean oil and egg lecithin [6]. This formulation of the product immediately causes problems for those with allergies to those ingredients, as no other formulations exist without these potential allergens. Also due to these ingredients there is frequently reported pain on injection of the emulsion, and so use of a local anaesthetic can be used, or injection into a larger vein can be used to mitigate these problems.

Propofol acts on the GABAa receptor and allosterically increases GABA binding to this receptor, causing hyperpolarization of this chloride channel nerve membrane. Unlike benzodiazepines, propofols effects cannot be reversed by Flumazenil.

Onset of action is very fast, and due to its 2-8 minute distribution half-life, awakening from a single administration is equally fast. This coupled with the fact there is relatively little “hangover” [6] produced after coming through from sedation from Propofol makes it an excellent choice for use in procedural sedation in the ICU. Propofol also possess unique effects like its antiemetic and antipruritic actions, which are invaluable when we consider Opiates used in combination tend to cause severe nausea and vomiting and morphine in particular causes histamine release which ca cause pruritus. Propofol possesses absolutely no analgesic action however and so analgesics must be co-provided.

On the cardiovascular system Propofol induces a decrease in arterial blood pressure due to a drop in systemic vascular resistance, preload, and cardiac contractility, caused by inhibition of sympathetic vasoconstrictor activity and impaired baroreceptor reflexes to the hypotension. This hypotension is usually countered during intubation or surgical incision due to the

sympathetic stimulation. Despite the above there is rarely and if at all transient decrease in heart rate and cardiac output in the healthy patient. However, those patients at extremes of age or receiving medications like B-blockers may be affected by this. Propofol can be used for continuous sedation and to keep a patient in a coma by either continuous bolus injections of the drug, or better still the use of an infusion pump to continually deliver set dosages of the drug can keep a patient very stably in an unconscious state for extended periods of time.

Like other strong sedatives, Propofol causes significant respiratory depression and inhibits the hypoxic ventilatory drive and normal response to hypercarbia. As a result, Propofol must only be used when full control of respiration is possible and by those able to take over respirations for the patient.

When it comes to cerebral circulation Propofol decreases cerebral blood flow, volume, and intracranial pressure. This is significant as the cerebral perfusion pressure can fall to <50 mm Hg which can be dangerous to the patient, and so interventions must be performed to make sure the pressures stay above toxic levels.

To summaries, Propofol possesses many favorable characteristics both with hemodynamic stability and quick onset and waking of the patient. This combined with low cost and easy dosing when set on an infuser pump makes propofol a very attractive option in the ICU.

Ketamine is an arylcyclohexylamine, similar in structure to other drugs like phencyclidine, both commonly abused for their euphoric dissociative effects. Ketamine is a water-soluble drug in the form of its hydrochloride salt, and can be diluted to any desirable concentration, and is also available in many different concentrations commercially. This means ketamine of one of few drugs that can be given intramuscularly alone in large enough dose for induction of general anesthesia [6]. The general desirable effects of ketamine, dose dependent, include anesthesia, amnesia, and analgesia.

Another demonstration of the versatility of the drug is combinations of the drug being commonly known, such as “Ketofol” which is a mixture of ketamine and propofol [7] in a standard infusion ratio of 1:10, meaning 10mg ketamine: 100mg propofol. This combination is commonly used as they work synergistically with each other, enabling decreased dosages of both, to provide analgesia and sedation, whilst maintaining hemodynamic stability and reducing side effects [7]. In the studies mentioned by the review " Combining Ketamine and Propofol (“Ketofol”) for Emergency Department Procedural Sedation and Analgesia “[7] it was shown the combination of ketamine and propofol produced a decreased time of onset of sedation and analgesia, and compared to the propofol alone group, none of the patients receiving Ketofol required ventilatory assistance, making the combination safer than propofol alone.

The mechanism of action of Ketamine is not well understood, however it is known to act on many different receptors including and inhibitor of N-methyl-D-aspartate (NMDA) channels, serotonin receptors and even opiate receptors. The effects of ketamine are very much dose dependent. Ketamine functionally “dissociates” sensory impulses from the limbic cortex, causing the patient to be in a seemingly conscious state, however not responsive to sensory input in a high dosage. When used in lower dosages, ketamine is an excellent analgesic. These properties make ketamine very much unique in its ability to act as both a sedative and analgesic, and so can be used as a stand-alone drug in many painful procedures requiring procedural sedation such as relocations of dislocated limbs. This property has seen ketamine gain great favor in the prehospital environment for patient extrications and Rapid Sequence Intubations [7]. Due to the dissociative effects, hallucinations and delirium are common with emergence of anesthesia and consequently it is commonly used in combination with benzodiazepines like midazolam to reduce these side effects.

Ketamine is the only general anesthetic that has stimulatory effects on the cardiovascular system. Ketamine increases arterial blood pressure, heart rate, and cardiac output, due to the stimulation of the sympathetic nervous system and its SNRI effects. These effects make the drug very useful for trauma victims or other patients where maintenance of a blood pressure or

cardiac output is important. Conversely it must be used with caution in patients with cardiovascular problems such as hypertension, heart failure, or coronary artery disease.

Ketamine alone generally has little effect on the respiratory system, even at induction dosages. It even has beneficial bronchodilator effects, making it an agent of choice for asthmatics. Increased salivation from ketamine is not a problem in the intubated patient, but these effects can be prevented by the administration of an anticholinergic agent such as atropine.

Etomidate acts directly on the GABA receptor complex, blocking neuroexcitation leading to its sedative / anesthetic effects. It also acts on the system that controls extrapyramidal motor activity which can explain the up to 60% incidence of myoclonus post induction with etomidate. The drug itself is insoluble in water at physiological PH, and so is provided as a solution in 35% propylene glycol, prohibiting its use in continual pump infusions.

Etomidate has minimal cardiovascular effects, save for a small decrease of peripheral vascular resistance and so drop in arterial blood pressure. For this reason, etomidate finds good use in cardiovascular surgery.

Very little if any apnea is produced by induction dosages of etomidate, and so has little effect on the respiratory system.

Etomidate has acceptable cerebral dynamics, decreasing cerebral blood flow, metabolism, and intracranial pressure, however maintaining cerebral perfusion pressure. One drawback to etomidate in this regard however is nausea and vomiting after etomidate are more common, and there are no analgesic effects from it.

Dexmedetomidine is a relatively novel agent in the ICU. It is an α2 -adrenergic agonist providing sedation, anesthesia, and analgesia along with reported anxiolysis. Unlike the other

α2 -adrenergic agonist currently used; Clonidine, it is 8 times more selective, and as a whole, its selectivity ratio for the α2 -adrenergic receptor to the α1 -adrenergic receptor is 1620: 1 [15]. The pharmacodynamics of the drug are relatively good. It is mainly (94% protein bound), has low oral bioavailability of 16% due to first pass metabolism, but other methods such as buccal or nasal are reliable. It is mostly used by IV infusion of 0.2-0.7ug/kg/hr however, so this first pass metabolism not very important. It has an elimination half-life of 2 hours and is cleared in the liver. Renal insufficiency therefore warrants no change in dosage requirements of the drug [15].

Some of the notable qualities of Dexmedetomidine is it provides a unique quality of natural sedation, most closely resembling that of natural sleep. This has its benefits in causing less Post Stress Syndrome as is seen in other sedatives used in the ICU. This is supported with clinical evidence in the SEDCOM trial where it was compared to other sedative hypnotics. [16] It does not cause respiratory depression like most other of the sedatives and so it is rather safer in this respect also.

The target for the drug as previously mentioned is the α2 -adrenergic receptor, and these are located both centrally and peripherally. Because of this, Dexmedetomidine has a variety of effects which seemingly contradict each other, a so-called biphasic action, depending on which receptor is being targeted, a factor influenced by dosage and time of the drug administration. On the cardiovascular system it causes either Hyper- or Hypotension, along with a Bradycardia. When the drug is given as a bolus injection, such as with a loading dose, the α2B -adrenergic receptors are targeted on the vascular smooth muscle tissue, causing Hypertension and Bradycardia [15].

Neurologically it causes sedation and anxiolysis as previously mentioned, and some analgesia. The sedation is caused by its central effect on the α2 -adrenergic receptor, causing disinhibition of the ventrolateral preoptic nucleus which then releases inhibitory neurotransmitters. Due to this more unique mechanism of action, the sleep is more “natural” in structure, and there is next to no depression of the respiratory system, as seen with the GABAergic sedatives like the Benzo’s and Propofol [15]. The analgesic effects can be taken

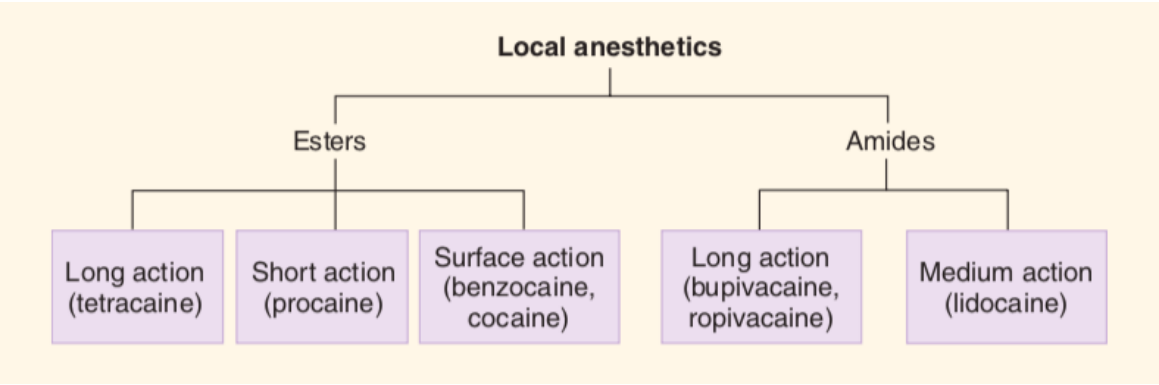
advantage of when it is used as an opioid-sparing agent in the ICU, and as always, the lower the amount of opiates we have to give in the ICU, the less side effects we will see.

When we look at its effect on the respiratory system, due to the absent depression of respiratory muscles, Dexmedetomidine is seen as a good choice for intubated patients whom we want to take off ventilation, as a strong respiratory drive is required for this, and a lack of any respiratory depressant in the patients system will allow for the best chance of this successful extubation and allow the patient to provide his own ventilation and adequate oxygenation.

The level of sedation Dexmedetomidine is generally used is between 0 and –3 on the Richmon agitation scale, as spoken about earlier in this thesis. This corresponds to alert and calm, to moderate sedation. This means patients sedated with the drug are arousable. [15]

It also has a few other obscure side effects such as reduced bowel motility and a diuretic effect via inhibition of ADH on the collecting duct.[15] The α2 -adrenergic agonist effects of Dexmedetomidine can be reversed by the α2 -adrenergic antagonist; Atipamezole. This is useful when trying to titrate the desired effects such as levels of sedation.

Local Anesthetics



[3]

Local anesthetics work by targeting membrane-associated voltage-gated Sodium channels in nerve axons. Normally, activation of these sodium channels causes temporary increase in permeability of the membrane to sodium ions, allowing a small number of sodium ions to come in and change the polarization of the nerve axon to +35mV. These channels produce and transmit action potentials by membrane depolarizations following electrical, chemical, or mechanical stimuli of the nerve. Baseline concentrations of ions in the cell, and consequently voltages, are maintained by Na-K pumps. The structure of the Sodium channels which local anesthetics target are one large α subunit, through which Sodium ions pass, and one or two smaller β subunits. The local anesthetics target the α subunit of the channel. When a local anesthetic is bound to the α subunit, the channel cannot allow sodium ions through, thus, does not allow an action potential, and thus the nerve impulse gets stopped at that point on the axon.

When it comes to which nerves are affected more readily than others, generally the thinner the nerve the more readily it is affected by local anesthetics, and conversely the thicker the nerve the less readily it will be affected by a local anesthetic. Whether a nerve is myelinated or not also will affect how much the nerve will be affected, myelin protecting the nerve from the anesthetic.

Systemic absorption of local anesthetics is what influences the *duration of action* / cessation of the action of the anesthesia. This systemic absorption depends on three factors:

1. *Site of injection*: The vascularity of the area injected influences how quickly a drug will be taken away from the area injected. The relative vascularity of sites is ranked as: Intravenous/intraarterial > intercostal > epidural > brachial plexus > subcutaneous tissue.
2. *Presence of additives*: the addition of a vasoconstrictor, commonly adrenaline, to the local anesthetic provides local vasoconstriction of the site injected, which causes a reduction in the absorption of the anesthetic and allows less anesthetic to be

administered with similar affect. Adding steroids like dexamethasone to the local anesthetic reportedly prolongs duration of action by 50% [6].

3. *Local anesthetic agent chosen*: as will be mentioned later, properties of the anesthetic compounds themselves influence how quickly they will be taken up by the body and removed.

The *onset of action* and *potency* of local anesthetics depends on two major factors; lipid solubility, and concentration of the lipid soluble base form (B). All local anesthetics exist in equilibrium with a charged form (BH^+), according to the following equation:

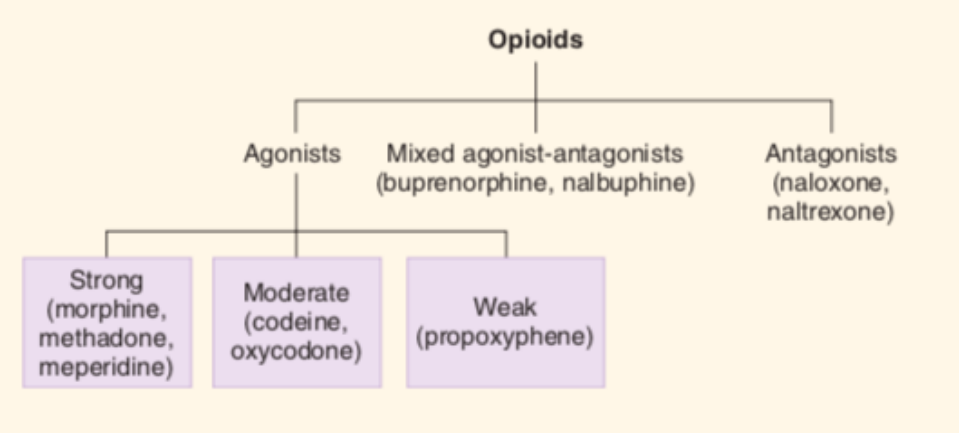
$$B + H^+ \text{ <--> } BH^+$$

The charged lipid insoluble form of the local anesthetic has a very long duration of onset and low potency, and conversely the lipid soluble form has fast onset and high potency.

Local anesthetics can be broadly classified into two groups, esters and amides, deduced from whether the local anesthetic has either bond in its structure. This distinction is important because if one has an allergy to ester local anesthetics, it is unlikely the person has an allergy to amides, and vice versa.

Local anesthetics can be formulated in creams, for example EMLA cream which is a topical formulation of Lidocaine and Prilocaine in a ratio of 2.5%:2.5%. Water based lubricating gels containing Lidocaine 2% are manufactured for use as lubricants in procedures in the ICU that would otherwise be painful for the patient such as endoscopies, catheter insertions, and nasogastric tube insertions etc.

Analgesic Agents



[3]

We can classify analgesics available into two main categories; Opioids, and Non-opioid analgesics. Opiates are based on the historic drug morphine, derived from the sap of the opium poppy. Non-opioid drugs consist of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), and Paracetamol. All different classes work in different ways to relieve pain, and each has its own advantages and drawbacks which will be discussed individually. The table below shows some of the Non opioid analgesics used in the ICU:

Drug Name	**How Supplied**	**Dosage Range [5]**
Paracetamol	Tab; 500mg Oral susp; 250-500mg/5ml Inj; 1000mg/100ml	500-1000mg PO/IV
Ibuprofen	Tab; 200mg, 400mg, 600mg Oral susp; 200-400mg/5ml Inj; 800 mg; 300 mg; 600 mg; 400 mg; 200 mg; 50 mg/1.25 mL	200 to 400 mg orally every 4 to 6 hours as needed Maximum dose: 3200 mg/day (prescription strength); 1200 mg/day (over-the-counter)
Diclofenac	Tab; sodium 25 mg; potassium 50 mg; sodium 75 mg; sodium 100 mg; sodium 50 mg; 37.5 mg/mL; potassium 25 mg; sodium; 18 mg; 35 mg Inj; 25mg/ml	25 -100 mg PO 4x/d 25 mg IV bolus over 15 seconds every 6 hours as needed for pain Maximum Dose: 150 mg per day

Ketoprofen	Tab; 25-75mg Inj; 50mg/ml	25-50 mg PO q6-8hr

Paracetamol was introduced in 1887, and has been one of our longest standing drugs in use for pain. It is unique in both its mechanism of action and class. Its mechanism of action is still not fully known. It has been postulated that it works via a so called COX3 isoenzyme in the CNS [8]. This is shown by its lack of anti-inflammatory action in the periphery but its ability to reduce fever and treat headache.

Due to paracetamols unique mechanism of action and synergistic effects with both opioids and NSAIDs it is useful as a standalone drug or one used in combination with others in the multimodal treatment of pain. It is available in many forms including oral tablets and intravenous formulations.

Ibuprofen, diclofenac, and **Ketoprofen** are examples of the class of analgesics called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). These all share common mechanisms of action, mainly the inhibition of peripheral cyclo-oxygenase enzymes (COX enzymes) [12]. The two main forms of COX enzymes are COX-1 and COX-2. These enzymes are involved in the synthesis of prostaglandins, and prevent their role in the inflammatory and consequently pain pathways. Other mechanisms of action suggested by studies include blocking G-protein-mediated signal transduction and centrally by endogenous opioid mechanisms [12].

Due to their mechanism of action in the reduction of inflammation, NSAIDs are particularly useful in pain caused by inflammatory reaction. They are also important as adjuvant drugs in analgesia when used in combination with stronger opioid analgesics, as will be described later on.

Below is a table of some of the more commonly used opioid analgesics in a hospital ICU setting:

Drug Name	How Supplied	Dosage Range [5]
Codeine	Tab; 15-60mg	15-60 mg PO q4-6hr PRN; not to exceed 360 mg/day
Tramadol	Tab; 50mg Inj: 50mg/ml	50-100 mg PO q4-6hr PRN; not to exceed 400 mg/day
Morphine	Tab; 5-30 mg Inj; 1-20mg/ml	15-30 mg PO q4hr PRN 2.5-5 mg IV q3-4hr PRN, infused over 4-5 minutes; dose range, 4-10 mg
Fentanyl	Inj; 0.05mg/mL	1-2 mcg/kg IV bolus or 25-100 mcg/dose PRN or 1-2 mcg/kg/hr by continuous IV infusion or 25-200 mcg/hr

There are two classes of opiates; synthetic opiates such as fentanyl and tramadol, and those derived from morphine, which is a drug isolated from the Opium Poppy. References of the use of morphine from the opium poppy go back as far as 1522, and nowadays we have a large amount of morphine derivates. These derivatives have structural changes to the morphine backbone, providing different effects, such as increased or decreased potency, increased or decreased duration of action, and side effects.

Important to note for opioids is that there is a wide difference in strength of opiates, according to the following scale:

Codeine < Tramadol < Morphine < Fentanyl

When it comes to the administration of opiates, the concept of tolerance is very important to keep in mind. Upon continuous administration of opiates to a chronic user, downregulation of the opioid receptors causes and increased 'tolerance' to the opioid, and so more of the opioid must be given to provide the same level of analgesia. Also, there is a degree of cross tolerance amongst the different opiates.

ICU Techniques for Sedation and Analgesia

Non-Pharmacological

It is very important to keep in mind, when it comes to sedation and analgesia, and generally keeping the patient comfortable, there are a few very simple things we can do to achieve this without the use of drug or and other techniques.

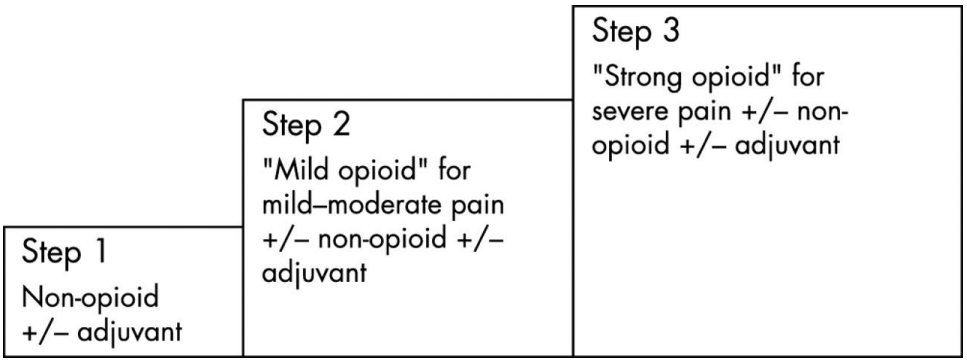
The first thing we must keep in mind is taking care of the patients. This involves nurses or other healthcare professionals checking up on the patient, making sure all their needs are met, including feeding, comfortable positioning, and emotional support when needed. This crucial aspect of patient care is often left out in a busy ICU due to numbers of patients and limited staff and resources, and so education on the importance of this is very neccesary.

Avoiding noise is one of these important steps. An ICU is generally a noisy place with constant monitor beeping and other sounds such as talking and patients making noises. This can be distressful for patients and make it hard for them to relax and settle. As a result, we must endeavor to provide as much of a noise free environment as possible to relax the patient staying in the ICU.

Keeping a good environment for the patients helps keep the patient comfortable and relaxed. This can include having privacy for the patient, and familiar faces around them. Privacy can be obtained either by having individual rooms for the patients, or on the other side of the spectrum, a simple curtain can be used to separate the beds in the ICU. The latter is often favorable because it provides ease of access to the patients by healthcare professionals, which is important in the ICU. The curtains can also be disposable and so it is easy to maintain a clean environment by changing the curtain if it gets contaminated.

Pharmacotherapy; How to start analgesia:

When it comes to providing analgesics to patients, we follow the World Health Organization Pain Ladder [9]. This three-step ladder is followed until the point of relief of pain and is the basis of pharmacotherapy for the treatment of pain.



To give an example of how this ladder is started, we begin treating the patient in pain with a simple NSAID and/or paracetamol. If this fails to work, we will add a mild opioid such a tramadol or codeine to try and control the pain. If this second step fails to control the pain, we will substitute the mild opioid for a stronger opioid such as morphine or fentanyl.

When providing analgesia in the form of analgesics, we much consider the length of time the patient will be taking the analgesia for. In the ICU patients are typically coming in with acute pain, either post operatively or following an acute accident and so we will need to provide strong analgesia straight away. For this, immediate release drug formulation tablets are best if the patient is able to swallow, or if not IV or IM formulations can be used. If longer term strong analgesia is going to be required there are a variety of formulations such as extended release tablets which can provide a steady dose of analgesia for up to around 12 hours, or transdermal patches of drugs like fentanyl which can last days.

One way of avoiding side effects from excessive dosages of drugs has been mentioned previously in the synergistic effect of combining drugs. This Multimodal Effect can be represented by combining paracetamol with tramadol to treat moderate pain. The combination of the two at lower dosages is more effective than those alone at higher dosage.

Strong intravenous medications can be provided to the patient in the form of Patient Controlled Analgesia Pumps (PCA pumps) [10]. These are IV infusion pumps loaded with a set concentration of strong opioid analgesics such as morphine or fentanyl. The pumps are operated by the patient themselves, hitting a button when a dose of the pain killer is required. The dose of the painkiller and the so called 'lockout time', that being the time between different doses can be provided can all be predetermined by the physician. Many studies have been performed on the efficacy of these PCA pumps versus nurse or doctor administered bolus injection of analgesics and studies have shown; "Patient-controlled analgesia (PCA) pumps have been shown to be more effective in treating pain than intermittent intramuscular or intravenous injections, providing higher patient satisfaction, increased perception of situational control, lower preoperative anxiety, lower postoperative depressive symptoms, and increased control over pain relief" [11].

With sedation, we need to keep in mind several aspects. Sedative and hypnotic drugs have significant cardiovascular effects and so monitoring must be in place at all times. Also, the ease of overdose of some sedatives to the point of a compromised airway necessitates the presence of a clinician able to fully manage the airway and intubate if not already.

Another effect of benzodiazepines and strong painkillers which can be detrimental in the long run in the ICU is muscle weakness, a decrease in the immune system, and delirium. This leads to muscle wasting and increased vulnerability to infection. As a result, it's important to use as little sedation as possible, with as smaller dose as needed, for the shortest duration as needed. And with sedation and analgesia, we need to taper down the analgesia and sedation when no longer required to avoid any adverse reactions. "Sedation Holidays", or "Drug Holidays" are periods of time in the ICU where patients are taken off sedation [14]. The point of these holidays is to reduce hospital stay required, reduced complications associated with the long-term consistent use of these drugs, and other beneficial properties [14].

Nerve Blocks

When it comes to providing acute analgesia for certain parts of the body, for a short period of time, we can consider the use of Nerve Blocks.

Within the field of blocks, we have Spinal, Epidural, Caudal, and Peripheral blocks. These are useful for operations where total general anesthesia is not necessary, but a certain are is needed to be treated.

With Peripheral nerve blocks we can go for blocks of the terminal nerves for example, such as; Median nerve block, Ulnar nerve block, Radial nerve block, etc. For these blocks we need to specially consider what local anesthetic to use based on the properties before mentioned, and understand they are temporary and time limited.

Intravenous Regional Anesthesia, also called a Bier Block, is there a tight cuff is inflated proximally on the arm, and a local anesthetic is injected directly into the blood supply. This means the entire arm is anaesthetized. This works great however if the cuff isn't inflated tight enough there is a chance for massive release of large amounts of local anesthetic into systemic circulation, and with that carry's high risks for deadly arrythmias and other local anesthetic toxicity problems.

Using Ultrasound is a very useful tool for when doing blocks like the Transversus Abdominis Plane block (TAP) which is great for post abdominal surgery pain in the ICU. Ultrasound is also useful in all other blocks to make sure the local anesthetic is going exactly where we want it to go, and as a skill is becoming increasingly important in everyday practice.

Neuroaxial anaesthesia includes spinal, epidural, and caudal blocks. These are useful for intraoperative as well as post-operative ICU analgesia. The only contraindications to them are elevated intracranial pressure (ICP), local infection, coagulopathy, local anesthetic allergy, or patient refusal. Lumbar injections are performed below L1 in adults and L3 in children to ensure no harm to the spinal cord. Spinal anaesthesisa is performed as a one-off injection, whereas with epidural anaesthesia a catheter can be placed and so a continues infusion can be set up to provide continuous anaesthesia to the patient. Epidural anesthesia is slower onset

than spinal, and with them we can add high concentrations of glucose to the anesthetic to cause the solution to be denser. This permits us to select the side of the body we want the anesthesia purely based on positioning using gravity.

Conclusion

To conclude this thesis, we have spoken about the different reasons why we need to provide analgesia and sedation in the ICU.

We have shown the importance of evaluation of the level of sedation of patients in the ICU, as this enables us to better provide good quality treatment in the forms of analgesia and physiological support of the patient. As mentioned, scales such as the Richmond Agitation scale provide a points classification of sedation-agitation from +4 to –5, depending on the state of the patient. With this scale we can accurately assess individual patient statuses and vary our treatment based on this scale's assessment of the patient.

We have also shown the physiological qualities of sleep, and the pathological sleep conditions than are present. We have shown that the use of certain medications for the sedation of patients in the ICU can cause pathologies to patients sleep and consequently mental and physical health, such as the appearance of Post Stress Syndrome. Through the use of different pharmacology, we have been able to better treat our patients in the ICU and prevent these different problems.

The variety of medications currently used in the ICU have been shown, giving some of their advantages like the duration of action, effects, and interactions, compared to their disadvantages such as anything ranging from cost to side effect profile.

Finally, we have shown the different methods for providing sedation and analgesia in the ICU, ranging from simple pharmacotherapy, to more advanced techniques that can be used to provide the patients with their needs in the most personal and situational way.

It is important to keep patients comfortable during a stressful period of their life whilst they are in the ICU, and by considering all the factors aforementioned, we can continue to do this to the best of our ability.

References:

[1] Saad A Sheta. Procedural Sedation Analgesia, Saudi J Anaesth. 2010 Jan-Apr; 4(1): 11–16.

[2] Moran, Thea & Kaye, Alan & Mai, Andrew & Bok, Leonard. Sedation, Analgesia, and Local Anesthesia: A Review for General and Interventional Radiologists. Radiographics: a review publication of the Radiological Society of North America, 2013, Inc. 33. E47-60. 10.1148/rg.332125012

[3] Bertram G. Katzung, Marieke Kruidering-Hall, Anthony J. Trevor. Katzung & Trevor's Pharmacology: Examination & Board Review, 11e. United States. McGraw-Hill Education. 2015.

[4] Nissar Shaikh, Saher Tahseen, Qazi Zeesan Ul Haq, Gamal Al-Ameri, Adel Ganaw, Arshed Chanda, et al. Published: November 5th 2018. DOI: 10.5772/intechopen.78708

[5] Medscape Reference, 1994-2019 by WebMD LLC. Available from https://reference.medscape.com/drugs

[6] Butterworth, J., Mackey, D., Wasnick, J., Morgan, G., Mikhail, M. and Morgan, G. (2013). Morgan & Mikhail's clinical anesthesiology. New York: McGraw-Hill.

[7] Sanjay Arora, MD. Combining Ketamine and Propofol (“Ketofol”) for Emergency Department Procedural Sedation and Analgesia: A Review. West J Emerg Med. 2008 Jan; 9(1): 20–23.

[8] Botting R1, Ayoub SS. COX-3 and the mechanism of action of paracetamol/acetaminophen. Elsevier. 2005 Feb;72(2):85-7.

[9] WHO, 2019 by WHO.int. Available from https://www.who.int/cancer/palliative/painladder/en/

[10] Lance S. Patak, MD, MBA, Alan R. Tait, PhD, Leela Mirafzali, Michelle Morris, MS, Sunavo Dasgupta, MD, Chad M. Brummett, MD . Patient Perspectives of Patient-Controlled Analgesia (PCA) and Methods for Improving Pain Control and Patient Satisfaction. Reg Anesth Pain Med. 2013 Jul-Aug; 38(4): 326–333.

[11] Dolin SJ, Cashman JN, Bland JM. Effectiveness of acute postoperative pain management: I. evidence from published data. Br J Anaesth. 2002;89:409–423.

[12] Cashman JN, The mechanisms of action of NSAIDs in analgesia. Drugs. 1996;52 Suppl 5:13-23.

[13] Michael J. Sateia , MD, International Classification of Sleep Disorders-Third Edition Highlights and Modifications, Contemporary Reviews in Sleep Medicine, 2014

[14] Frontera JA. Delirium and sedation in the ICU. Neurocrit Care. 2011;14:463-474

[15] VL Scott-Warren, J Sebastian, Dexmedetomidine: its use in intensive care medicine and anaesthesia *, BJA Education*, Volume 16, Issue 7, July 2016, Pages 242–246

[16] Riker R, Shehabi Y, Bokesch PM et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial, *J Am Med Assoc* 2009, 30:489-99