Analgesia, Sedation and Delirium (ASD) in Critical care

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Introduction

In critical care patients receive painful interventions.[1] Their mobility is reduced, and they are connected to various monitors and machines. Patients loose time perception[2]; they are exposed to artificial lights twenty four hours of the day. Their sleep-wake cycle is completely destroyed due to intervention that happens to them and other patients around the clock.[2] Clinicians attempt to alleviate these distresses by administering analgesia and sedation. Unfortunately, these medications along with the critical care environment and factors described above make patients more disoriented. Along with the illness and added side effects of medications patients become delirious. When patients become delirious they start to disconnect various lines and tubes attached to them to keep them alive and cause harm to themselves. This delirium is poorly managed and patients receive more and more sedation. Eventually this becomes a vicious cycle and prolongs their critical care stay and increases morbidity and mortality of critical care patients.

Early days in critical care medicine patients were ventilated with basic ventilators which were unable to synchronise patients' spontaneous breaths. Hence patients have to be deeply sedated and paralysed. Current ventilators have solenoid or servo valves which are microprocessor controlled and they can synchronise very well with patients' spontaneous breaths. New medications have come into clinical practice which are more potent and shorter acting. Some short acting drugs do not even depend on patients' physiology for elimination. Hence their elimination is predictable even in organ failure. Also, awareness among critical care community on these issues has led to invent various tools and scoring systems to identify individual patient's anxiolytic and analgesic needs. Awareness about delirium is also high and various diagnostic tools are available to diagnose this early. Hence it is important to diagnose pain, deep sedation and delirium ('ICU triad' similar to triad of anaesthesia) and address them individually rather than to mask them by over managing one component to reduce the length of stay, morbidity and mortality in critical care units.[3]

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Analgesia

Pain when not treated will consume higher energy and cause immune modulation in the short term and post traumatic stress disorder in the long term.[4,5,6] Accurate assessment of pain will reduce analgesic intake.[7] Pain is actually a subjective feeling hence need to be described by the patient; in critical care it is difficult or impossible. Physiological parameters such as heart rate and blood pressures do not correlate well with actual pain perceptions. Critical care pain scales such as Behavioural Pain Scale or Critical Care Pain Observation Tool help in the assessment of pain with reasonable accuracy.[8] Therefore critical care patients could receive individualised pain management. This will potentially remove the negative impact on recovery of the critical care patients. Even when patients are deeply sedated for any other reason they should receive adequate pain relief. The challenge is when patients receive neuromuscular paralysis for the management of their condition.

Behavioural Pain scale[9]

Facial Expression	Relaxed	1
	Partially tightened (brow lowering	2
	Fully tightened (eyelid closing)	3
	Grimacing	4
Upper Limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with Ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Asynchrony with the ventilator	3
	Unable to control ventilation	4

Critical care Pain Observation Tool[10]

Indicator	Description	Score
Facial Expression	No muscular tension- Relaxed	0
	Frowning, brow lowering, orbit tightening, levator contraction- Tense	1
	All of the above facial movements plus eyelid tightly closed- Grimacing	2
Body movements	Does not move at all - Still	0
	Slow cautious movements - Protection	1
	Pulling tubes and lines, thrashing - Restlessness	2
Muscle tension on Passive flexion and extension of upper limb	No resistance – Relaxed	0
	Resistance passive movements - Rigid	1
	Strong resistance to passive movements, inability to complete them – Very tense	2
Compliance with the ventilator or Vocalisation (Extubated patients)	Easy ventilation	0
	Coughing but tolerating	1
	Ventilator asynchrony	2
	Talking normal	0
	Moaning and groaning	1
	Crying out, sobbing	2

In critical care analgesia is usually opioid based. Shorter acting opioid such as remifentanil helps in keeping patients awake and appropriate at the same time pain free. Remifentanil also has shown to reduce the duration of mechanical ventilation and helps in the weaning process.[11] Cautious management is required when using remifentanil as it has high vagotonic effect, it can cause severe bradycardia especially when co administered with propofol.[12] It can also cause opioid withdrawal symptoms if it is stopped abruptly.[13] Post operative patients may benefit from regional analgesia in critical care for a shorter period.[14] However this mode of analgesia is not useful for long term pain control in critical care.

Sedation

It is widely accepted that sedation means minimally depressed conscious level where a person is able to respond to verbal commands and physical stimulation. Various scoring systems are available to use in critical care to achieve this level of sedation for patients including ventilated patients. A small group of critical care patients need to be sedated deeply and continuously, such as patients with raised intra cranial pressure, severe respiratory failure patients requiring neuromuscular paralysis for advanced ventilator modes such as Airway Pressure Release Ventilation (APRV) and status epilepticus not responding to conventional management.

Main focus of this review is the other majority of patients who are invasively ventilated. They should be minimally sedated where they are calm and respond appropriately to verbal and physical stimuli. This is fundamental to achieve adequate analgesia as patients can indicate if they are in pain and help to achieve short term pain control and avoid long term consequences of inadequate analgesia. Communicating patients can be involved in their overall management plan as any other ward patients. However often patients in critical care are deeply sedated because their pain and anxiety are not addressed appropriately and adequately.[15] All recent evidences suggest the use of minimum possible sedation for these patients to achieve a good outcome. Patients who are sedated too deep or too long also do not do well in critical care. Their length of stay and mortality increases. In contrast to a popular belief that compared to deep sedation, lighter sedation neither causes short term adverse events nor long term psychiatric issues.[16] Deep sedation was independently associated with prolonged ventilation, hospital mortality and death within 180 days of admission.[17]

To administer sedation appropriately proper assessment of sedation is required. However, depth of sedation is observed infrequently and inappropriately in critical care units.[18] This is surprising as there are evidences to prove that monitoring sedation may improve outcomes of patients in critical care. There are several sedation scores available of which Riker sedation agitation scale and Richmond agitation scale are commonly used. For invasively ventilated patients score of either 3 or 4 on the Riker Sedation Agitation Scale or -2 to 0 on the Richmond Agitation Scale is appropriate level of sedation. Both scales are equally good.

Riker Sedation-Agitation Scale[19]

Description	Category	Score
Pulling tubes and line, thrashing side to side	Dangerous agitation	7
Biting endotracheal tube, requires physical restraint	Very agitated	6
Mild agitation, calm on verbal instruction	Agitated	5
Easily arousable and follows command	Calm & cooperative	4
Difficult to arouse awakens with verbal stimuli	Sedated	3
Arouses only to physical stimuli	Very sedated	2
No response to noxious stimuli	Unarousable	1

Richmond Agitation-Sedation Scale (RASS)[20]

Description	Category	Score
Combative, violent, danger to staff	Combative	4
Pulls or removes tubes and lines	Very agitated	3
Frequent non purposeful movement, ventilator asynchrony	Agitated	2
Anxious but movements are not aggressive	Restless	1
Alert and calm		0
Not fully alert, eye contact to voice ≥ 10 seconds	Drowsy	-1
Briefly awakens to voice eye contact ≤ 10 seconds	Light sedation	-2
Movement or eye opening to voice, no eye contact	Moderate sedation	-3
No response to voice but eye opening to physical stimuli	Deep sedation	-4
No response to physical stimuli	Unarousable	-5

Sleep is affected in critical care patients. Lack of proper sleep and other factors cause disorientation in patients. Whether sleep disturbances affect outcome of patients in critical care has to be confirmed. There are tools available to measure the quality of sleep. However they are not validated in critically ill patients. Anxiety can be a factor in affecting patients' sleep.[21] Similar to sedation score patient anxiety is not properly estimated and treated in critical care. Short versions of standard psychological measurement instruments (State – Trait Anxiety Inventory- state subscale[STAI-s], Brief symptom inventory Anxiety- subscale [BSI-A]) are available to reliably assess anxiety.[22]

Non-pharmacological techniques to improve the quality of sleep are preferable to pharmacologically induced sleep.[23] However this is not always possible in critical care. Melatonin has shown some evidence in reducing the day time sleep and promoting the night time sleep. Also it has shown to reduce the need for extra sedation and the need for restraints in critical care. However, it has not shown to reduce hospital mortality or post traumatic stress disorder.[24] Some benzodiazepines are also recommended for sleep with variable evidence. Using benzodiazepines will reduce the anxiety in critically ill patients. However whether anxiolytic response can be monitored by the anxiety assessment scales are yet to be known.

Adequately and appropriately sedated patients' length of stay and mortality is reduced in critical care. There are several sedatives available for the use in critical care however no one agent is clearly superior to the other. The difference in preference of sedatives is largely due to the culture of the critical care unit.[3] Common sedatives such as benzodiazepines and propofol act on Gama Amino Butyric Acid type A ($GABA_A$) receptors. A metanalysis has shown that sedating with propofol may decrease the critical care length of stay when compared with other sedatives but not with midazolam, also it does not reduce critical care mortality.[25] Dexmedetomidine and clonidine act on Alpha 2 receptors. This provides an additional advantage over other sedatives as they can provide some analgesic effects too. Since minimising depth and duration of sedation is in favour of good patient outcome, it is reasonable to use shorter acting agents which can be rapidly adjusted for the need. Agents which haven't got active metabolites or do not depend on hepatic or renal metabolism might offer advantages over the agents which have active metabolites. In addition to provide better outcome to critical care patients Dexmedetomidine will reduce the cost of sedation for the duration of critical care stay compared to other sedatives.[26]

Delirium

Delirium is defined as sudden severe confusion and rapid changes in the mental function that occur due to mental or physical illness. There are four components in delirium: disturbance in attention (reduced ability to direct, focus, sustain, and shift attention) and awareness; change in cognition (memory deficit, disorientation, language disturbance, perceptual disturbance) that is not better accounted for by a pre-existing, established, or evolving dementia; disturbance that develops over a short period (usually hours to days) and tends to fluctuate during the course of the day; and there is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by a direct physiologic consequence of a general medical condition, an intoxicating substance, medication use, or more than one cause. [27] Delirium is unpredictable but usually reversible. Some subgroups are more at risk than the other. Pathophysiology of delirium is still not fully understood. There are suggestion that GABAergic and cholinergic system play a role, but there are also hypotheses suggestive of excess doperminergic activity and neurotoxic effect from inflammatory cytokines.[3] Hence largely pharmacological management of delirium is empirical. A metanalysis on magnetic resonance imaging in delirium has shown that neurovascular changes are associated with the occurrence of delirium in the post operative

patients and may identify patients at increased risk of these conditions. However whether this was a cause or effect is not well established.[28] Delirium can lead to accidental removal of lines and tubes connected to patients. It is a serious and a frequent problem in critical care. Despite this diagnosis of delirium is still a clinical diagnosis in critical care. Hence the incidence can go up to 80% of which 72% goes undetected when there isn't a routine monitoring system.[29] The risk factors for delirium are advanced age, history of substance misuse, coma, sedatives medication, neurological illness and increased severity of critical illness. Delirium increases the morbidity and mortality in critical care. Delirium has two forms hypoactive and hyperactive. In hypoactive delirium patients are inattentive with disordered thinking and may well have reduced level of consciousness. Hyperactive agitated delirium incidence is much lower than the hypoactive delirium. In mixed delirium patients have both features. Although mortality is higher in hypoactive delirium compared to hyperactive delirium, patients who survive hypoactive delirium have a better long term function.

Regular assessment of delirium is important to recognise delirium as delirium is under detected and poorly managed in critical care. Delirium assessment in critical care can be difficult because of the severity of illness and the use of multiple sedatives or analgesics. There are various tools available to diagnose delirium among them some are better than the others. They all have various specificities and sensitivities. Confusion Assessment Method for ICU (CAM-ICU) and Intensive Care Delirium Screening Check (ICDSC) are the common and accepted screening tools available to use in critical care for delirium assessment. At any point of time CAM-ICU can determine whether a patient has delirium. Patients need to be observed over a period of time for ICDSC tool. However neither of these tools differentiates hyperactive from hypoactive delirium. Sometimes unstructured assessment of a bed side nurse who actively detect delirium is sensitive than above tools, but it is not well proven by studies.

Confusion Assessment Method for the ICU (CAM-ICU)[30]

Altered Mental Status or fluctuating course	No	Delirium negative
Yes		
Inattention (10 point test to either letters or pictures) Squeeze my hand for letter 'A' 'SAVEHAART'	0-2 errors	Delirium positive
>2 errors		
Altered level of consciousness	Yes	Delirium positive
No		
Disorganised thinking (4 yes or no questions and a 2 step command) Will stone float on water Are there fish in the sea Does one pound weigh more than two pound Can you use a hammer to pound a nail Command: "Hold up this many fingers" (hold up the fingers). "Now do the same with the other hand (do not demonstrate)	>1 error < 1 error	Delirium positive Delirium negative

Intensive Care Delirium Screening Check[31]

Description	Score
Anything other than normal wakefulness	1
Inattention	1
Disorientation	1
Hallucination or delusions	1
Psychomotor agitation or retardation	1
Inappropriate speech or mood	1
Sleep/wake cycle disturbance	1
Symptom fluctuation	1
Total score ≥ 4 is Delirium positive; 1-3 Subsyndromal delirium	

Treating delirium is difficult however there is some evidence that delirium can be prevented. Studies have shown that elderly patients in the hospital, who are repeatedly oriented, cognitively stimulated and mobilized early have less delirium.[32] Expectation is to mobilise early to reduce the duration of delirium in critical care too. Also maintaining the sleep wake cycle has shown to prevent delirium.[33] Managing delirium can be challenging as none of the tools detect the varying degrees of delirium therefore cannot be used to detect the efficacy or the effect of specific treatment. Quetiapine along with haloperidol has shown to be effective in treating delirium in critical care patients in very small study.[34] Low dose haloperidol and low dose risperidone has shown to reduce the incidence or duration of delirium in the elective post operative patients. In some studies, dexmedetomidine compared to other standard therapies has been beneficial in critical care delirium. However, in some studies

the incidence of delirium was no different in patients who received dexemedetomidine.

Practical approach

As mentioned above lack of clear evidence for the management of critical care patients in analgesia, sedation and delirium has been detrimental to critical care patient outcome. To limit this guidelines and care bundles have been published such as "pain, agitation and delirium guidelines" and "spontaneous awakening and breathing coordination, attention to the choice of sedation, delirium monitoring and early mobility and exercise" (ABCDE) bundle with the aim of improving outcome in critical care. Of this kind the latest concept is eCASH concept. Early Comfort using Analgesia, minimal Sedatives and maximal Humane care. Aim is to create optimal patient comfort with minimal sedation as a norm for critical care except in certain clinical condition.[35]

Conclusion

Sedation and analgesia in critical care has changed a lot over the years. Completely sedated and paralysed patients are very few in critical care now. Delirium is a complication in critical care patients and was under recognised and poorly managed. Even shorter duration of deep sedation in critical care has detrimental effects on the length of stay and the outcome of patients, while affects the post intensive care syndrome (PICS). Critical care patients are also constantly exposed to pain and distress. Pain is the most common symptom patients recollect of their critical care stay. On the other hand delirium causes accidental removal of tubes and lines required to keep patients alive in critical care.

Traditional practice of deep sedation and paralysis for invasive ventilation currently does not exist in most cases except for few indications. New generations of ventilators with microprocessor controlled valve synchronise patients own breath well without the need for deep sedation or paralysis. Newly available drugs with lower context sensitive half life and higher potency have changed the analgesia and sedation practices in critical care completely. Awareness of delirium is high in the critical care community now. Delirium diagnostic tools with preventive measures are widely being used. Current focus in critical care is to individually address pain, delirium and sedation with specific management modalities or use guidelines or care bundles and use lower doses of all classes of drugs to improve the long term outcome of critical care patients.

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