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SPECIAL K (ETAMINE): OLD DOGMAS AND NEW TRICKS

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INTRODUCTION

The use of ketamine in the neurosurgical patient has been a source of great debate and concern since the 1970s. Owing to its reported role in increasing cerebral blood flow (CBF), intracranial pressure (ICP) and cerebral metabolic oxygen consumption (CMRO2), it has been considered contraindicated in the setting of raised ICP. This premise has been based on flawed evidence from over 40years ago, as will be discussed further.

However, its rapid onset of action and unique cardiovascular stimulating effects makes it an attractive drug to use, especially in the often haemodynamically unstable patient with traumatic brain injury (TBI).

Management of the TBI patient is complex and involves balancing several variables (ICP, CBF, CPP, and CMRO2) on a background of a heterogeneously impaired autoregulation.

The evidence supporting the use of ketamine in TBI, challenging the old dogmas regarding this drug AND highlighting the need for more research, has increased in recent years.

Furthermore, the possible neuroprotective properties of ketamine warrant a reevaluation of this drug and its use in the anaesthetic and intensive care management of TBI.

PHARMACOLOGY OF KETAMINE (1) (2)

Ketamine is a structural analog of phencyclidine. Commercial ketamine is a racemic mixture of the S (+) and R (-) stereoisomers (the S (+) isomer having increased anaesthetic potency and decreased psychotomimetic side effects. It was synthesised in 1962 and first used in humans in 1965.

Mechanism of Action

Despite the fact that ketamine has been used for the past 51 years, its precise mechanisms of action are not clearly understood and there is still a lot to be learnt. The mechanism of action of ketamine is said to be complex as it interacts with multiple binding sites throughout the central nervous system (CNS). These include: N-methyl-D-aspartate (NMDA) and non-NMDA glutamate receptors, nicotinic and muscarinic cholinergic receptors, opioid, monoaminergic and opioid receptors. Interactions with voltage-gated ion sodium and L-type calcium channels have been described. All of these interactions play a role in ketamine's pharmacological and clinical effects, however, NMDA receptor antagonism accounts for most of its analgesic, amnestic, psychotomimetic and neuroprotective effects[3][4].

The NMDA receptor is a ligand gated receptor that is activated by the excitatory neurotransmitter, glutamate. Ketamine binds to and inhibits glutamate activation of the

Action site	Mechanism	Clinical effect
NMDA receptors	Antagonist	General anesthesia
Muscarinic receptors	Antagonist	Bronchodilation and sympathomimetic
μ Opioid receptors	Agonist	Analgesia
Monoaminergic	Inhibitor	Antinociception
Voltage-gated Na^+ channels	Inhibitor	Local anesthesia
L-type Ca^{2+} channels	Inhibitor	Inconclusive
Catecholamine uptake	Inhibitor	Bronchodilation and sympathomimetic
IL-6 and O_2^-	Inhibitor	Anti-inflammatory

NMDA receptor in a time-, concentration- and stimulation frequency-dependent manner.

Table 1. Mechanism of Action of Ketamine[5]

The effects of ketamine (such as in chronic pain), far outlast the actual serum drug levels which indicates that the drug binding to receptors and its resultant clinical effects, is much more complex than previously thought and likely due to a wider range of molecular effects. The immediate binding effects of ketamine disrupts a number of downstream and more longer lasting cellular processes (i.e. gene expression and protein regulation).

Among these long-lasting effects are[6]:

- Suppression of NMDA gene expression at the site of mechanical injury (zif/268, c-fos, junB, fosB, c-jun, junD).
- Altered regulation of NMDA receptor phosphorylation and mRNA expression (shown in rat and mouse models)
- Limitation of astrocytic and microglial activation.
- Enhanced brain-derived neurotrophic factor in animal models resulting in modification in the number and function of synaptic connections.

Although these effects have been linked to ketamine's role in reduction of neuropathic pain and its antidepressant effects, it highlights the fact that ketamine and its effect on the central nervous system is complex.

Pharmacokinetics

Ketamine may be administered orally, intranasally, intravenously or intramuscularly. It has a large volume of distribution (3L/kg) owing to its high lipid solubility and low protein binding. These characteristics lead to its rapid brain uptake and redistribution (redistribution half-life: 10-15minutes). Ketamine undergoes biotransformation in the liver and the end products of this biotransformation are excreted renally.

Pharmacodynamics
Cardiovascular Effects

Ketamine has direct myocardial depressant effects (demonstrated in animal models). Centrally mediated, indirect sympathetic stimulation usually override its depressant effects. The result is cardiovascular stimulation which is associated with increases in blood pressure, heart rate and cardiac output. These haemodynamic changes (which are not related to dose of ketamine administered) are accompanied by an increase in myocardial oxygen consumption.

Respiratory Effects

Ventilatory drive is minimally effected and upper airway reflexes remain intact.
Ketamine is a potent bronchodilator but its use does result in sialorrhea

Central Nervous System

Ketamine produces a "dissociative-state" which is said to result from electrophysiologic inhibition of thalamocortical pathways (involved in relaying sensory input from the reticular activating system to the cerebral cortex) to the limbic system (which is involved in awareness of sensation). This is evidenced clinically, by profound analgesia (or anti-nociception) and amnesia and a patient that appears conscious (eye opening, swallowing, etc.) but is unable to process or respond to sensory stimuli.

Ketamine also produces undesirable psychological reactions which occur during awakening and are termed "emergence phenomena". These include: vivid dreams, extracorporeal experiences and illusions. They usually occur within the first hour and with varying severity. The incidence of emergence phenomena ranges from 10-30% of adults who receive ketamine as a sole anesthetic agent. Benzodiazepines have been shown to be effective in attenuating these psychomimetic affects.

The cerebrovascular effects of Ketamine remain controversial and are dependent on the presence or absence of intact autoregulation and the variables that affect auto regulation (e.g.PaCO2) as well the presence of other anaesthetic agents. Emerging evidence has highlighted the fact that ketamine's effect on the neurological system is not as simple as what was once thought. While ketamine was previously vehemently avoided in all neurosurgery, it is now being looked at in a different light. Even after half a century of ketamine use and research, we are still left with many questions regarding its use in neurosurgery.

These are the questions we will try to address in this presentation:
What is the effect of ketamine on Cerebral Autoregulation, ICP, CBF and CMRO2?
Does it provide neuroprotection and how?

PHYSIOLOGY OF CEREBRAL AUTOREGULATION

Cerebral pressure autoregulation is the intrinsic ability of the brain to maintain constant cerebral blood flow (CBF) over a range of blood pressures. Normal CBF varies according to tissue metabolic demands. Flow in the grey matter is approximately 80ml/100g/min and 20ml/100g/min in the white matter, therefore CBF averages 50ml/100g/min. Irreversible neuronal damage occurs at CBF below 10-15ml/100g/min and reversible blood flow is noted at CBF between 15-25/100g/min[7][8].

L. Rangel-Castilla et al.

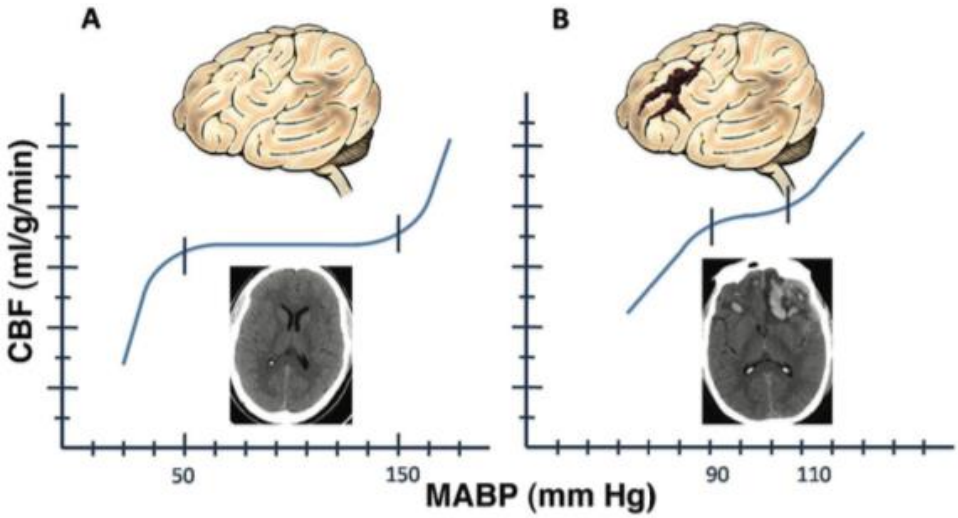

FIG. 1. Graphs showing cerebral pressure autoregulation curves in normal (A) and traumatically injured (B) brain.

Cerebral pressure autoregulation mechanisms protect against cerebral ischaemia during periods of hypotension and excessive flow during hypertension. It is a complex process that involves myogenic, metabolic and neurogenic mechanisms that act together.

- Myogenic mechanisms: intrinsic ability of the vascular smooth muscle to change its diameter by contracting or relaxing in response to transmural pressure changes.
- Metabolic mechanisms: likely occurs in smaller vessels that are exposed to changes in the local microenvironment. When tissue demands exceed blood flow, the release of tissue metabolites (CO2, hydrogen ions, nitric oxide, adenosine, etc) causes vasodilatation and increases flow. Auto-regulatory vasoconstriction occurs to a much smaller extent compared to vasodilatation and predominantly occurs in the larger arterioles.
- Neurogenic mechanisms: mid-sized intracranial vessels are innervated by sympathetic, parasympathetic and nonadrenergic noncholinergic fibres. The normal physiological function of this innervation is uncertain but it may play a role in pathological states. The activation of alpha-adrenergic sympathetic nerves shifts the limits of auto regulation toward higher pressures and induces vasoconstriction in these vessels.

Cerebral Blood Flow and Cerebral Perfusion Pressure (1) (2)

Cerebral Blood Flow (CBF) = Cerebral Perfusion Pressure (CPP) / Cerebral Vascular Resistance (CVR)
CVR is determined by cerebral autoregulation (as discussed before).

CPP is the difference between mean arterial pressure and intracranial pressure:

CPP = MAP - ICP (n = 80-100mmHg)

Moderate to severe increases in ICP can greatly compromise CPP, even in the presence of a normal MAP. Slowing of the EEG occurs at CPP below 50mmHg while sustained CPP below 25mmHg results in irreversible brain damage.

Raised ICP and decreased CPP has been consistently associated with poor neurological outcomes[(9)].

Cerebral Autoregulation in Traumatic Brain Injury (TBI)

TBI is one of the leading causes of death and disability worldwide, with the burden of disease being greatest in lower- and middle-income countries. One-third of patients experience moderate or severe disability with one-quarter dying within 6 months of their injury[(10)].

Impaired cerebral autoregulation has been demonstrated in multiple studies involving patients with TBI, including those with mild TBI and normal ICP and MABP. This places patients at significant risk for secondary brain injury in the first few hours after TBI when CBF is markedly reduced and patients may be haemodynamically unstable. In addition to this, impaired cerebral autoregulation may affect the response to drug treatments administered to patients with severe TBI (e.g, Mannitol, and vasopressors).

Cerebral autoregulation is not uniformly impaired throughout the brain but exists in varying degrees and irregular distribution throughout the injured brain. In areas where autoregulation is intact, a decrease in CPP will result in vasodilatation and an increase in blood volume which will raise ICP (due to decreased compliance of the cranial vault). Where autoregulation is impaired, a decrease in CPP will be paralleled by a decrease in cerebral blood flow as there will be no vasodilatory compensation, thus resulting in ischaemia.

It is well known that all the neurological injury that occurs with TBI does not occur at the time of injury but evolves over hours and days (secondary brain injury). This secondary brain injury can be prevented and with the appropriate treatment, improved outcomes are possible![11][12][13]

The ideal anaesthetic agent for use in TBI should have the following characteristics[5]:

1. Neuroprotective properties and reduction of the processes that cause neuronal cell death and secondary brain injury
2. Maintain cerebral autoregulation
3. Reduce cerebral metabolic rate
4. Reduce cerebral blood volume and ICP
5. Prevent seizure activity

Currently no ideal anaesthetic agent exists.

KETAMINE'S EFFECT ON CEREBRAL AUTOREGULATION

There is paucity of evidence regarding the effects ketamine on the cerebrovascular autoregulation.

However, one study by Engelhard K. et al, consisting of 24 ASA I-II patients without any neurological injury, demonstrated that dynamic cerebrovascular autoregulation remained intact in patients receiving S(+)ketamine/propofol based total intravenous anaesthesia compared to patients undergoing anaesthesia with sevoflurane.[14] In this study, a sudden drop in MAP was induced in order to activate auto-regulatory vasodilatation in both groups of patients (one receiving propofol TCI and a stat dose of ketamine and the other receiving a remifentanil bolus, initial plasma-targeted propofol infusion for induction followed by sevoflurane maintenance). Transcranial doppler of middle cerebral artery velocity was used to determine dynamic cerebral autoregulation. Based on the findings of this small study, the authors concluded that S (+) ketamine in conjunction with low doses of propofol did not affect cerebral dynamic autoregulation.

Using transcranial doppler measurement of middle cerebral artery flow velocity (Vmca) and pulsatile index (which was used as an index of CVR) in elective surgical, ASA I-II patients receiving Isoflurane anaesthesia, Nagase et al[15]. Were able to demonstrate an attenuation of the cerebrovascular response to hypercapnia while maintaining cerebral blood flow, with ketamine, in contrast to propofol which decreased CBF and did not alter the cerebrovascular response to hypercapnia. The control group underwent induction with fentanyl, thiopentone and vecuronium and anaesthesia was thereafter maintained with oxygen/isoflurane/air. MAP was maintained within 20% of baseline and isoflurane concentration remained constant. Vmca and PI was then measured under conditions of normocapnia, hypocapnia and hypercapnia, by supplementing CO2 into inspired gas. Patients were then given either ketamine or propofol and measurements were repeated.

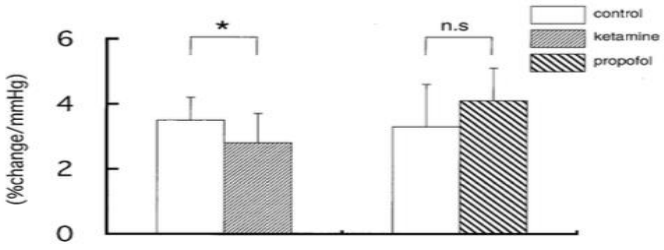

Figure 2. Relative carbon dioxide (CO_2) reactivity of ketamine and propofol. Ketamine, unlike propofol, significantly reduced relative cerebral CO_2 reactivity ($p < 0.05$). Values are means ± SD. *$p < 0.05$, control *vs.* ketamine.

Figure 2 illustrates that compared to propofol, Ketamine decreased cerebral CO_2 reactivity

However, the limitations of this study included:

- The small size of the study (30 patients)
- All patients were ASA I-II with no TBI. We cannot infer that the same results would be achieved in TBI patients.
- Patients in the propofol group received an initial bolus, followed by an infusion of propofol, whereas those in the ketamine group only received a bolus dose of ketamine.

KETAMINE'S EFFECT ON INTRACRANIAL PRESSURE, CEREBRAL PERFUSION PRESSURE AND MEAN ARTERIAL BLOOD PRESSURE (MABP)

Due to concerns of it causing uncontrollable raised ICP, Ketamine has long been avoided in the neurosurgical patient and especially in TBI patients suspected of having raised ICP.

The majority of studies implicating ketamine as being deleterious in neurosurgery, quote 4 studies done in the 1970s. All of these studies included a very small number of patients (2-11 patients). 3 out of the 4 studies involved patients with obstructed CSF flow (some with clinically apparent raised ICP as a baseline) and all patients were spontaneously breathing. Ketamine was administered and ICP was measured via a ventricular or lumbar catheter.[16][17][18][19]

Elevated $PaCO_2$ in the spontaneously breathing patient resulting in large vessel vasodilatation and small vessel vasoconstriction (secondary to Nitric oxide synthase inhibition) leading to increased cerebral oxygen extraction, have been the mechanisms proposed. Our current practice of avoiding ketamine in TBI patients is largely based on these studies and cannot therefore be completely justified

Ketamine has not been proven to cause clinically significant elevations in ICP, in recent literature. Studies have compared its use as continuous infusion and as intermittent boluses in patients with severe TBI already receiving sedation with either a benzodiazepine, opioid or propofol and have NOT found that its use was associated with any elevations or fluctuations in ICP[20][21]. In fact, when given as boluses, ketamine was shown to decrease ICP even in studies conducted on paediatric patients[22][23][24].

In a study by Kolenda et al.[25] which included 24 patients with moderate to severe head injury receiving either sedation with midazolam/fentanyl or midazolam/ketamine, MABP and CPP were higher in the ketamine group and patients in this group showed greater haemodynamic stability as well as a lesser requirement for vasopressors. Sedation was comparable between the 2 groups.

The sympathetic stimulation produced by ketamine and resultant increase in cardiac output, MAP and heart rate makes ketamine an ideal drug in the setting of polytrauma patients who are often haemodynamically unstable.

A small comparative cohort study of major trauma patients undergoing prehospital-RSI compared a group of patients receiving fentanyl, ketamine and rocuronium to a second group receiving etomidate and suxamethonium. Hypotension was uncommon in both groups and although an admittedly small sample size, ketamine did not appear to have any adverse outcomes on these patients with TBI[26]

Importantly, these effects were noted in carbon-dioxide controlled-mechanically ventilated patients. The effectiveness of ketamine in reducing ICP when used in isolation is uncertain as all studies utilised low-dose infusions or bolus doses of other anaesthetic agents as mentioned before. When ketamine is used as an adjunctive anaesthetic agent along with mechanical ventilation to maintain normocapnia, it has not been shown to have adverse cerebral haemodynamic effects.

THE DIRECT ROLE OF KETAMINE IN NEUROPROTECTION

Interest in ketamine as a neuroprotective anaesthetic agent has been promoted by a shift in thinking about neuroprotection in anaesthetics: focus from suppression of brain metabolism to inhibition of excitotoxicity.

NMDA Receptors (NMDAR)[3]

The activation of extrasynaptic-NMDA and non-NMDA receptors caused by cerebral hypoxia and ischaemia initiates a pathophysiological cascade that leads to cell membrane destruction and neuronal death.

This occurs as a result of cellular influx of calcium which:

1. Induces extracellular release of glutamate which further activates NMDA receptors
2. Activates phospholipase which convert membrane lipids to free fatty acids which are converted to arachidonic acid and prostaglandin derivatives which damage cell membranes
3. Activates proteases which results in generation of free radicals
4. Inhibits the functioning of mitochondria and prevents energy production

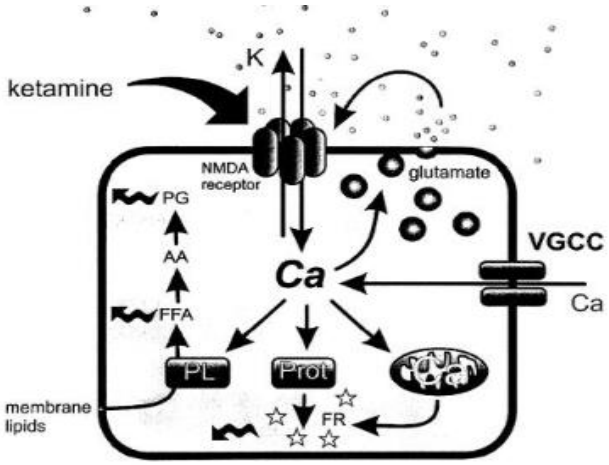

Figure 3. Schematic diagram depicting the neurodestructive cascade[3]

The pharmacological antagonism of extrasynaptic-NMDA receptors during ischaemia and inhibition of the neurodestructive cascade and glutamate excitotoxicity by ketamine provides neuroprotection and prevention of neuronal cell death.

However, the paradox lies in the fact that physiologic levels of *synaptic* NMDA receptor activity is in fact, neuroprotective. It is thus, the location of the NMDA receptor that determines whether it is neuroprotective or neurodestructive and disruptions in the balance between synaptic and extra-synaptic activity contributes to neuronal injury in ischaemia. Synaptic NMDA receptor activity promotes neuroprotection that lasts beyond the duration of the stimulation and after most signalling pathways are no longer active.

This results from changes in gene expression that have effects at multiples levels in the cell such as[4][5]:

- enhancement of mitochondrial health
- boosting antioxidant defences
- suppression of caspase activity

All of the above preserve neuronal function. Activation of synaptic NMDAR results in influx of calcium which enters the cell nucleus and activates neuronal gene expression. Several genes have been identified, the transcription of which have been shown to provide neuroprotection. Synaptic NMDAR activity is also involved in the suppression of transcription of components of the intrinsic apoptosis cascade and enhances oxidative defences.

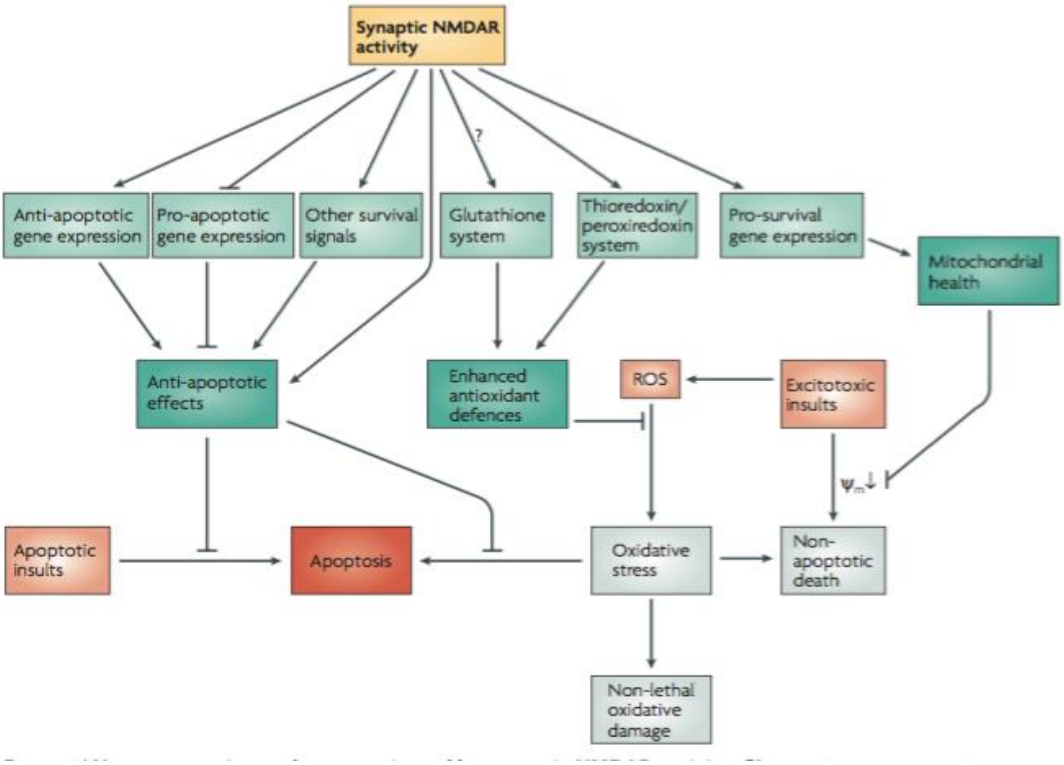

Figure 4.Neuroprotective pathways activated by synaptic NMDAR activity[4]

These 2 different physiologic processes highlights the difficulties faced in determining correct timing of ketamine administration, the appropriate dose and duration therapy required to maintain the balance between the neuroprotective and neurodegenerative properties of NMDA receptors

Inflammation

The neuroprotective properties of ketamine have been tested in patients undergoing cardiopulmonary bypass (CPB). Patients undergoing CPB are also at risk for neuronal injury related to the neuronal ischaemia and cellular inflammation associated with surgical trauma, extracorporeal circuit apparatus and reperfusion injury. The inflammation activated by CPB results in increased activated neutrophils (brought about by activation of IL-6 cascade) and a resultant increase in superoxide anions. Three studies were able to demonstrate reductions the pro-inflammatory pathways when ketamine was used in patients on CPB and although this did not bring about any improvement in cognitive outcomes (as patients demonstrated equivalent neurologic morbidity), it does highlight the fact that ketamine plays a role in decreasing inflammatory markers which may be an area for further investigation in future studies.[27][28][29]

Spreading Depolarisation

Spreading depolarisation is a wave of electrophysiological hyperactivity followed by a wave of inhibition, it describes a phenomenon characterised by the appearance of depolarisation waves of the neurons that propagates across the grey matter at a velocity of 2-5mm/min. It is induced by hypoxic conditions and facilitates neuronal death in energy-compromised tissue. Blockage of spreading depolarisation by ketamine antagonism of NMDA receptors has recently been shown in case reports of patients with traumatic and spontaneous intracerebral haemorrhage.[30]

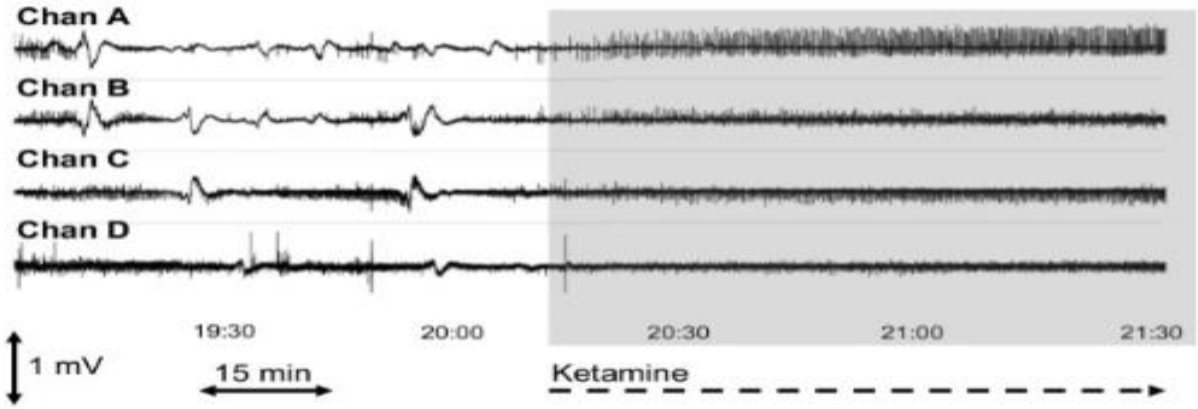

Figure 2. Electrocorticography readings before and after ketamine infusion was commenced

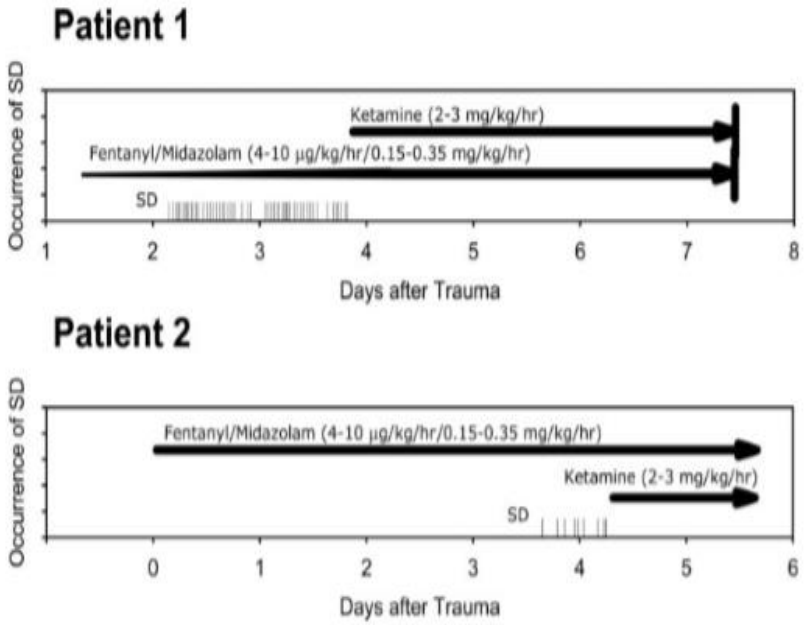

Figure 5. Overview of analgosedation, time course of SDs (hairline markers), onset of ketamine infusion and SD abortion. Patients 1 and 2 respectively

Return of electrocorticography to regular burst suppression pattern and cessation of spontaneous depolarisations following ketamine administration possibly indicates a metabolic improvement in areas of ischaemia. Further studies are required to elucidate whether this conveys neuroprotection to patients with acute neuronal injury in whom spontaneous depolarisations are detected.

KETAMINE AND ELECTROCONVULSIVE THERAPY (ECT)

ECT is a procedure done under general anaesthesia in which small electric currents are passed through the brain. A brief seizure is triggered which causes changes in brain chemistry that can reverse symptoms of treatment-resistant depression.

Recently, ketamine has been highlighted in psychiatry for its rapid and effective treatment of depression. It has long been used in ECT and is thought to act synergistically to successfully treat treatment-resistant depression. A concern with ECT, is the cognitive deficits associated with its use. These deficits are usually temporary and reversible. The type of anaesthetic agent used in ECT may have an impact on the degree of cognitive impairment and so, different agents have been compared.

Etomidate, thiopentone and propofol are considered safe to be used in ECT but they are all potent anticonvulsants and may influence the quality of the seizure that is induced in ECT. When compared to propofol, patients receiving ketamine anaesthesia were shown to have earlier improvement, however their response did not differ at the end of 4 weeks (8 ECT sessions)[31]. Ketamine anaesthesia was shown to have a more favourable influence on short-term memory when compared to etomidate and fewer ECT sessions as well as shorter post-seizure reorientation time were noted for patients receiving ketamine compared to those receiving thiopentone[32].

Several possible mechanisms have been proposed for the observed effects of ketamine anaesthesia in ECT:

- Increased activity in the anterior cingulatecortex, AMPA and sigma receptors and neurotrophic substances (vascular endothelial growth factor and brain-derived neurotrophic factor)
- Inhibition of excitotoxic glutamate activation of NMDA receptors that occurs due to seizure activity elicited during ECT.
- Blocking long-term potentiation induction during ECT facilitates better memory outcomes.

Although more research is required, ketamine appears to be a favourable drug in the anaesthetic management of treatment-resistant major depressive disorder.

USE OF KETAMINE IN REFRACTORY STATUS EPILEPTICUS (RSE)

When status epilepticus (protracted continuous or intermittent seizure activity without full recovery of consciousness between seizures, lasting atleast 30minutes) does not respond to typical anti-epileptic drugs, it is termed refractory status epilepticus. It occurs in 10-40% of patients and is associated with prolonged hospitalisations and functional disabilities. Intravenous anaesthetics (propofol, barbiturates, and benzodiazepines) are used in the

treatment of status epilepticus (SE) and their anti-epileptic effects relies on the inhibition of seizure activity via GABA receptors. After prolonged seizure activity, the concentration of these receptors decrease as they are internalised into the cell and their inhibitory activity is lost. Once this occurs, there is an increase in excitatory glutamate receptors which are mobilised to the cell surface. This finding has been demonstrated in animal models.

Inhibition of glutamate binding to NMDA receptors by ketamine has shown promise in the treatment of RSE. There are only a few case reports but they all point toward the efficacy of ketamine in treating RSE. Ketamine was given in addition to other standard anti-epileptic drugs and the time to cessation of seizures varied between patients.[33][34] Hypotension is commonly seen in patients receiving infusions of propofol and barbiturates and patients often require vasopressors. With ketamine, there was an added advantage of haemodynamic stability and decreased need for vasopressors. In some cases, ketamine allowed for patients already on vasopressors, to be weaned off.

This is a new and promising use for ketamine and further studies are required to determine adequate dosing regimens, appropriate duration and timing of treatment as well as determining whether ketamine may be effective when used on its own, without the use of other anti-epileptic drugs.

CONCLUSION

Traumatic Brain Injury is a leading cause of death and disability worldwide and specifically in lower and middle income countries where it has been shown that patients are most likely to die (in comparison to patients in higher income countries).

The pathophysiological changes seen in TBI is known to evolve over hours and days: the initial (primary) injury occurring at the time of impact and the secondary injury occurring as a result of inflammatory processes, oedema, raised ICP and reduced CPP. The preoperative period is of particular importance in the course of TBI management and specifically, prevention of secondary brain injury. It is an opportunity to initiate interventions that may improve outcomes.

Recent literature has challenged the idea that ketamine has no role in neuroanaesthesia because of its “undesirable haemodynamic effects”. There is increasing evidence that there is a place for the use of ketamine, in conjunction with other anaesthetic agents and in mechanically ventilated patients.

However further studies are required to elucidate its role as a neuroprotective agent and to delineate the appropriate timing, dosage and duration of administration that best balances the neuroprotective effects of synaptic NMDA activity and the prevention of neurotoxicity from extra synaptic NMDA antagonism.

Ketamine with its beneficial cardiovascular effects, has shown promise in studies as an induction agent for RSI, as a sedative for TBI patients in the ICU setting and as an agent to prevent ICP spikes when given as boluses in sedated and ventilated patients.

As yet, ketamine cannot be completely removed from the neurosurgical anaesthetic armamentarium and it appears that we are bound to see its usefulness in many other areas of neurosurgery and neurological disorders.

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