ANTEROGRADE AMNESIA FOLLOWING MIDAZOLAM CONSCIOUS SEDATION: AN UPDATE.

INTRODUCTION:

The prevalence of the dental anxiety is said to vary from 2.5% to 20%\textsuperscript{1} and thus is the major cause for avoidance of dental treatment.\textsuperscript{2} The dentally anxious individuals often describes their dental experiences as ‘terrifying’ and/or ‘painful’ and thus we get to hear almost every other patient admitting to ‘hating dentists’ instead of dental treatment. Over past several decades dental professionals are trying to come up with ways to manage patient’s anxiety and fear and convert these patients into dentally friendly.

Among several strategies to manage anxiety in the dental office,\textsuperscript{3} conscious sedation has gained popularity in the last 3 decades almost replacing the role of general anaesthesia in dental treatment.

There are several types of conscious sedation oral, inhalational, intranasal, buccal, rectal (not in practice in the UK) and intravenous.\textsuperscript{4} Based on the individual’s state of anxiety the type of sedation is chosen and the assessment of anxiety is carried out during the assessment visit.
The evaluation of the anxiety trait can be carried out with the help of anxiety scales such as modified Dental anxiety scale and the need of sedation can also be assessed using certain indices such as the index of sedation need [IOSN].

Conscious sedation: Conscious sedation has been defined as: ‘A technique in which the use of a drug or drugs produces a state of depression of the central nervous system enabling treatment to be carried out, but during which verbal contact with the patient is maintained throughout the period of sedation and protective reflexes are intact’. Midazolam, belonging to the benzodiazepine group has established itself as a safe drug and has become favourite of many sedationists owing to many desirable characteristics. This drug has rapid onset of action, short acting, rapid recovery and limited side effects. Besides the action of the drug can be quickly reversed by Flumazenil is an imidazobenzodiazepine which is competitive antagonist at the benzodiazepine binding site. Thus if necessary the actions of the midazolam can be reversed.

**Physiological anatomy of the brain:**

CNS is functionally and anatomically quite complex than any other systems in the body. The higher centres of the brain are involved in motor and sensory system co-ordination. The brain stem houses pons, medulla and midbrain. Cerebrum is the top portion of the brain and is divided in to right and left by deep crevice, the longitudinal sulcus. In each hemisphere cerebral cortex, basal ganglia and limbic system are housed. The right and left hemispheres are connected by a structure called as Corpus callosum, which is nothing but a massive bundle of nerve fibres. The significant structure, hippocampus related to memory is in the limbic system.
Holistic theory of thoughts.

Thought is a resultant of stimulation of different parts of the brain at the same time, primarily involving cerebral cortex, thalamus, limbic system and upper reticular formation of the brain stem. However specific stimulated parts of the cerebral cortex can determine the distinct characteristics of the thoughts, such as localising sensations, feeling texture of silk, recognition of a geometric pattern and overall awareness of a particular instant. Consciousness is suggested to be continuing outflux of awareness of either our surrounding or our sequential thoughts.\(^8\)
Classification of memories:

A simple classification based on the duration of the retained thoughts over a period of time.

1. Short term memory
2. Intermediate long term memory and
3. Long term memory
   a. Episodic memory stored in a serial manner, which can be reconstructed.
   b. Semantic memory, is factual memory where new facts can be learnt through experiences.

Short term memory lasts only for few seconds to minutes, Intermediate lasts for few days to weeks and then fades away and long term memory stay and stored for the longest period like years together or lasts for life time.

Based on the type of information stored:

- Declarative memory – is a memory of diverse details of an amalgamated thought. Examples include memory of surroundings and memory of experiences.
- Skill memory – Related to motor activities of the individuals body.

Positive and negative memory: these memories are resultant of facilitation and inhibition of synaptic transmission.

Working memory is another type which can be described as many bits of information stored in the prefrontal area of the brain during a task and it can be categorized under short memory and this is concluded once the task is completed. This is usually applied during problem solving and cognitive skills.
Memory traces: memories essentially are stored in the brain by altering the fundamental/basic sensitivity of synaptic transmission between neurons as a consequence of previous neural activity. Biochemically, memories are stored in the brain by structural alteration of synaptic transmission between neurons as a result of prior neural activity. These new or facilitated pathways are termed as memory traces. The significance is the thinking mind can reconstruct the past memories by triggering these traces.

**Memory consolidation:**

The process of conversion of short term memory into long term memory is known as consolidation, this consolidated memory stays for weeks to years. This process can take from 5 to 10 minutes for minimal consolidation to one or more hours for stronger consolidation. This process can also be explained as repeated activation of short term memory initiates number of physical, chemical and anatomical changes in the synapses for consolidation. During the consolidation process, trauma or sudden administration of the drug such as GA can interfere with this process thus affecting the memory of an individual.

The consolidation of memory are usually ‘codified’ and placed in appropriate class of information. In other words, the memories are categorized based on the similarities and thus help in the access and recall of the information at a later date. This codifying of information thus is not a random process, but logically carried out to help in future search for similarities and difference.
**Reconsolidation of memory:** There is plenty of evidence to suggest that consolidated fear memories can enter a phase of temporary lability following the retrieval of the memory. Subsequently memory will re-stabilise dependent on new protein synthesis. This process is known as reconsolidation.\(^1\)

Midazolam affects the explicit memory than implicit memory.\(^2\)

**Molecular mechanisms underlying memory process:** \(^3,\)\(^4,\)\(^5,\)\(^6,\)\(^7,\)\(^8,\)\(^9,\)\(^10,\)\(^11,\)\(^12,\)\(^13,\)\(^14\)

Most of the molecular mechanisms of human memory process are understood based on the studies and experiments conducted on primitive animals such as snail (Aplysia) and mouse. Shaheen E Lakhan in 2007 outlined some key molecular mechanisms associated with memory formation and storage from synapse to nucleus and back at synapse:

- Secretion of neurotransmitters and firming the short term synapses
- Establishing the balance between the activities of kinase and phosphatase at the synaptic level
- Reverse transport from synapse to the nucleus
- Nuclear transcription factor activation
- Activity based gene expression
- Chromatin and epigenetic alteration in gene expression
- Capture of newly formed gene products by synapse
- Local protein formation at active synapses
- Formation and development of new synapses
- Activation of dormant synapses and
- Molecular basis of memory persistence
Thus the above events emphasizes the memory formation is not just chemical change but predominantly structural changes occurring at the synapse and learning is an active process at molecular level.

There is ample evidence now to suggest that changes in gene expression within seconds or hours following the process of learning is essential for conversion of short term memory into long term memory.

Additionally, following the activation of N-methyl D aspartate receptor (NMDR) in the neurons, an influx of \( \text{ca}^{2+} \) in the cytoplasm ensues. This increased intracellular \( \text{ca}^{2+} \) concentration activates the extracellular signal related kinase [ERK] pathway, which is responsible for the regulation of gene transcription factors. These factors are essential to affect the extremely coordinated pattern of transcription, subsequently leading to the formation and stabilisation of long term memory. However for the transcription to happen, the structure of chromatin needs to be disrupted. The chromatin is made of a group of highly basic proteins known as histones and is highly inhibitory to transcription. Nevertheless histone acetylation can disrupt this condensed chromatin and the process of histone acetylation is tightly regulated by histone acetyl transferases and histone diacetylases (HDAC). Thus it has been suggested that enhanced histone acetylation by the selective hiring of HDAC inhibitors can assist formation of long term memory.\(^{14}\)

Some general anaesthetic agents such as isoflurane has an inhibitory effect on the hippocampal histone acetylation 60 mins after contextual fear conditioning, leading to reduction in c-Fos expression and thus resulting in amnesia.\(^{15}\)
Types of memory loss:

Amnesia is a term used to describe the intense loss of memory in the presence of relatively intact cognitive capacities. Hippocampus is the structure in the brain which promotes storage of memory. Any alteration in this structure can result in anterograde amnesia. Any thalamic or sometimes even hippocampus damage or lesions can cause retrograde amnesia.\textsuperscript{17}

Causes of amnesia ranges from lesion of the brain, trauma and drugs. Anterograde amnesia, is a type of memory loss for particular information which manifests after precipitating lesion. In the context of sedation it is after the administration of sedative drug. In other words the individual can remember till the insertion of the needle and is unable to remember after the sedation has taken into effect which is few seconds in case of intravenous sedation. On the contrary retrograde amnesia is inability to remember events even before the precipitating lesion.\textsuperscript{17}

Transient global amnesia is a type of amnesia is a self-limiting disease with sudden initiation of isolated amnestic events lasting up to minutes to hours.\textsuperscript{18}

Assessment tools

Neuroimaging techniques, implicit and explicit memory tests, Wisconsin Card Sorting Test, Phonemic Verbal Fluency Test and Stroop Color word interference test for Prefrontal assessment.\textsuperscript{13}

Continuous recognition task (CRT) measures the functioning of conscious memory along with providing measures of sedation. Recognition of an item is assisted by two different memory processes known as familiarity and recollection. These can be measured by event
related potential [ERP]. The ERP is an old/new effect dependent on episodic memory function which is slight when the potency of memory is trivial.  

**Assessment tools for the depth of sedation:**

Traditionally, sedation was monitored with clinical sedation scales such as the Observers Assessment of Alertness Sedation Scale (OAA/S), Modified Ramsey Scale, or a Visual Analog Scale (VAS), overall about 20 different tests have been reported in the literature to measure the amnestic effect of midazolam, however bispectral index is gaining popularity owing to its simplicity. Bispectral index system (BIS) is non-invasive technique with a good sensitivity for the assessment of the profundity of sedation. The electroencephalography (EEG) device outlines the values on a scale of 0-100. The value 100 indicates full consciousness and a value between 60 and 90 suggests adequate sedation. For general anaesthesia values range from 40-60 in, 60-70 in profound sedation, and 70-90 in moderate sedation.

Masato Nakasuji et al 2009 conducted a study with an objective of predicting anterograde amnesia with bispectral index in patients who were undergoing epidural puncture under premedication of intramuscular midazolam and they reported that BIS assessment was informative for the clinicians to predict amnesia.  

Alireza Eshgi et al 2016 employed this index to compare the effects of sedation with midazolam, propofol and ramifentanyl versus midazolam, propofol and ketamine in uncooperative individuals during dental procedures. This was tested in children and the employment of this index during intravenous sedation in adults during dental procedures can be a good way forward to assess depth of sedation and hence predicting the anterograde amnesia during dental procedures.
Midazolam:

Midazolam, an imidazobenzodiazepine derivative, was introduced in the UK for the first time in 1983. This water soluble drug has a fused imidazole ring which remains closed at the blood pH when injected intravenously. This enables increased binding of the drug with proteins in the blood. Besides this also facilitates rapid uptake by nerve tissue.

The distribution and elimination of the drug is affected by several factors such as age, obesity and potential interactions with some drugs. In older and obese individuals this drug is eliminated at a slower rate due to the slower metabolism and excessive deposition of midazolam into the fatty tissue respectively. Hence the recovery period in these individuals can be longer than normal.

Benzodiazepines has an affinity towards the GABA (gamma aminobutyric acid) mediated systems. GABA is a neurotransmitter, at inhibitory neurons along with glycine. They control chloride ion channel, which is responsible for hyperpolarization of neuronal tissue, subsequently leading to inhibition of neurotransmission. However this phenomenon is different in developing brains because the immature neurons already have high chloride concentration intra-neuronally and when the central pore becomes permeable due to the effect of benzodiazepines, the already excess choride concentration starts moving outward, causing the excitatory state instead of the desirable inhibitory effect. Thus the intravenous sedation with benzodiazepines in children can respond unpredictably.

Receptors of GABA are extensively in the CNS structures such as cerebral cortex, thalamus, limbic system mono-aminergic neurons and motor neurons and thus more so in hippocampus, the region responsible for storing explicit memory. The effects of midazolam on memory is dose dependent and since this drug is water soluble and metabolized quickly is largely considered to be safe. Heekyeong Park et al 2004 showed that midazolam affected explicit
memory and also few aspects of implicit memory, however skill learning which is a part of implicit memory seemed unaffected. Thus they concluded supporting the concept that anterograde amnesia induced by midazolam may have an influence on learning that is based on building novel associations in memory along with explicit memory.\textsuperscript{12}

Further administration of midazolam during the reconsolidation phase may affect the traces of memory and thus interfering with the reconsolidation of memory. This particular property of midazolam can be utilized as a potential treatment for anxiety related disorders.\textsuperscript{26}

D-cycloserine, a partial agonist of the glycine recognition site of the N-methyl D-Aspartate receptor, is capable of assisting the vulnerability to midazolam’s disruptive effects in resistant fear memory before reactivation of the memory.\textsuperscript{26}

Silvia Gabriela Bustos et al 2010, conducted an animal experiment with an objective of assessing the vulnerability to midazolam after reactivation of both recent and remote contextual fear memories in male wistar rats who experienced a stressful situation before learning. In addition they also evaluated the influence of pre-reactivation D-cycloserine (DCS) midazolam’s effect on fear memory reconsolidation in these stressed Wistar rats. They suggested that DCS pre-reactivation administration enhanced retrieval-induced lability in a resistant memory trace of these stressed rats without influencing the destabilization phase after reactivation in control unstressed rats. These finding can be clinically relevant as midazolam could be a potential drug to interfere with traumatic memories, besides this the combination of DCS and midazolam can help in attenuating the emotional incidence of undesired resistant memory.\textsuperscript{26}
Conclusion:

Intravenous midazolam sedation has offered options for patients to undergo the dental procedures without apprehension, however the monitoring of sedation and adaptation of Index of sedation need and use of NMDA receptor sites should be explored in the field of dentistry to make advancements in the intravenous sedation.

Image of limbic system is sourced from "Blausen 0614 LimbicSystem" by BruceBlaus, Blausen.com staff. "Blausen gallery 2014". Wikiversity Journal of Medicine

References


13. Lakhan SE.


21. Overly FL, Wright RO, Connor FA, Jay GD, Linakis JG.


