"A RANDOMIZED CLINICAL TRIAL TO COMPARE THE AMNESTIC EFFECT FOLLOWING ORAL PREMEDICATION WITH MIDAZOLAM AND ALPRAZOLAM IN PATIENTS UNDERGOING SURGERY UNDER GENERAL ANAESTHESIA – COMPARATIVE CLINICAL TRIAL AT KLES DR. PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE"

By

Dr. NANDISH KORI M.
(REG. NO. BA0109001)

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
ANAESTHESIOLOGY

Under the Guidance of

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MAY - 2012

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LIST OF ABBREVIATIONS USED

CVS	-	Cardiovascular system
DBP	-	Diastolic blood pressure
ECG	-	Electrocardiogram
GA	-	General anaesthesia
HR	-	Heart rate
Hr	-	Hour
Inj	-	Injection
IP No.	-	In patient number
IV	-	Intravenous
Kg	-	Kilograms
LD	-	Loading dose
MAP	-	Mean arterial blood pressure
Min	-	Minutes
OR	-	Operating room
PACU	-	Post anaesthesia care unit
Pre op	-	Pre operatively
SBP	-	Systolic blood pressure
SD	-	Standard deviation
Sl. No.	-	Serial number
VAS	-	Visual analogue scale
W-PTA	-	Westmead-post traumatic amnesia
Wt	-	Weight

ABSTRACT

Background and Objectives

Anaesthetic memory and awareness continues to occur both in adults and at a higher rate in children. Anaesthetic awareness and memory is a potent precipitant for anxiety, depression and post-traumatic stress disorder (PSTD). Various benzodiazepines are used with varying efficacy to prevent memory formation, to produce anxiolysis and sedation. In this study we compare the efficacy of oral midazolam and alprazolam on amnesia, anxiolysis and sedation.

Methods

This one year comparative clinical trial was done on 120 patients scheduled for surgeries under general anaesthesia at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. Patients were allocated into two groups. Anaesthetic technique was standardized for all patients. Patients were given oral midazolam 7.5 mg (Group-B) or oral alprazolam 0.5 mg (Group-A) 60 minutes before surgery. Amnesia, memory test, anxiety and sedation were assessed using abbreviated Westmead post-traumatic amnesia (PTA) scale, questionnaire, 0 to 100 mm VAS and five-point objective scale respectively.

Results

Amnesia was better with midazolam with a mean of 0.25 when compared to alprazolam of 2.5 using a modified W-PTA scale. It was also better with a mean of 0.58 when compared to alprazolam with a mean of 2.56 in the memory questionnaire. At 60 min,at arrival and discharge from PACU, the mean VAS

scores for alprazolam were lower than midazolam. At 60 minutes, at arrival and discharge from PACU, sedation scores were higher in the midazolam group.

Conclusion and interpretation

The results of present study showed midazolam provides better amnesia and sedation than alprazolam, while latter is a better anxiolytic.

Keywords

Alprazolam; Amnesia; Anxiety; General anaesthesia; Midazolam; Sedation;

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INTRODUCTION

General anaesthesia (GA) is the most common anaesthetic technique used in anaesthesia practice. Anaesthetic memory and awareness continues to occur both in adults (0.13%) and at a higher rate in children(0.8-1.2%).[1,2] Anaesthetic awareness and memory is a potent precipitant for anxiety, depression, nightmares, flashbacks and post-traumatic stress disorder (PSTD).[3] There have been few direct awareness descriptions written by patients in the medical literature, but these are dramatic and describe an awareness episode recognized as a real event distinct from dreams.[4,5] Auditory perceptions are reported by 50% of the patients.[6]

It has been demonstrated that auditory processing and memory are possible under propofol anaesthesia and that surgical stimulation facilitates learning and memory during anaesthesia.[7,8] The effect of a drug on memory is frequently defined as a decrement from baseline or maximal possible performance. Amnesia is not an "all or none" phenomenon, but rather presents a spectrum of effects depending on the intensity of stimulus, the method used to present it, and the methods used for later retrieval .Sedative-hypnotic drugs affect memories as they are progressively transferred from initial registration through short term memory to long term memory recall.[9,10] Midazolam is a sedative hypnotic drug with amnestic properties.[11,12] Previous studies have found that anterograde amnesia can be demonstrated with midazolam but not retrograde amnesia.

The distinction between explicit (declarative) memory and implicit (nondeclarative) memory involves whether or not a memory is accompanied by conscious recollection, that is, an ability to report the memory. Studies of neuropsychological patients have shown that individuals who suffer from amnesia have impairment on explicit memory tasks but no performance deficit on measures of implicit memory. Because of this selective impairment, it has been claimed that different memory systems are subserved by different brain regions. Accessibility to consciousness has been considered as the criterion for different memory systems although others have suggested using as the distinction whether the formation of new memories depends on the medial temporal lobe.

Midazolam causes anterograde amnesia,affecting learning that depends on building novel associates in memory and that this deficit does not hinge upon accessibility to conciousness. The amnestic effects of midazolam seem to begin between 6 and 27s after stimulus registration, suggesting that it has some impact on memory function soon after registration.[13] Alprazolam another sedative anxiolytic also increases reaction time in various memory tests. So, the amnestic property of these sedative drugs is helpful in preventing explicit recall of peri-operative events.[14]

Many patients are anxious before surgery yet there is sometimes a reluctance to provide sedative medication because it is believed to delay discharge from hospital. Anxiety is an unpleasant emotion and may cause patients to avoid a planned operation.[15] It also may adversely influence anaesthetic induction and patient recovery, as well as decrease patient satisfaction with the perioperative experience. Preoperative anxiety can be divided into three

distinct dimentions of anxiety, that is fear of the unknown, fear of feeling ill and fear for one's life. The first factor correlates highest with the different measures of anxiety.

Preoperative anxiety affects most patients and some factors contribute for this: separation from the family, postoperative pain, disability, and loss of independence. Studies have demonstrated that midazolam has several benefits and, among them, we could mention a reduction in preoperative anxiety, better cooperation, and it has a short half-life and good absorption after oral administration. It would be desirable to find a benzodiazepine for oral premedication with a strong anxiety reducing effect and minimal psychomotor impairment.

Midazolam premedication is associated with increased sedation. However, it doesn't affect the recovery profile. It's short duration of action makes it a recommended benzodiazepine for surgical procedure in out patients. Alprazolam at 0.5 mg has the second highest anxiolytic activity(index of 2.26).It has an onset time of 1.4 h and an elimination half-life of 10.6h in normal weight subjects. Given these pharmacokinetic properties and its major anxiety reducing effects in patients with primary anxiety and panic attacks, alprazolam could be a possible alternative to midazolam for premedication in surgical outpatients. Although the sedative, anxiolytic and amnestic properties of midazolam may be desirable before the induction of general anaesthesia, residual effects in the immediate post-op period may contribute to post-op sedation as well as delayed recovery and discharge readiness after brief out-patient surgery.

Most patients awaiting elective surgery experience preoperative anxiety. This anxiety is influenced by the uncertainty of the impending anaesthetic and surgical procedures, past experience, and a patient's personality and coping style. Assessment of anxiety and evaluation of the effectiveness of interventions directed to reduction of such anxiety need a statistically valid and useful measurement tool. The idea of using a VAS, which allows patients to easily indicate their degree of anxiety by simply marking a point on a horizontal line, is appealing. Because anaesthesiologists appear to be inaccurate in assessing patient anxiety during the preoperative visit, the VAS would provide a tool for defining, then addressing patient anxiety.

In this study, comparison between oral midazolam 7.5 mg and alprazolam 0.5 mg is made for their amnestic,anxiolytic and sedative effects in KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. This would determine a better drug for amnesia, anxiolysis and sedation with minimal or no adverse effects.

OBJECTIVES

The objectives of the present study were;

1. To compare oral midazolam 7.5 mg and alprazolam 0.5 mg for their amnestic effects.

2. To compare the same drugs for their anxiolytic and sedative effects.

REVIEW OF LITERATURE

The clinical guideline 26 by the National institute for clinical excellence, 2005 describes that the anaesthetic awareness is a potent precipitant for post-traumatic stress disorder (PTSD). Although a routine referral for specialist PTSD assessment is recommended for those in whom unambiguous awareness has occurred, PTSD symptoms will spontaneously remit in a significant minority. Trauma-focused cognitive behavioural therapy is best reserved for those whose PTSD symptoms have persisted beyond one month.[19]

One of the most common uses of intravenous sedative agents today is to produce amnesia during surgical procedures. Amnesia can occur while the patient is still awake and cooperative. The benzodiazepine drugs have been used for many years as intravenous sedation agents. They are widely used in surgeries for their anxiolytic and amnestic properties. Anterograde amnesia is often considered to be a beneficial effect of intravenous conscious sedation. Since the introduction of midazolam as an agent for intravenous conscious sedation, there have been many reports on its ability to produce anterograde amnesia.

Anterograde amnesia is a lack of recall of events occurring from the time of injection of a drug onwards. This is to be distinguished from retrograde amnesia, a lack of recall of events occurring before the drug's administration. Anterograde amnesia is an accepted pharmacologic action of a number of commonly used intravenous sedative agents, most notably the benzodiazepine diazepam and the anticholinergic scopolamine. Reports have indicated that the duration of midazolam-induced anterograde amnesia may be longer than that

produced by diazepam.[28,29] This is usually considered to be beneficial to the surgical procedure, as it provides the patient with the "feeling" of being unconscious (of not being able to recall what has happened during a procedure) without the added risks attendant upon general anaesthesia.

Veselis and colleagues studied event-related potentials (ERP) which are correlates of memory processing in 2008. They concluded that subanaesthetic doses of drug did not affect performance on the encoding task but did impair ERPs and long-term retention of memory.[17] The amnestic effects of propofol and midazolam seem to begin between 6 and 27s after stimulus registration, suggesting that they have some impact on memory function soon after registration. The effect of a drug on memory is frequently defined as a decrement from baseline or maximal possible performance. Avidan MS and colleagues studied the aspects of anaesthetic awareness and the role of BIS in measuring the depth of anaesthesia in 2008. They highlighted all the aspects of perioperative awareness and depth of anaesthesia monitoring.

Jenkins and colleagues in 2001 studied the molecular aspects of memory formation and the effects of general anaesthetics on memory formation and processing at the molecular level.They re-emphasized the concepts of molecular interaction between anaesthetic drugs and $GABA_A$ receptor.[18]

Sebel and colleagues in 2004 studied the incidence of awareness during anaesthesia. They concluded that despite increased attention from clinicians, patients and media, awareness continues to occur in both adults (0.13%) and at a higher rate in children (0.8-1.2%).[1]

Myles PS and colleagues in 2004 studied incidence of awareness and the role of BIS in monitoring the depth of anaesthesia. They found definitive awareness with an incidence of 0.21%.They also concluded that their findings do not support routine BIS monitoring as part of standard practice.[20]

The distinction between explicit (declarative) memory and implicit (nondeclarative) memory involves whether or not a memory is accompanied by conscious recollection, that is, an ability to report the memory. Studies of neuropsychological patients have shown that individuals who suffer from amnesia have impairment on explicit memory tasks but no performance deficit on measures of implicit memory.

Because of this selective impairment, it has been claimed that different memory systems are subserved by different brain regions. Accessibility to consciousness has been considered as the criterion for different memory systems, although others have suggested using as the distinction whether the formation of new memories depends on the medial temporal lobe. Dundee and colleagues showed that midazolam had amnestic properties as early as 1980. But the study lead to further evaluation of the nature of amnesia like retrograde or anterograde.[22]

Koth A and colleagues in 1997 studied the retrograde nature of midazolam and concluded that midazolam can induce retrograde amnesia and flumazenil can reverse the retrograde amnesia caused by midazolam.[23]

In recent years there has been a drive to find an effective, safe, short acting, non-injectable sedation agent to prevent amnesia. Oral midazolam has emerged as such an agent, and has the added benefit of inducing amnesia.

Alprazolam also provides good amnesia,anxiolysis and sedation[33]. Flumazenil (10 mg/kg) attenuated anterograde and retrograde amnesia produced by alprazolam. It is proposed that anterograde amnesia produced by alprazolam may be mediated through the activation of benzodiazepine receptors.[34]

Alprazolam produced pronounced impairments on a word recall task in a study conducted by curren et al proving the amnestic property of alprazolam[35]. The amnestic property of alprazolam is not well evaluated.

Extreme preoperative anxiety in children may prolong the induction of anaesthesia and lead to new-onset postoperative negative psychologic effects, such as nightmares, eating disturbances, and enuresis. Preoperative use of midazolam has previously been reported to decrease the incidence of these postoperative negative psychologic outcomes, and midazolam-related amnesia has been suggested as the mediator for this phenomena.In this study conducted by Twersky and colleagues in 1993, midazolam enhanced anterograde amnesia but not retrograde amnesia in pediatric patients.[24]

Veselis RA and colleagues in 1997 studied the compative amnestic effects of midazolam, propofol, thiopental and fentanyl at equisedative concentrations. The extent of sedation as measured by BIS was correlated with anterograde amnesia as measured by event recall. The midazolam induced anterograde

amnesia demonstrated in this study could also be because of the propofol's property of retrograde amnesia.[25]

Myles and colleagues and Sandin and colleagues in their separate studies in 2002 and 2000 concluded that the amnestic properties of midazolam can be used to treat suspected awareness. However, the dose of midzolam required to achieve such an effect can still result in memory formation in patients who have received midazolam. The study also concluded that midazolam cannot be used to reliably produce retrograde amnesia, even of very short duration. Immediate anterograde amnesia can be achieved, and this may be of some clinical utility in reducing the risk of awareness at specific times during surgery.[26,27]

Pre-operative anxiety can affect the operative outcome. A study was conducted by Yang et al in 2009 to investigate the peri-operative incidence of depression and anxiety of patients undergoing general anaesthesia, and assessed the relationship between peri-operative characteristics with depression and anxiety. Anxiety was found pre- and post-operative in 23% and 17% of patients respectively while the rate of depression was 20% and 16% respectively. Middle or high-level ($p<0.05$) education was associated with pre-operative anxiety. Pre-operative anxiety and depression are interactional ($p<0.01$). Post-operative depression ($p<0.01$) predicted post-operative anxiety; in female patients ($p<0.05$), pre-operative depression, post-operative anxiety ($p<0.05$) and discomfort of pharynx ($p<0.05$) predicted post-operative depression. They concluded that, patients may experience anxiety or depression during peri-operation. Anxiety and depression are interactional. Level of education, sex and discomfort of pharynx may influence pre- or post-operative anxiety or depression respectively.[36]

Jan L D Witte and colleagues described the pharmacokinetic and pharmacodynamic properties of alprazolam in their study in 2002. As per their study, Alprazolam at 0.5 mg has the second highest anxioselective activity (index of 2.26). It has an onset time of 1.4 h and an elimination t1/2 of 10.6 h in normal-weight subjects. Given these pharmacokinetic properties and its major anxiety-reducing effects in patients with primary anxiety and panic attacks, alprazolam is a possible alternative to midazolam for premedication in surgical outpatients.[16]

Oral midazolam (7.5 mg) does not produce significant sedation before surgery in comparison to placebo, other studies demonstrate a significant sedative effect (sleepy, but easily arousable). In a recent study of Brosius and Bannister, only 40% of patients treated with the large dose of 20 mg of midazolam exhibited detectable sedation, with marked interindividual variability in plasma midazolam levels. Detectable preoperative sedation was predictive of prolonged emergence.[37]

In our study, an effort is made to compare oral midazolam 7.5 mg and alprazolam 0.5mg for their amnestic, anxiolytic and sedative effects in patients undergoing surgery under general anaesthesia.

BASIC SCIENCES

Memory

Neuropsychologist Karl Lashley once said "We may know that limited regions may be essential for learning and retention but these regions do not as such house memory". Memory is the ability to code, store and retrieve information. Memory involves coding the input of the senses (visual, auditory).It is one of the higher functions of the nervous system along with learning, judgement, language and speech.

A characteristic of animals and particularly of humans is the ability to alter behaviour on the basis of experience. Learning is acquisition of the information that makes this possible, and memory is the retention and storage of that information. The two are obviously closely related and should be considered together.

Forms of memory: Larry Squire's memory taxonomy

Definitions

Declarative memory (explicit)

Knowledge to which we have conscious access, including personal and world knowledge.[30]

Nondeclarative memory (implicit)

Knowledge to which we typically have no concious access, such as motor and cognitive skills.

Episodic memory

Stored information about events in one's life, including information about when they happened and what happened.

Semantic memory

A category of memory that is believed to support memory for facts and the ability to extract generalizations across experiences.

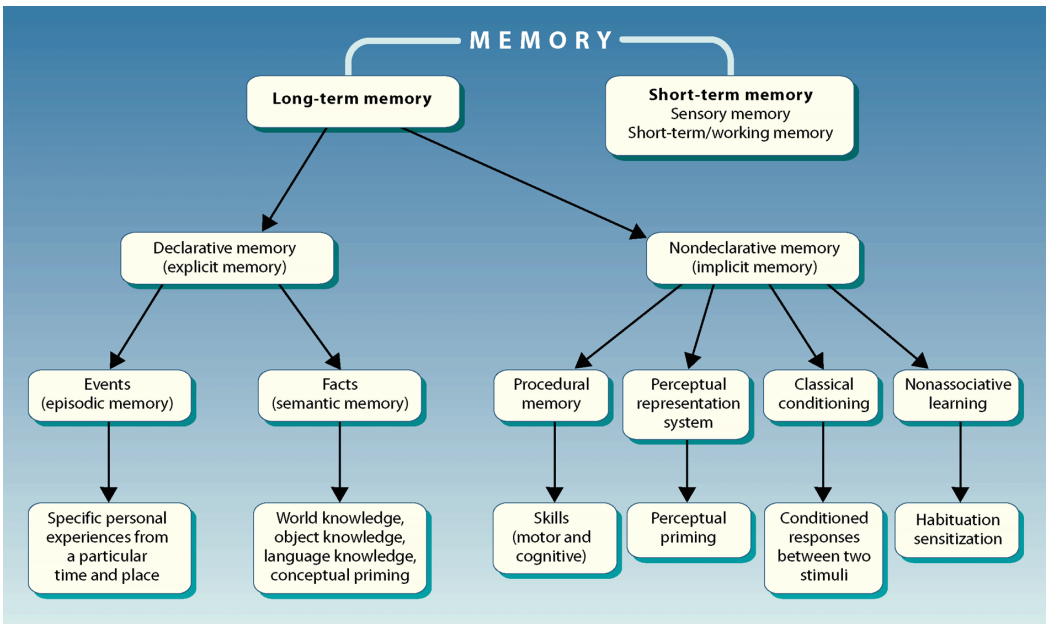


Figure 1. Memory classification

Forms of memory

Brain areas related to memory

Working memory areas are connected to the hippocampus and the adjacent parahippocampal portions of the medial temporal cortex. In humans, bilateral destruction of the hippocampus cause striking defects in short-term memory. However, they have intact working memory and remote memory. Their implicit memory processes are generally intact.

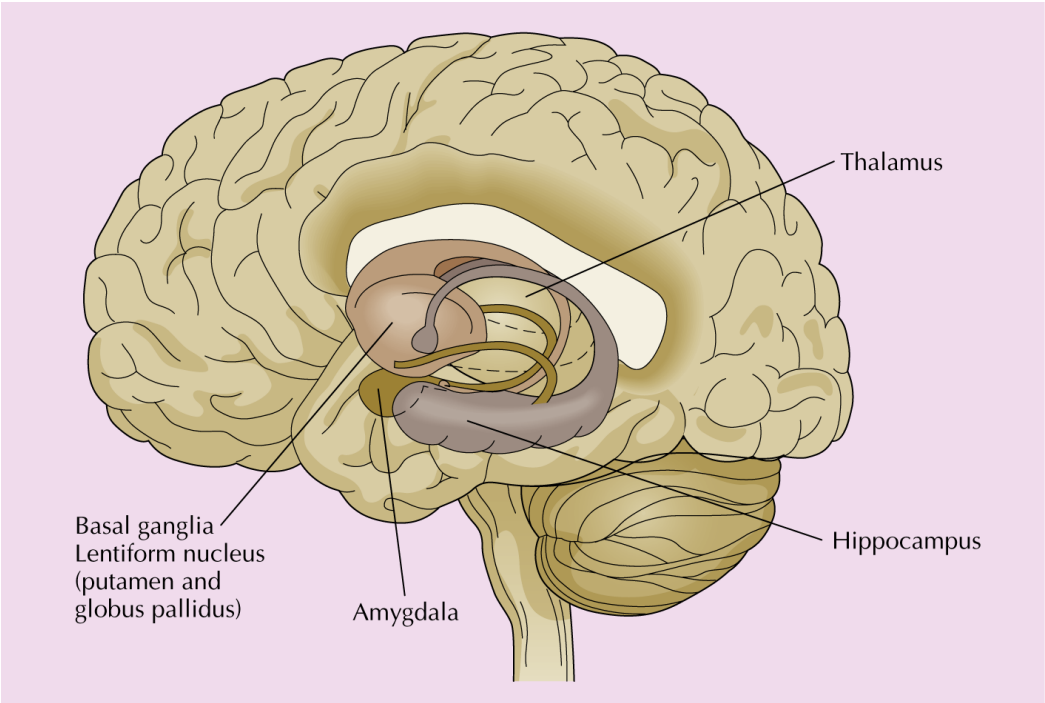


Figure 2. Brain areas related to memory

- Hippocampus
- Adjacent areas such as entorhinal cortex and parahippocampal cortex
- Basal forebrain nuclei
- Diencephalon

Hippocampus is the most important area for memory consolidation.[31]

Position of hippocampus in the brain

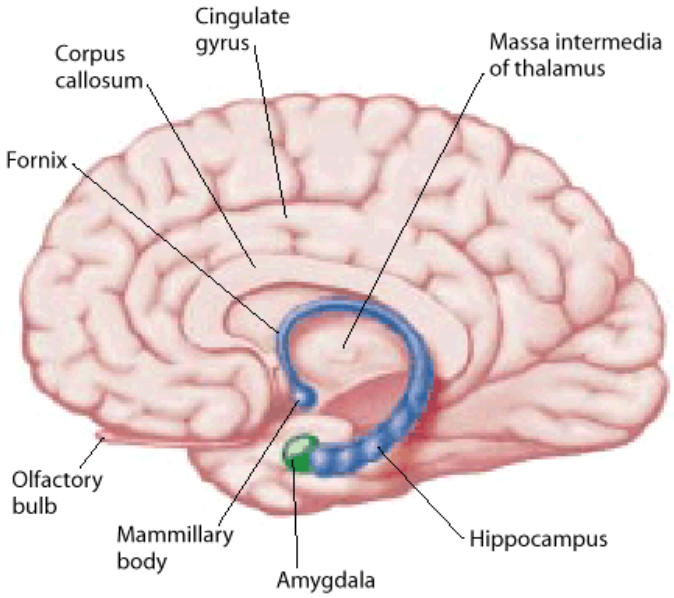


Figure 3. Position of hippocampus in the brain

Parahippocampal gyrus and other structures

The hippocampus is closely associated with the overlying parahippocampal cortex in the medial frontal lobe. Recall of words activates left frontal lobe and left para-hippocampal cortex.Recall of pictures or scenes activates right frontal lobe and para-hippocampal cortex on both sides.

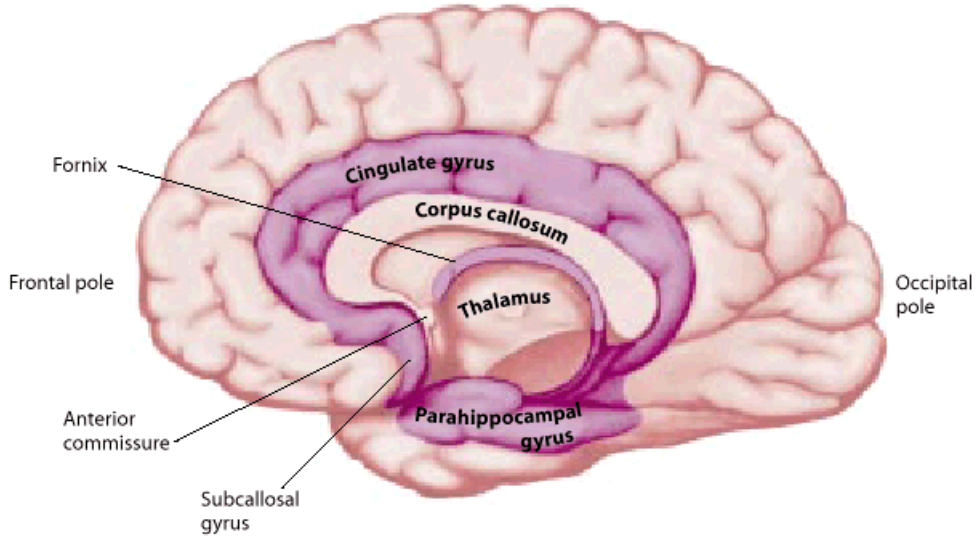


Figure 4. Para-hippocampal gyrus and other structures

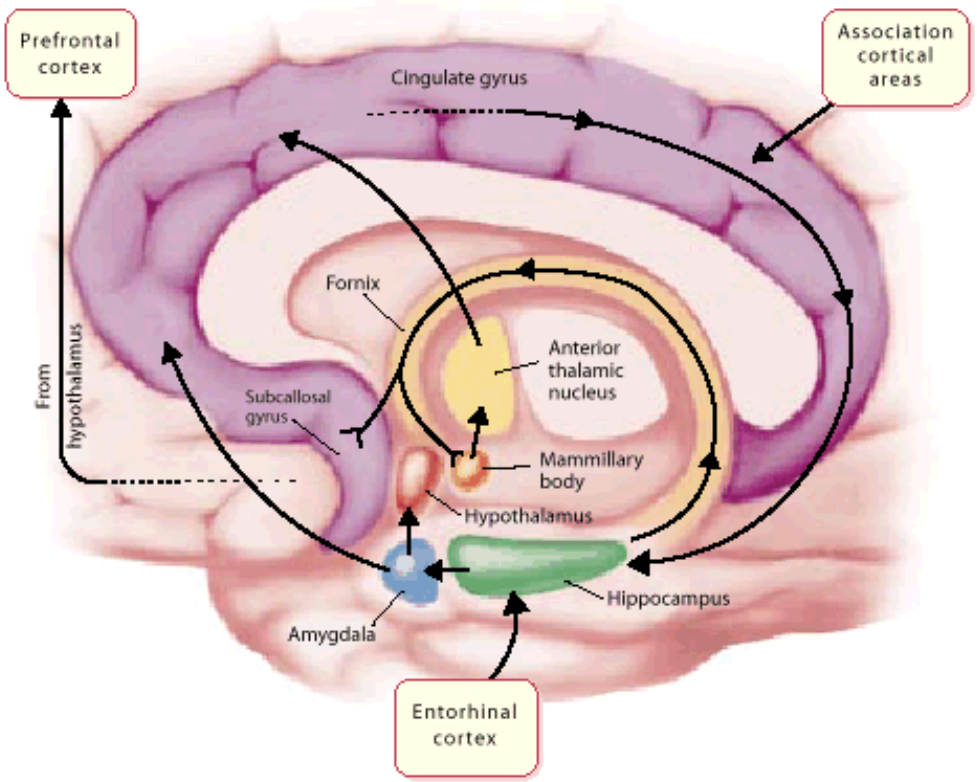


Figure 5. Connections to and from hippocampus

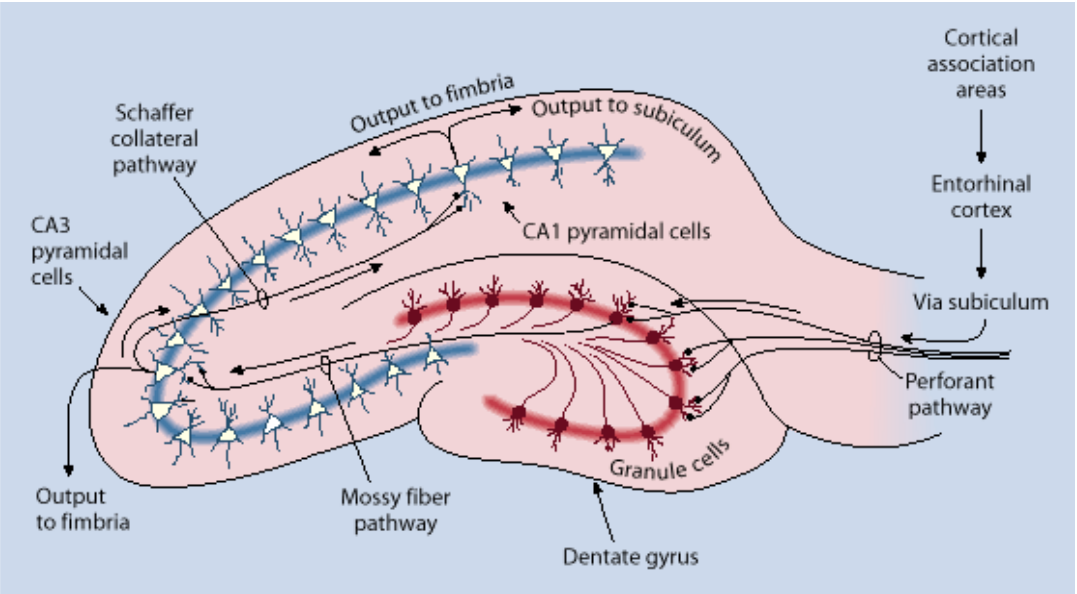


Figure 6. Connectivity within the hippocampus

Synaptic communication: Biological Basis of Memory

Synaptic theories of memory

- Classical conditioning of snails (Kandel).
- Amount of neurotransmitter in synapse increased – synapse holds memory.
- Drugs that interfere with protein synthesis block memory formation.
- Consolidation – fragile memories grow more permanent over a few minutes.

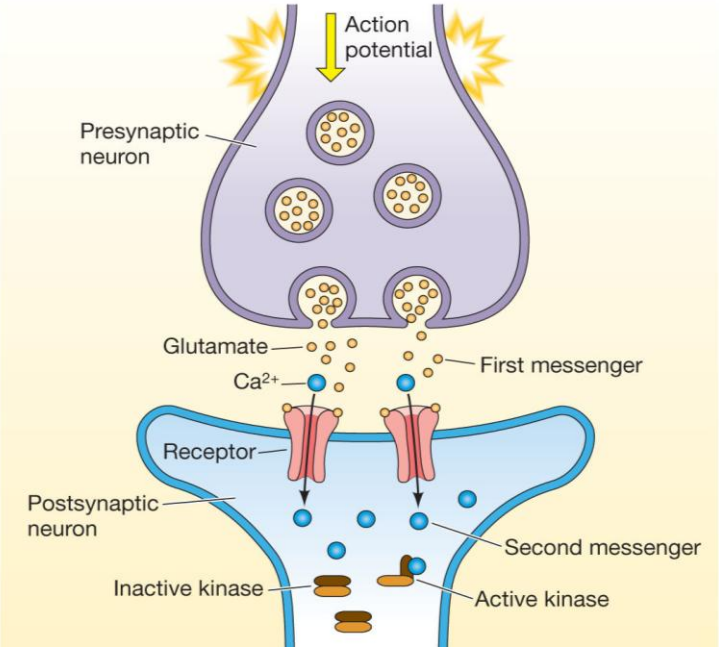


Figure 7. Neurobiology of learning and memory

Neurotransmission in memory

This diagram shows transmission at a synaptic cleft, the synaptic vesicles are stimulated by a electrical impulse and the neurotransmitter is released and it interacts with the receptors.

Benzodiazepines have been used to reduce anxiety in clinical settings, but they also have a temporary, functional amnesic effect on encoding information . Benzodiazepines facilitate the action of γ-aminobutyric acid (GABA) by increasing the binding of GABA to $GABA_A$ receptors.[32] GABA is the primary inhibitory neurotransmitter in the mammalian central nervous system, and $GABA_A$ receptors are expressed throughout the brain with a very high density in the hippocampal system, which has been established as critical for explicit memory . Midazolam is a benzodiazepine that has the benefits of being

metabolized quickly and of being water-soluble. These attributes help minimize potential side effects without disturbing other cognitive functions when midazolam is given in low doses, thereby providing a tool to investigate distinct forms of memory based on conscious accessibility in healthy participants.

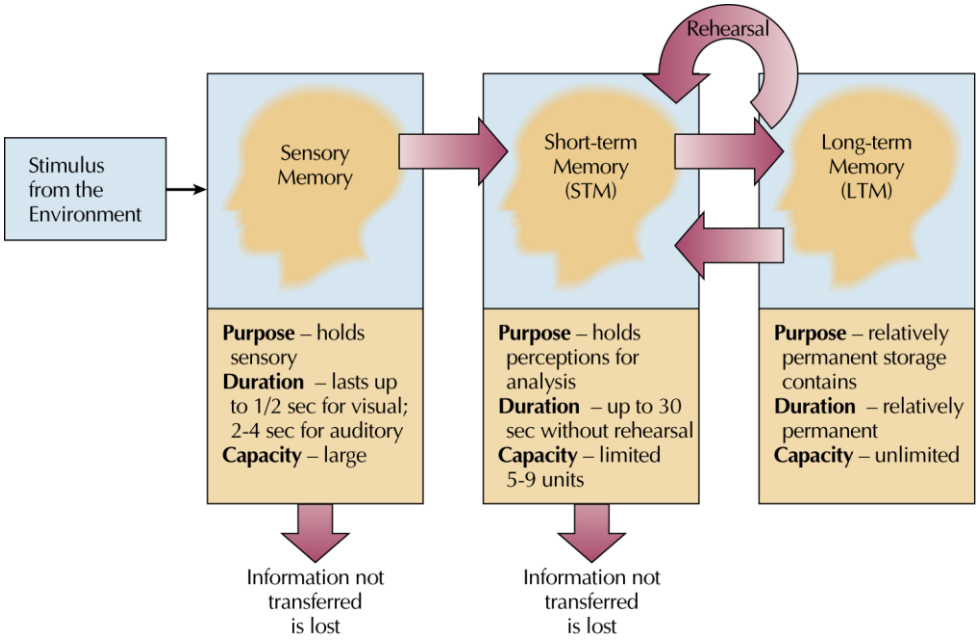


Figure 8. Overview of Memory Model

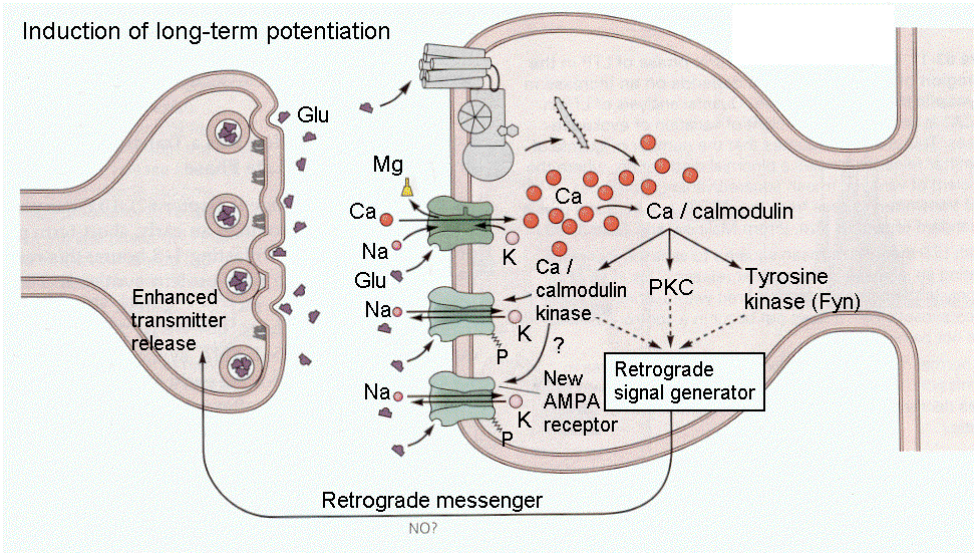


Figure 9. Long Term Potentiation (LTP)

- Lasting enhancement of synaptic transmission.
- Occurs all areas known to be involved in memory.
- Hippocampus CA3 → CA1.
- Glutamate main transmitter involved.
- NMDA and AMPA channels.
- Calcium and Sodium dependant.
- Ca/Calmodulin.
- Plasticity.

Amnesia

Théodule Ribot proposed that during disease of the brain, memories disappear in an orderly fashion.

Ribot's Law: Ribot also proposed that old memories are more resistant to disease/disruption than new memories.

- Retrograde amnesia[40]
    - No memory of what happened immediately before an accident or highly stressful event.
        - Little or no disruption in STM.
        - New long-term memories can be formed.
        - Usually memory loss does not last lifetime.
        - Stress of event disrupts consolidation and retroactive interference blocks retrieval.

- Anterograde amnesia
    - Inability to store and retrieve new information.
        - Does not affect procedural memory abilities but disrupts episodic memory formation.
        - Hippocampus involved in episodic memory.
            - Damage prevents formation of new long-term declarative memories.

Causes of Amnesia

- Concussion
- Migraines
- Hypoglycemia
- Epilepsy
- Electroconvulsive shock therapy
- Specific brain lesions (i.e. surgical removal)
- Ischaemic events
- Drugs (esp. anaesthetics)

Pharmacology of alprazolam

History

Alprazolam was first released by Upjohn in 1981.

Chemistry

Alprazolam is used to treat anxiety and panic disorders. It belongs to a class of medications called benzodiazepines which act on the brain and nerves (central nervous system) to produce a calming effect. It works by enhancing the effects of a certain natural chemical in the body (GABA).Alprazolam which is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds. The chemical name of alprazolam is 8-Chloro-1-methyl-6-phenyl-4H-s-triazolo [4,3-I] [1,4] benzodiazepine. Each Tablet, for oral administration, contains 0.25, 0.5, 1 or 2 mg of alprazolam.

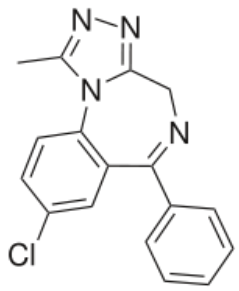


Figure 10. Chemical structure of Alprazolam

Structural formula: 8-Chloro-1-methyl-6-phenyl-4H-s-triazolo [4,3-I] [1,4] benzodiazepine.

Formula: $C_{17}H_{13}ClN_4$

Molecular mass: 308.765

Alprazolam is a white crystalline powder, which is soluble in methanol or ethanol but which has no appreciable solubility in water at physiological pH. Inactive ingredients: Cellulose, corn starch, docusate sodium, lactose, magnesium stearate, silicon dioxide and sodium benzoate. In addition, the 0.5 mg tablet contains FD&C Yellow No. 6 and the 1 mg tablet contains FD&C Blue No. 2.

Pharmacodynamics

Alprazolam is classed as a high-potency benzodiazepine and is a triazolobenzodiazepine more specifically–a benzodiazepine with a triazole ring attached to its structure. Benzodiazepines produce a variety of therapeutic and adverse effects by binding to the benzodiazepine receptor site on the $GABA_A$ receptor and modulating the function of the GABA receptor, the most prolific inhibitory receptor within the brain. The GABA chemical and receptor system mediates inhibitory or calming effects of alprazolam on the nervous system. The $GABA_A$ receptor is made up of 5 subunits out of a possible 19, and $GABA_A$ receptors made up of different combinations of subunits have different properties, different locations within the brain, and, importantly, different activities with regard to benzodiazepines. The therapeutic properties of alprazolam are similar to other benzodiazepines and include anxiolytic, anticonvulsant, muscle relaxant, and amnesic effect.

Pharmacokinetics[41]

Absorption

Following oral administration, alprazolam is readily absorbed. Peak concentrations in the plasma occur in 1 to 2 hours following administration. Plasma levels are proportionate to the dose given; over the dose range of 0.5 to 3.0 mg, peak levels of 8.0 to 37 ng/mL were observed. Using a specific assay methodology, the mean plasma elimination half-life of alprazolam has been found to be about 11.2 hours (range: 6.3-26.9 hours) in healthy adults.

Distribution

Alprazolam is bound (80 percent) to human serum protein. Serum albumin accounts for the majority of the binding.

Metabolism/Elimination

Alprazolam is extensively metabolized in humans, primarily by cytochrome P450 3A4 (CYP3A4), to two major metabolites in the plasma: 4-hydroxyalprazolam and α-hydroxyalprazolam. A benzophenone derived from alprazolam is also found in humans. Their half-lives appear to be similar to that of alprazolam.. The benzophenone metabolite is essentially inactive.

Alprazolam and its metabolites are excreted primarily in the urine .

Uses

Alprazolam is used to treat anxiety disorders, panic disorders, and anxiety caused by depression and panic disorders.

Side effects

Alprazolam causes allergic reactions like hives, difficulty breathing, swelling of your face, lips, tongue, or throat. It causes depressed mood, thoughts of suicide or hurting yourself. It can cause hyperactivity, agitation, hostility, hallucinations, feeling light-headed, fainting, seizure (convulsions),muscle twitching, tremor, jaundice (yellowing of the skin or eyes),drowsiness, dizziness, feeling irritable. It can also cause amnesia or forgetfulness, trouble concentrating, muscle weakness, lack of balance or coordination, slurred speech. It can cause blurred vision, nausea, vomiting, constipation, appetite or weight changes, dry or watery mouth, and increased sweating.

Indications

Alprazolam tablets are indicated for the management of anxiety disorder (a condition corresponding most closely to the APA Diagnostic and Statistical Manual [DSM-III-R] diagnosis of generalized anxiety disorder) or the short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

Dosage

Treatment may be initiated with a dose of 0.5 mg three times daily. Depending on the response, the dose may be increased at intervals of 3 to 4 days in increments of no more than 1 mg per day. Slower titration to the dose levels greater than 4 mg/day may be advisable to allow full expression of the pharmacodynamic effect of alprazolam. To lessen the possibility of interdose

symptoms, the times of administration should be distributed as evenly as possible throughout the waking hours, that is, on a three or four times per day schedule.

Drug interactions

Alprazolam is primarily eliminated by metabolism via cytochrome P450 3A (CYP3A). Most of the interactions that have been documented with alprazolam are with drugs that inhibit or induce CYP3A4.Alprazolam, produce additive CNS depressant effects when co-administered with other psychotropic medications, anticonvulsants, antihistaminics, ethanol and other drugs which themselves produce CNS depression.

Contraindications

Alprazoalm tablets are contraindicated in patients with known sensitivity to this drug or other benzodiazepines. Patients with acute narrow angle glaucoma.

Pharmacology of midazolam

History

Midazolam was synthesised in 1975 by Walser and Fryer at Hoffmann-LaRoche. inc, in the United States.[21] It has sedative, amnestic, anxiolytic, hypnotic, anti-convulsant and skeletal muscle relaxant properties.

Chemistry

Midazolam is an 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo [1,5-a] [1,4] benzodiazepine. The unique chemical structure of midazolam confers a number of physicochemical properties that distinguish it from other benzodiazepines in terms of its pharmacologic and pharmacokinetic properties.[38] It has a fused imidazoline ring. The imidazoline ring accounts for the basicity, stability and rapid metabolism. The pka of midazolam is 6.15. The drug is prepared either as a hydrochloride salt or a maleate salt. At physiological pH, it becomes highly lipophilic and is one of the most lipid soluble of the benzodiazepines. High lipophilicity accounts for the rapid absorption of the drug from the gastrointestinal tract. It is extensively protien bound. The degree of binding averages 96-97% and is independent of the dose and plasma concentration of midazolam.[39]

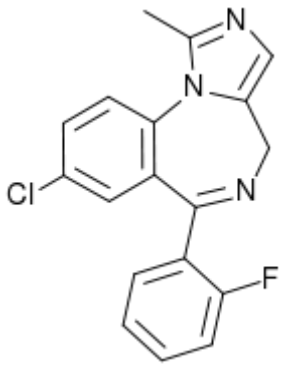


Figure 11. Chemical structure of midazolam

Structural formula

8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-a][1,4]benzodiazepine

It is a benzodiazepine drug with an imidazole structure. Its molecular mass is 325.78.

Chemical formula: $C_{18}H_{13}ClFN_{3.}$

Bioavailability: Oral ~36% IM 90%+

Protein binding: 97%

Pharmacokinetics

Midazolam is a short-acting benzodiazepine in adults with an elimination half-life of one to four hours; however, in the elderly, as well as young children and adolescents, the elimination half life is longer. Midazolam is metabolised in liver into an active metabolite alpha1-hydroxymidazolam. Age related deficits, renal and liver status affect the pharmacokinetic factors of midazolam as well as its active metabolite. However, the active metabolite of midazolam is minor and

contributes to only 10% of biological activity of midazolam. Midazolam is absorbed orally with 50% of the drug reaching the bloodstream. Midazolam is metabolised by cytochrome P450 (CYP) enzymes and by glucuronide conjugation and excreted in urine. Volume of distribution is 1 to 2.5 L/kg. Total clearance of midazolam is 50% of the hepatic blood flow.

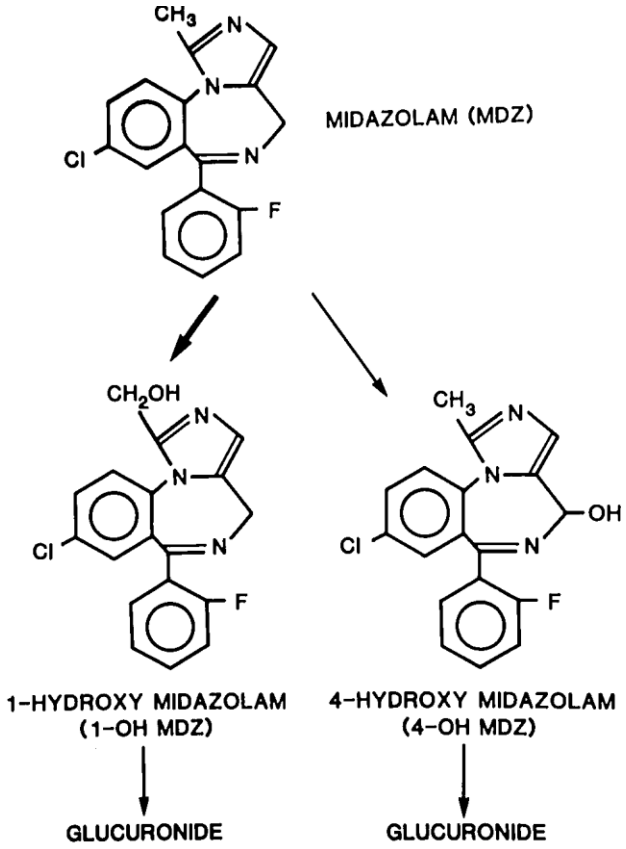


Figure 12. Metabolic pathway of midazolam in humans

Mechanism of action

The therapeautic as well as adverse effects of midazolam are due to its effects on the GABA-A receptors located in the hypothalamus, cerebellum, midbrain, hippocampus, striatum, medulla oblongata, pons and spinal cord; midazolam does not activate GABA-A receptors directly but, as with other

benzodiazepines, it enhances the effect of the neurotransmitter GABA on the GABA-A receptors (↑ frequency of Cl− channel opening) resulting in neural inhibition. Almost all of the properties can be explained by the actions of benzodiazepines on GABA-A receptors. This result in the following pharmacological properties being produced: sedation, hypnotic, anxiolytic, anterograde amnesia, muscle relaxation and anti-convulsant.

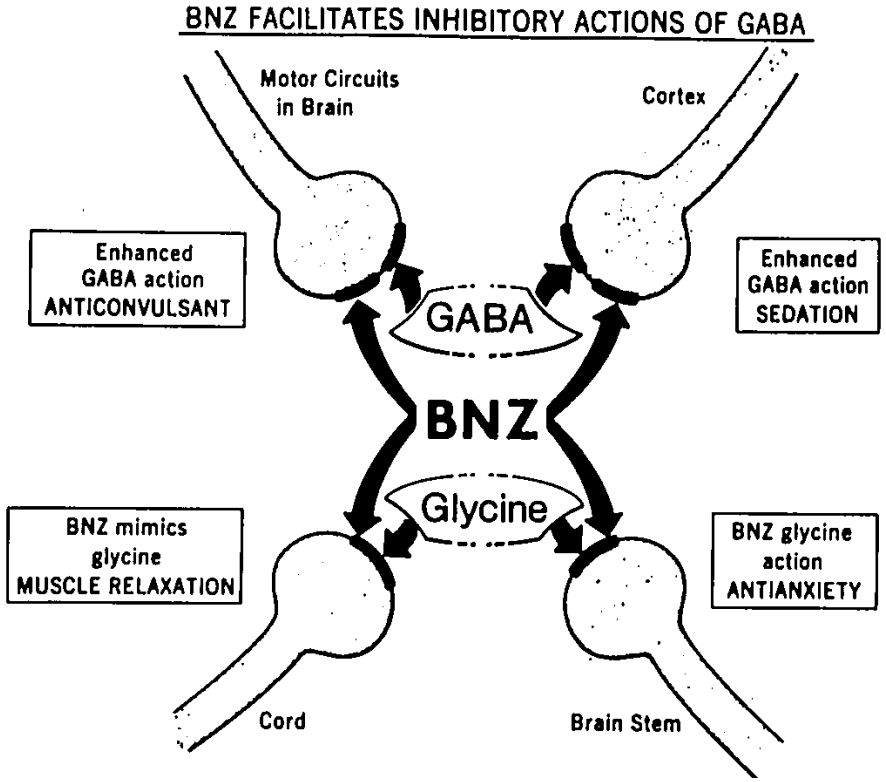


Figure 13. BNZ mimics inhibitory actions of glycine

Side effects

Long-term use of benzodiazepines has been associated with long-lasting deficits of memory. Some of the side effects are paradoxical reactions like anxiety, involuntary movements, aggressive or violent behavior, uncontrollable

crying or verbalization, sleepiness and impaired psychomotor and cognitive functions. It can cause sedation, respiratory depression and hypotension.

Indications

Midazolam tablets are indicated for use in patients for sedation, anxiolysis and amnesia prior to diagnostic, therapeutic or endoscopic procedures or before induction of anaesthsia, moderate to severe insomnia.

Dosage

Midazolam oral tablets are indicated in a dose of 7.5 to 15.0 mg in adults for preprocedural sedation, anxiolysis and amnesia.

Drug Interactions

Midazolam is metabolized by cytochrome P450 3A4 enzyme system. Drugs that are known to inhibit the P450 3A4 enzyme system such as cimetidine (not ranitidine), erythromycin, diltiazem, verapamil, ketoconazole and itraconazole can prolong the action of midazolam. These drug interactions may result in prolonged sedation due to a decrease in plasma clearance of midazolam.

Contraindications

Midazolam tablets are contraindicated in patients with kidney disease, liver disease, breathing problems (e.g., chronic obstructive pulmonary disease-COPD, sleep apnea), heart disease (e.g., congestive heart failure), hypersensitivity, acute narrow angle glaucoma, shock, hypotension or head injury.

METHODOLOGY

The present study was conducted in the Department of Anaesthesiology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2010 to December 2010.

Source of Data

Patients undergoing surgeries under GA at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Study design

One year comparative randomized clinical trial.

Study Period

One year from January 2010 to December 2010.

Sample Size

A total of 120 patients undergoing surgeries under GA randomized into two groups of 60 each.

Sampling procedure

The sample size was calculated using the formula as mentioned below.

$$n = \frac{2\,(Z\alpha + Z\beta)^2\ P(1-P)}{(P_0 - P_1)^2}$$

Where, α = 0.05

β = 0.2

P = 80%

P_0 = 0%

P_1 = 10%

P = 5%

$Z\alpha$ = 1.65

$Z\beta$ = 0.84

P = $(P_0 + P_1) / 2$

Randomization

Patients were randomly allocated into one of the two groups using sequentially numbered envelopes that is Group A (n=60; receiving Tablet Alprazolam 0.5 mg orally, 60 minutes before surgery) and Group B (n=60 receiving Tablet Midazolam 7.5 mg orally, 60 minutes before surgery).

Selection Criteria

Inclusion criteria

- ASA physical status I or II.
- Age between 18 to 50 years.
- Surgery lasting for 60 to 90 minutes.
- Body weight 60 to 70 kg.

Exclusion criteria

- Patients receiving sedatives, anticonvulsants.
- Endocrine and neuropsychiatric disease.
- Suspected allergy or contraindication to study agents.
- Pregnancy.

Procedure

The study was approved and ethical clearance was obtained from Human Ethics Committee, Jawaharlal Nehru Medical College, Belgaum. After finding the suitability according to selection criteria patients were selected for the study and briefed about the nature of the study and written informed consent was obtained (Annexure–I). Further, descriptive data of the patients like name, age, sex, detailed history, were obtained and recorded on predesigned and pretested proforma (Annexure-II).

Relevant investigation like complete blood count (CBC), urine routine, blood urea, serum creatinine, fasting blood sugar, chest X-ray and ECG were carried out.

Further, patients were randomly divided into two groups according to randomization procedure that is, Group A (alprazolam 0.5 mg) and Group B (midazolam 7.5 mg) to receive the drugs orally 60 minutes before surgery with sips of water.

Intravenous access was obtained and slow infusion of crystalloids was commenced. Monitoring consisting of ECG, NIBP, $EtCO_2$ and SPO_2. Prior to

induction, all patients were pre oxygenated with 100% O_2 at 8 L/min using Bain's circuit for three minutes and premedicated with glycopyrrolate 0.005 mg/kg IV and fentanyl 2 µg/kg IV in both groups. A familiar object was shown to the patient just before induction of anesthesia (Annexure III Photograph No). Induction was done with IV thiopentone 5 mg/kg. Loss of eyelash reflex was considered for induction. Intubation was facilitated with Inj. vecuronium 0.1 mg/kg.

Anaesthesia was maintained with O_2, N_2O 50:50%, vecuronium, one fourth the of LD and halothane 0.5%.

After the surgery, reversal was done with glycopyrrolate 0.01 mg/kg IV and neostigmine 0.05 mg/kg IV. Spontaneous breathing was allowed when patient was awake and extubated.

In PACU, O_2 by ventimask at 5 L/min was given. PACU patient discharge criteria included;

- Being awake.
- Orientated.
- Able to breathe deeply, cough freely.
- Blood pressure within 20% of pre operation values.
- Minimal pain and no nausea.

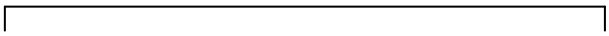
Effect of the study drugs on amnesia was assessed at the time of discharge from post anesthesia care unit. Effect of study drugs on anxiety and sedation level was assessed five times at following intervals.

- Baseline values.

- 30 minutes after drug intake.
- 60 minutes after drug intake.
- Arrival at PACU.
- At the time of discharge from PACU.

Amnesia was assessed using an abbreviated Westmead post-traumatic amnesia (PTA) scale wherein a patient was shown a set of familiar pictures before induction and asked to recollect after a period. Memory test was also performed using a questionnaire. The extent of sedation was correlated with anterograde amnesia as measured by event recall.

Anxiety was scored using 0 to 100 mm VAS by patients.



0 Completely relaxed, Calm.

100 mm Extreme anxiety

Sedation was assessed on a five-point objective scale[16] and was scored as below.

0	Alert
1	Arouses to voice
2	Arouses with gentle tactile stimulation
3	Arouses to vigourous stimulation
4	Lack of responsiveness.

Statistical analysis

The data was tabulated on Microscoft excel worksheet and difference between two groups was calculated using student's 't' test for demographic data, Mann whitneys test for amnesia and Chi-square test with Yate's correction for anxiety and sedation. Results were presented as mean ± standard deviation (SD). A probability value (p value) of less than 0.05 was considered statistically significant.

RESULTS

The present one year comparative randomized clinical trial was conducted in the Department of Anaesthesiology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2010 to December 2010 on 120 patients undergoing surgeries under GA randomized into two groups of 60 each.

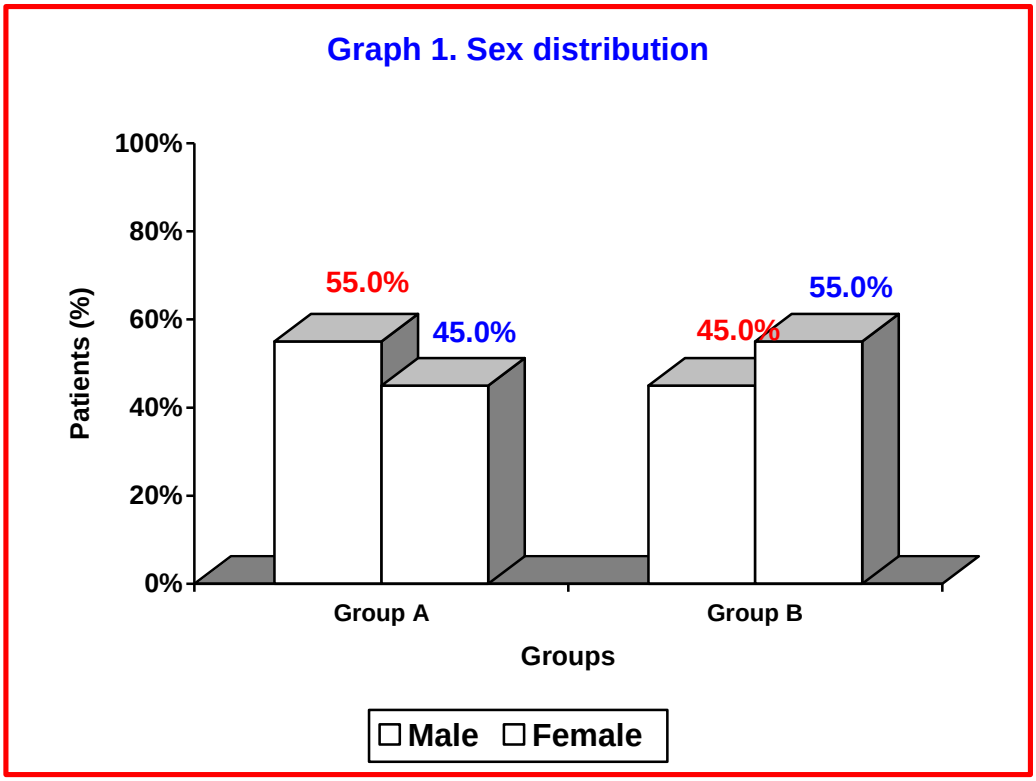
Patients were randomly allocated into one of the two groups using sequentially numbered envelopes that is Group A (n=60; receiving Tablet Alprazolam 0.5 mg orally, 60 minutes before surgery) and Group B (n=60 receiving Tablet Midazolam 7.5 mg orally, 60 minutes before surgery).

Demographic data were similar between the two groups. There were no differences with respect to patient characteristics between the two groups studied. The data obtained was tabulated on Microscoft excel worksheet and analysed as below

Table 1. Sex Distribution

Gender	Group A (n=60)		Group B (n=60)	
	Number	**Percentage**	**Number**	**Percentage**
Male	33	55.0	27	45.0
Female	27	45.0	33	55.0
Total	**60**	**100**	**60**	**100**

x^2=1.200 p=0.273

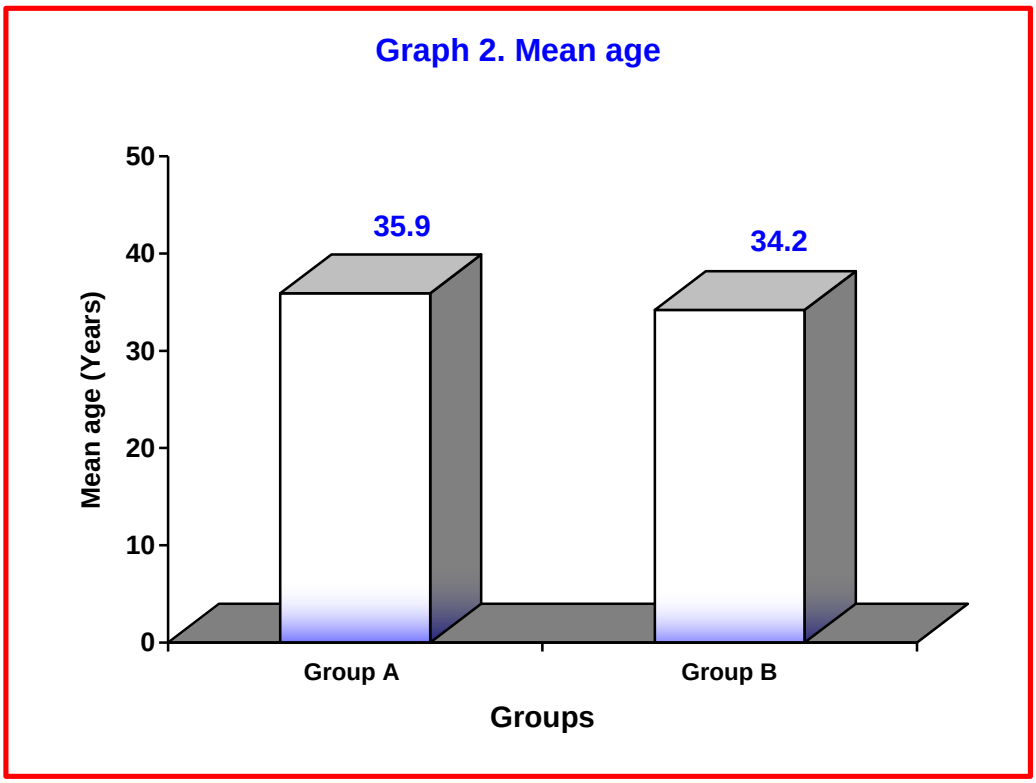


In this study males outnumbered females in group A and females outnumbered males in group B suggesting no difference of sex distribution in both the groups (p=0.273).

Table 2. Mean age

Age	Group A (n=60)		Group B (n=60)	
	Mean	**SD**	**Mean**	**SD**
Mean age (Years)	35.9	9.76	34.2	10.31

t=0.946 p=0.346

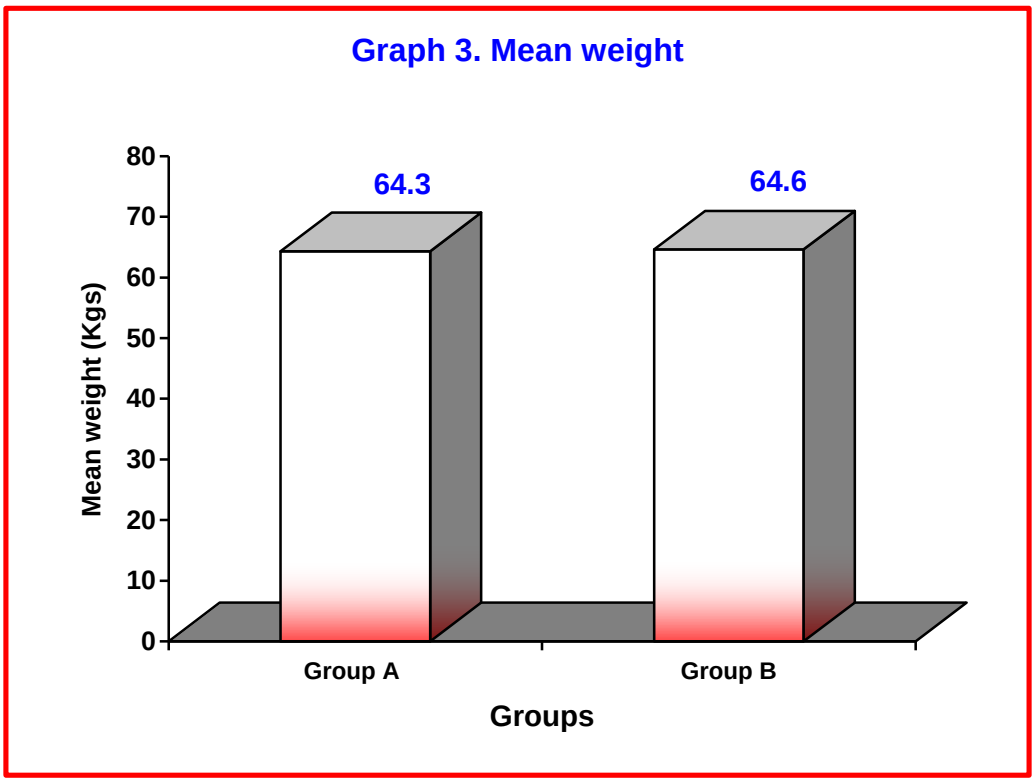


In the present study comparison of mean age between group A and group B showed no statistically significant difference between the ages of patients in both the groups (35.9 ± 9.76 vs 34.2 ± 10.31 years; p=0.346).

Table 3. Mean weight

Weight	Group A (n=60)		Group B (n=60)	
	Mean	**SD**	**Mean**	**SD**
Mean weight (Kgs)	64.3	3.08	64.6	2.98

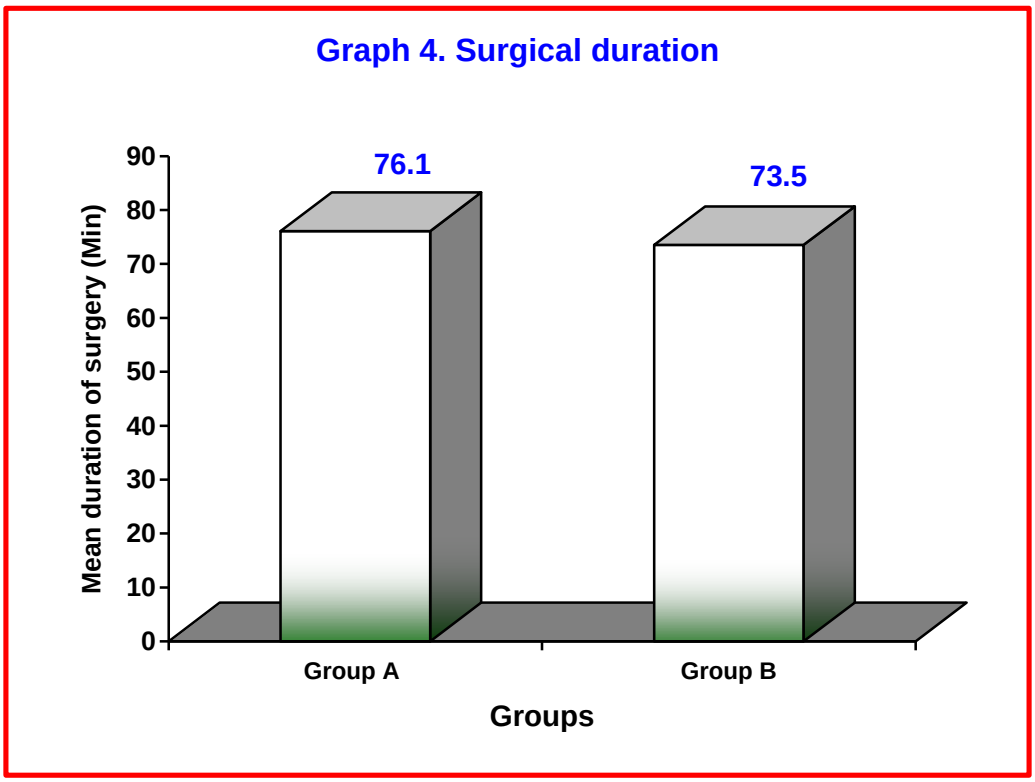
t=0.487 p=0.631



In this study no statistically significant difference was seen between the mean weight of patients in both the groups (64.3 ± 3.08 vs 64.6 ± 2.98 Kgs; p=0.631).

Table 4. Surgical duration

Duration	Group A (n=60)		Group B (n=60)	
	Mean	**SD**	**Mean**	**SD**
Mean duration (Minutes)	76.1	10.09	73.5	10.05
t=1.499				p=0.150



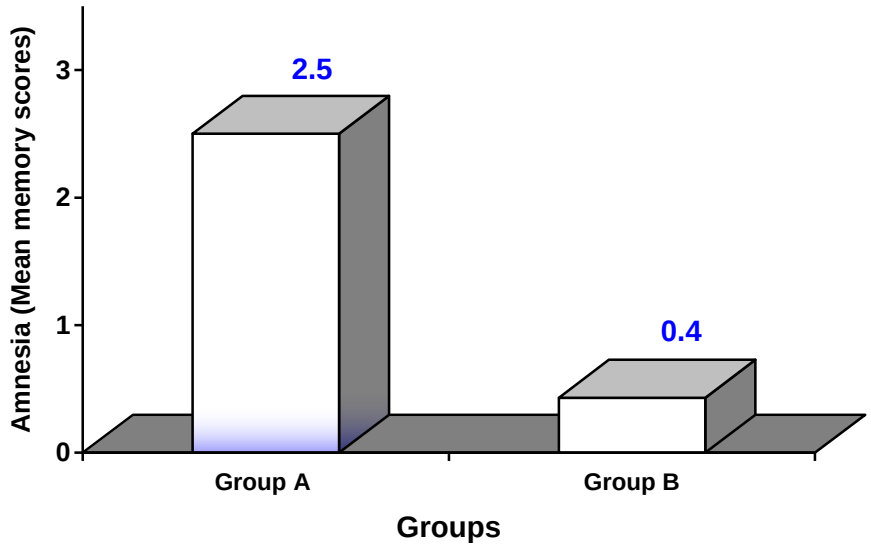
In the present study surgical durations did not differ significantly between the two groups (76.1 ± 10.09 vs 73.5 ± 10.05 minutes; p=0.150).

Table 5. Comparison of quality of amnesia between the two drugs (Memory score)

Amnesia	Group A (n=60)		Group B (n=60)	
	Mean	SD	Mean	SD
Mean Memory scores	2.50	0.70	0.25	0.43

p<0.0001 (Mann Whitney U test)

Graph 5. Comparison of quality of amnesia between the two drugs (Memory score)



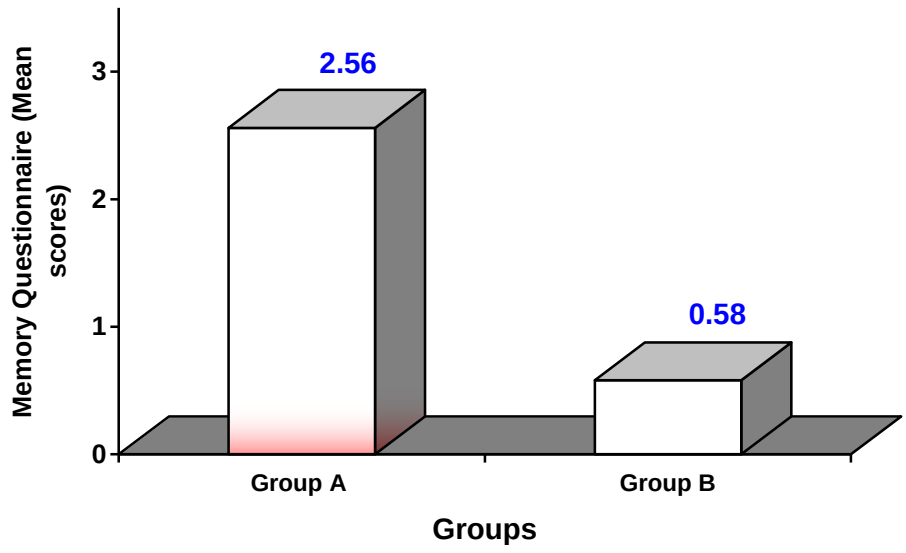
In this study, the visual component of memory using a modified Westmead PTA scale showed that, amnesia was significantly better with midazolam that is, a mean of 0.25 ± 0.43 when compared to alprazolam of 2.5 ± 0.70 (p<0.0001).

Table 6. Comparison of quality of amnesia between two groups (Memory questionnaire)

Amnesia	Group A (n=60)		Group B (n=60)	
	Mean	SD	Mean	SD
Mean Memory questionnaire scores	2.56	1.16	0.58	0.67

p<0.0001 (Mann Whitney U test)

Graph 6. Comparison of quality of amnesia between two groups (Memory questionnaire)



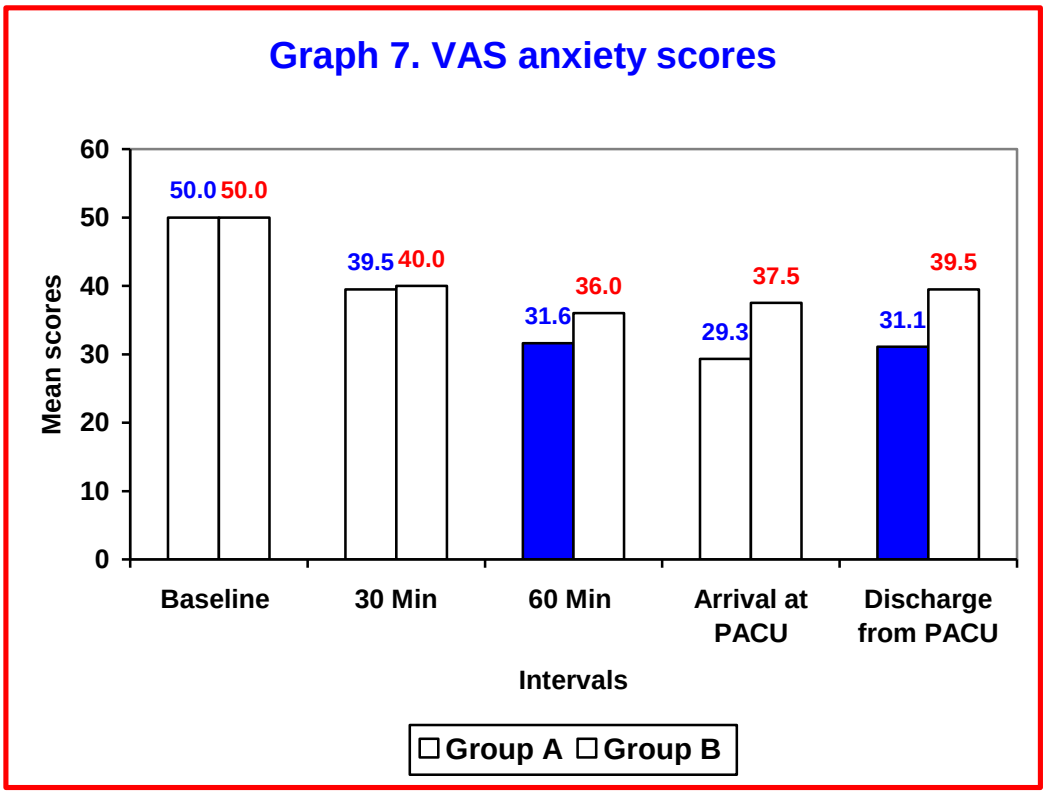
The memory questionnaire as answered by the subjects showed that midazolam provided better amnesia with a mean of 0.58 ± 0.67 when compared to alprazolam with a mean of 2.56 ± 1.16 (p<0.0001).

Table 7. VAS anxiety scores

Interval	Group A (n=60)		Group B (n=60)		'p' value*
	Mean	SD	Mean	SD	
Baseline	50.0	0.00	50.0	0.0	0.100
30 minutes	39.5	2.86	40.0	0.0	0.156
60 minutes	31.6	4.92	36.0	4.94	<0.0001
Arrival at PACU	29.3	6.07	37.5	4.73	<0.0001
Discharge from PACU	31.1	5.84	39.5	2.19	<0.0001

x^2=10.540 (with Yate's correction) p<0.0001

*Mann Whitney U test



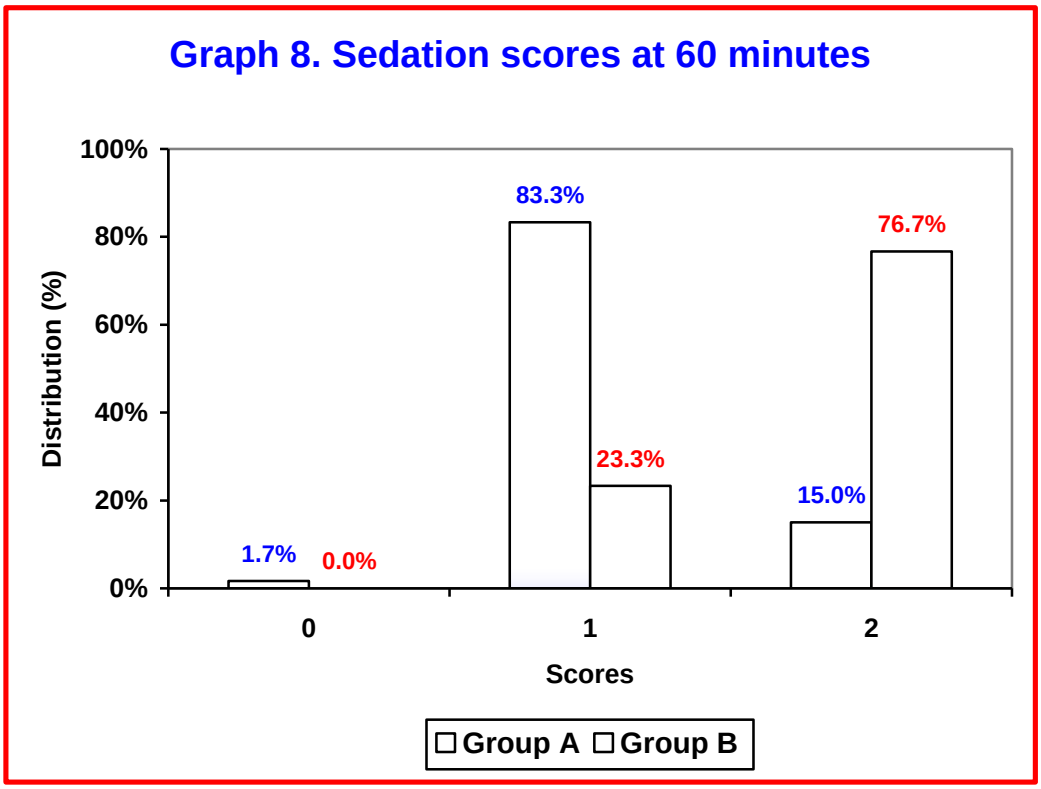
Anxiety was assessed by VAS. The drugs did not vary in there anxiolytic properties at 30 min after drug ingestion. However, at 60 minutes, the mean VAS score for alprazolam was significant less 31.6±4.92 when compared with midazolam of 36.0±4.94 ($p<0.0001$). The mean scores at arrival and discharge from PACU were significantly less that is, 29.3 ± 6.07 and 31.1 ± 5.84 for alprazolam when compared to 37.5 ± 4.73 and 39.5 ± 2.19 for midazolam respectively ($p<0.0001$).

All patients were alert before drug ingestion. At 30 minutes patients in both the groups had a sedation score of 1 implicating that they were arousable to voice.

Table 8. Sedation scores at 60 minutes

Scores	Group A (n=60)		Group B (n=60)	
	Number	Percentage	Number	Percentage
0	1	1.7	0	0.0
1	50	83.3	14	23.3
2	9	15.0	46	76.7
Total	**60**	**100**	**60**	**100**

x^2=45.502 p<0.0001

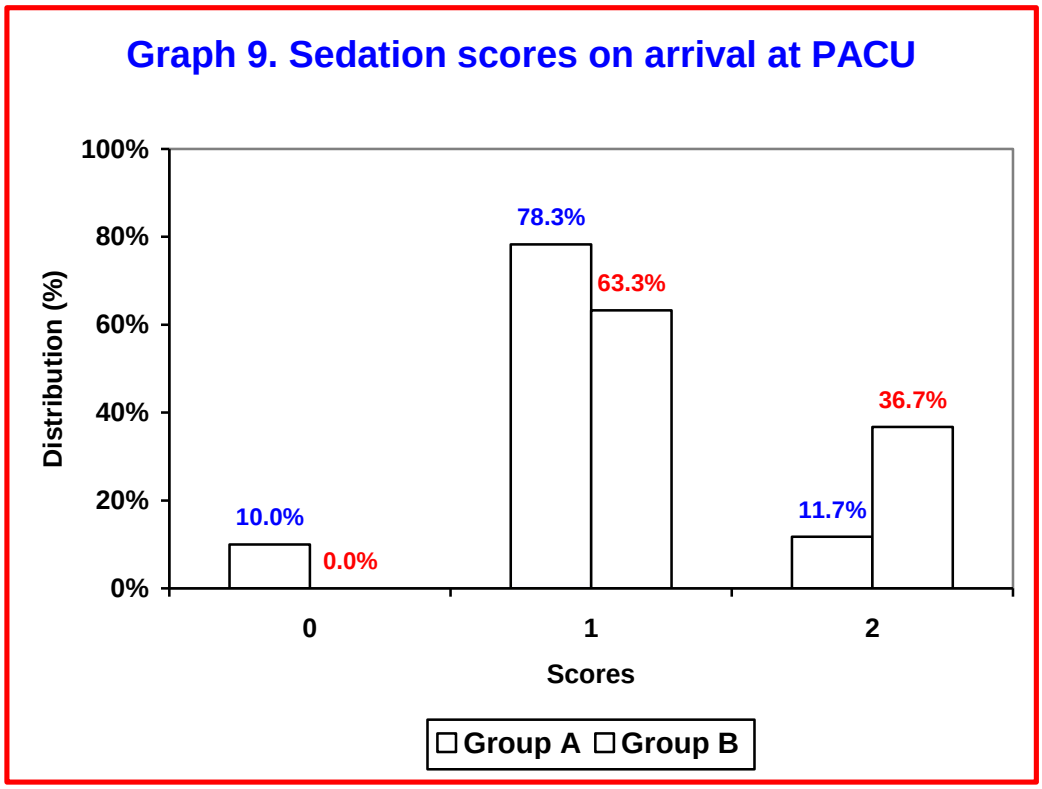


At 60 minutes, 83.3% of the patients in the alprazolam group were arousable to voice as compared to 76.7% of the patients in the midazolam group who were arousable to gentle stimulus with a sedation score of 2 and this difference between score was statistically significant (p<0.0001).

Table 9. Sedation scores on arrival at PACU

Scores	Group A (n=60)		Group B (n=60)	
	Number	**Percentage**	**Number**	**Percentage**
0	6	10.0	0	0.0
1	47	78.3	38	63.3
2	7	11.7	22	36.7
Total	**60**	**100**	**60**	**100**

x^2=14.712 p<0.001



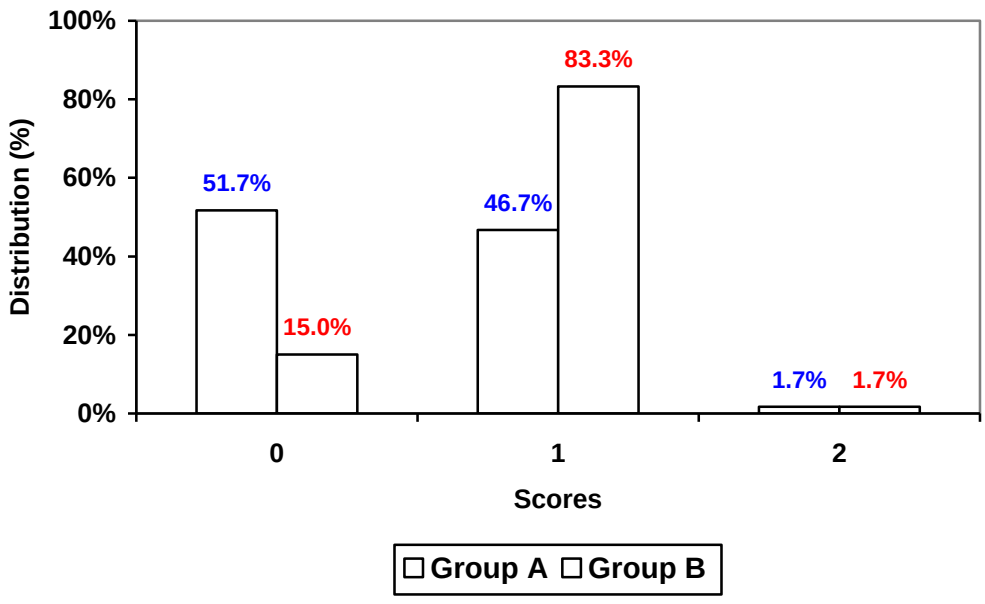
Upon arrival at PACU, 78.3% of patients in the alprazolam group had scores of 1 when compared to 63.3% of patients in the midazolam group with a score of 1 and this difference between score was statistically significant (p=0.001).

Table 10. Sedation scores on discharge from PACU

Scores	Group A (n=60)		Group B (n=60)	
	Number	**Percentage**	**Number**	**Percentage**
0	31	51.7	9	15.0
1	28	46.7	50	83.3
2	1	1.7	1	1.7
Total	**60**	**100**	**60**	**100**

x^2=18.305 p<0.0001

Graph 10. Sedation scores on discharge from PACU



Upon discharge from PACU, 51.7% of patients were alert in the alprazolam group when compared to 83.3 % of patients in the midazolam group who still had a sedation score of 1 and this difference between score was statistically significant ($p<0.0001$). However, 1.7% of the patients in both the groups were arousable to gentle tactile stimulation.

DISCUSSION

A one year randomized clinical trial was conducted comparing oral midazolam 7.5 mg and oral alprazoalm 0.5 mg for their amnestic, anxiolytic and sedative properties in 120 patients undergoing surgery under general anaesthesia.

This study demonstrates which drug out of these two that is, oral midazolam and alprazoalm, is better for perioperative amnesia,anxiolysis and sedation in patients undergoing surgery under general anaesthesia.

In our study, visual component of memory was tested using a modified Westmead PTA scale where in the patients had to recall 3 familiar pictures upon arrival at PACU which were shown to them before. The mean scores in the midazolam group were significantly less when compared to alprazolam group (0.25 vs 2.5; $p<0.0001$).

In our study, a memory questionnaire was also used to assess memory. A set of 4 questions were asked to assess the perioperative memory. The mean scores in the midazolam group were significantly less when compared to alprazolam group (0.58 vs 2.56; $p<0.0001$).

So, in our study, oral midazolam 7.5 mg produces significant amnesia when compared to alprazolam 0.5 mg in patients undergoing surgery under general anaesthesia. The amnesia with midazolam is anterograde as analyzed by Mann-whitney's U test with p values which are statistically significant.

Anterograde amnesia as a result of benzodiazepine use is a robust phenomenon that is well-described in the scientific literature.[12,47,48] Previous investigations that involved adults have shown that midazolam-induced amnesia is associated with a dose–response curve. Twersky *et al.*[12] compared a group of children premedicated using nasal midazolam with a group of children premedicated using nasal placebo. The midazolam group experienced a significant postoperative reduction in ability to recall and recognize cards shown subsequent to nasal midazolam administration (anterograde amnesia).

In a similar investigation, Payne *et al.*[48] demonstrated that midazolam administered orally resulted in a 60% incidence of amnesia, as compared with a 16% amnesia in a control group. Payne, *et al.*[48] also reported that the induction process was remembered by 50% of the children who received midazolam, compared with 81% of the control group.

In a double-blind, placebo-controlled, randomized trial, done by Jan et al, in the midazolam group, 33% could not recall the object shown at arrival in the OR or their time in the OR[16]. A comparable incidence of transient anterograde amnesia after 7.5 mg of midazolam has been observed previously[43,44]. A dose-response effect of midazolam on memory is suggested, because 15 mg of oral midazolam [43,44] and 0.1 mg/kg of IM midazolam [45] result in increased incidences of anterograde amnesia. In contrast, 0.5 mg of alprazolam did not induce amnesia in the studied patients. Even at a larger dose of 1.0 mg, no amnesic effect of alprazolam was noted [46]. Midazolam provides better amnesia when compared to alprazolam.

Anaesthesiologists may consider the administration of anxiety-reducing drugs unnecessary when anxiety levels are low in outpatients presenting for minor surgery, and most adults having ambulatory surgery are not premedicated[49] . Previous studies have shown that, up to 80% of outpatients expressed a preference for a combination of anxiety-reducing and hypnotic premedication before surgery.[50]

However, in our study, VAS was used to assess anxiety at 30min, 60min, at arrival and at discharge from PACU. At 60 minutes, the mean VAS scores for alprazolam were significantly less when compared to midazolam (31.6 vs 36; $p<0.0001$).

The mean VAS scores were significantly less upon arrival and discharge from PACU in the alprazolam group when compared to in the midazolam group ((29.3 and 31.1 vs 37.5 and 39.5; $p<0.0001$).

Our study clearly showed that, alprazolam is a better drug for anxiety than midazolam. The anxiolytic effect of alprazolam is significantly better at 60 minutes, upon arrival and discharge from PACU when compared to midazolam.

In a similar study conducted by Jan et al[16], Oral premedication with 0.5 mg of alprazolam decreased anxiety to the same extent as the reference drug, 7.5 mg of midazolam. Eighty percent of the patients judged alprazolam as an effective anxiety-reducing drug, a percentage that does not differ significantly from the midazolam group. In contrast, only 33% of the patients given placebo were satisfied with their premedication.

Benzodiazepines available in oral preparation have been used for premedication in adult patients. Preoperative discomfort and apprehension significantly decrease with benzodiazepine premedication. Oral midazolam (7.5 mg) does not produce significant sedation before surgery in comparison to placebo, other studies demonstrate a significant sedative effect (sleepy, but easily arousable). In a recent study of Brosius and Bannister, only 40% of patients treated with the large dose of 20 mg of midazolam exhibited detectable sedation, with marked interindividual variability in plasma midazolam levels. Detectable preoperative sedation was predictive of prolonged emergence.[37]

In our study, we used a 0 to 4 scale to assess sedation. The drugs differ in there sedative effects significantly at 60 min with 50% of the patients in the alprazolam group having a sedation score of 1 as against 46% of the patients in the midazolam group having a sedation score of 2.The Chi square test value of 45.502 with a p=0.000 shows a statistical significance.

Upon arrival at PACU, 47% of patients in the alprazolam group had a score of 1 as against 38% of the patients in the midazolam group with a score of 1. This difference was statistically significant ($p<0.0001$).

Upon discharge from PACU, 31% of the patients in the alprazolam group had a score of 0 as against 50% of the patients in the midazolam group with a score of 1. This difference was statistically significant ($p<0.0001$).

So, our study shows that midazolam is a better sedative than alprazolam. The drugs differ in there sedative effects significantly at 60 minutes, upon arrival at PACU and upon discharge from PACU with midazolam being a better

sedative. However, neither the extubation nor discharge were delayed because of sedative effects of midazolam.

CONCLUSION

In this Randomized Comparative Clinical trial between oral midazolam 7.5 mg and alprazolam 0.5 mg, conclude that midazolam has better amnestic effects with a mean memory score of 0.25 as against alprazolam of 2.5. It proved to be a better drug for amnesia even with a subject assessed memory questionnaire with a mean score of 0.58 as against 2.56 of the alprazolam group..Both the drugs are good anxiolytics. However, alprazolam is a superior anxiolytic than midazolam. Midazolam is a better sedative than alprazolam. Overall, oral midazolam 7.5mg is a better amnestic, anxiolytic and sedative drug for premedication in patients undergoing surgery under general anaesthesia.

SUMMARY

Oral midazolam at a dose of 7.5 mg and alprazolam at a dose of 0.5mg produces amnesia ,anxiolysis and sedation. However, there has been discrepancies regarding the amnestic properties of alprazolam. Some studies conclude both midazolam and alprazolam to be equally anxiolytic while others conclude alprazolam to be a better anxiolytic drug. Hence this study was undertaken to see which drug is better for anxiolysis,amnesia and sedation as a premedicant.

One hundred and twenty patients undergoing GA for surgeries were studied by dividing into two groups of sixty each that is, alprazolam and midazolam group. Amnesia was assessed using modified Westmead PTA scale and a memory questionnaire. Anxiety was assessed by a VAS (0 to 100 mm) scale. Sedation was assessed using a sedation scale (0 to 4).

Patients were randomized into two groups to receive oral alprazolam 0.5 mg and midazolam 7.5 mg 60 min before the surgery. A set of three familiar pictures were shown and was asked to recall upon arrival at PACU. A memory questionnaire was asked upon arrival at PACU. VAS and sedation scores were noted at 30 minutes, 60 minutes, upon arrival at PACU and upon discharge from PACU following a baseline reading.

Amnesia and sedation were significant with midazolam when compared to alprazolam. Both drugs gave a satisfactory anxiolysis. However, alprazolam was better an anxiolytic.

In conclusion, oral midazolam 7.5 mg given 60 minutes prior to surgery as a premedicant gives a satisfactory amnesia, anxiolysis and sedation in patients undergoing surgery under general anaesthesia.

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ANNEXURE I - CONSENT FORM

A study, "**A RANDOMISED CLINICAL TRIAL TO COMPARE THE AMNESTIC EFFECT FOLLOWING ORAL PREMEDICATION WITH MIDAZOLAM AND ALPRAZOLAM IN PATIENTS UNDERGOING SURGERY UNDER GENERAL ANAESTHESIA"** is being conducted by Dr. Nandish Kori M, Post Graduate in Anaesthesiology at J. N. Medical College Belgaum, Karnataka. Under guidance of Dr. C. S. Sanikop, Professor and Head, Department of Anaesthesiology, J. N. Medical College, Belgaum, KLE University, Belgaum.

Respected Sir/Madam _____ we request you to participate in our study as you are eligible to be included. During the study you will be asked questions regarding your present and past medical history and you are suppose to answer to the best of your knowledge.

Your participation in this study is voluntary. Your decision whether or, not, to participate in the study will not affect your relationship with Jawaharlal Nehru Medical College, Belgaum. If you decide to participate you are free to withdraw at any point of time. The purpose of the study is to compare anxiolysis and amnestic effect using oral premedication with alprazolam 0.5 mg and midazolam 7.5 mg

Procedure involved

If you agree to enroll yourself in this study, you will be interviewed regarding your present, past and family history then you will be clinically examined in detail and investigated accordingly. You will be sequentially

allocated either into study Group A or Group B , if you are in Group A, you will receive alprazolam 0.5 mg, if you belong to Group B you will receive midazolam 7.5 mg.

Benefits and Risks

The benefits of taking part in this study are that, midazolam and alprazolam reduces anxiety and reduces awareness with recall during GA. There are no observable risks associated with this study.

Privacy and Confidentiality

The only people to know that you are a research subject are members of the research team. No information about you or information provided by you during the research will be disclosed to other without your written permission except:

1. In emergency to protect your rights and welfare.
2. If required by law.

Authorization to publish results

When the results of research are published or discussed, in conference, no information will be displaced that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed with your permission.

Voluntary participation / Withdrawal

Taking part in the study is voluntary. You may choose not to enroll

yourself in this study. Your decision will not change present or future health care services offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Alternatives

Even if you decline the participation in the study, you will get the routine line of management.

Financial Incentives for participation

No financial incentives are being offered to enrolled patients. It is purely being done with the idea of research and all the cost of the study will be borne by the investigator.

Compensation

In the event of injury, related to the study, treatment will be made available at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. No reimbursement, compensation or free medical care will be given, by law. If you are injured, you may contact Dr. Nandish Kori M. at Department of Anaesthesiology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum or by Ph. No. 9986604776.

Queries/ Contact details

If you have any queries, in future or in case of study related injury or illness, you may contact. Dr. Nandish Kori M. at Department of Anaesthesiology,

KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum Ph No. 0831-2473777 or on mobile 9986604776 and Dr. C. S. Sanikop $_{MD}$ (Guide), Professor and Head, Dept. of Anaesthesiology, J. N. Medical College, KLE University, Belgaum 590 010 Ph No. 94488 63688.

If you have any queries about your rights as a study subject, you may call Dr. V. D. Patil, Principal and Chairman, J. N. Medical College Institutional Ethical Committee for Human Subjects Research, Ph. 0831-2473777 at J. N. Medical College, Belgaum.

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

I, Mr./ Mrs. _____

voluntarily agree to take part in this study, by signing this consent form I am not giving up my legal rights. I may withdraw at any time. I am signing after having read, or been read to me in the vernacular language including risks and the benefits and having all queries cleared.

_____ _____

Signature of the study patient Date

_____

Name of Study patient _____ Date

_____ _____

Signature of the legally authorized representative Date

_____

Relationship with the patient

_____ _____

Name and Signature of Witness Date

_____ _____

Signature of investigator/ designee obtaining Date

ANNEXURE II – PROFOMA

STUDY: "A RANDOMISED CLINICAL TRIAL TO COMPARE THE AMNESTIC EFFECT FOLLOWING ORAL PREMEDICATION WITH MIDAZOLAM AND ALPRAZOLAM IN PATIENTS UNDERGOING SURGERY UNDER GENERAL ANAESTHESIA"

Patient Name	:	I.P. No	:
Age	:	Weight	:
Height	:	Gender	:
Date of Operation	:	Occupation	:
Address	:	Anaesthesiologist	:

Preanaesthetic evaluation

Chief Complaints

Past History

a. HTN / DM / IHD

b. Any other -

Family history

General Physical Examination

Weight (Kg)	:	Temperature (^{0}F)	:	Pallor	:
Cyanosis	:	Pedal oedema	:	Clubbing:	
PR	:	BP	:	RR	:

Systemic examination

R.S. : CNS :

CVS : GIT :

Airway & Spine assessment :

Investigations

Hb% : Haematocrit :

Urine routine : Blood urea :

Serum Creatinine: Fasting blood sugar:

CXR : ECG :

Diagnosis :

Proposed Surgery :

Preoperative physical status: ASA Grade I II III IV V

Inclusion criteria

- Age between 18 to 50 years.
- ASA Grade I and II.
- Body weight 60 to 70 Kgs.
- Surgery lasting for 60 to 90 minutes.

Exclusion criteria

- Patients receiving sedatives, anticonvulsants.
- Allergy or contraindications to study drugs.
- Pregnancy.
- Endocrine and neuropsychiatric disease.

Procedure

After obtaining written informed consent and institutional ethical clearance, patients were randomly divided into two groups of each, Group A (alprazolam 0.5 mg) and Group B (midazolam 7.5 mg).

To receive the drugs orally 60 minutes before surgery with sips of water. Intravenous access will be obtained and slow infusion of crystalloids will be commenced. Monitoring will be consisting of ECG, NIBP, SPO_2. Prior to induction, all patients are pre oxygenated with 100% O_2 at 8 L/min using Bain's circuit for three minutes and premedicated with glycopyrrolate 0.005 mg/kg IV and fentanyl 2 µg/kg I.V. in both groups. A familiar object is shown to the patient just before induction of anesthesia.Induction will be with I.V. thiopentone 5 mg/kg. Loss of eyelash reflex will be considered for induction.Intubation will be facilitated with inj.vecuronium 0.1mg/kg. Anaesthesia will be maintained with O_2, N_2O 50:50% , vecuronium, ¼ the of LD and halothane 0.5% .

After the surgery,reversal will be done with glycopyrrolate 0.01mg/kg i.v and neostigmine 0.05mg/kg i.v.Spontaneous breathing will be allowed when patient is awake and extubated.

In PACU, Oxygen by ventimask (5 L/min) will be given. PACU discharge criteria will include;

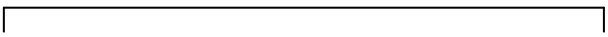
- Being awake.
- Oriented
- Able to breathe deeply, cough freely.
- BP within 20% of pre operation values.
- Minimal pain and no nausea.

Effect of the study drugs on amnesia will be assessed at the time of discharge from post anesthesia care unit. Effect of study drugs on anxiety and sedation level will be assessed five times.

- Baseline values.
- 30 minutes after drug intake.
- 60 minutes after drug intake.
- Arrival at PACU.
- At the time of discharge from PACU.

Amnesia is assessed using an abbreviated Westmead post-traumatic amnesia (PTA)scale wherein a patient is shown a set of familiar pictures before induction and asked to recollect after a period.Memory test is also performed using a questionnaire.The extent of sedation was correlated with anterograde amnesia as measured by event recall.Sedation will affect consciousness of current events and can be expected to impair memory processing.

Anxiety will be scored using 0 to 100 mm VAS by patients.



0 Completely relaxed, Calm.

100 mm Extreme Anxiety

Sedation was assessed on a five-point objective scale.[16] Sedation will be scored as below.

0	Alert
1	Arouses to voice
2	Arouses with gentle tactile stimulation
3	Arouses to vigourous stimulation
4	Lack of responsiveness.

Observations

Memory component of abbreviated westmead post-traumatic amnesia scale (A-WPTAS):

Can the patient remember the pictures showed to them ?(1 point for each picture remembered)

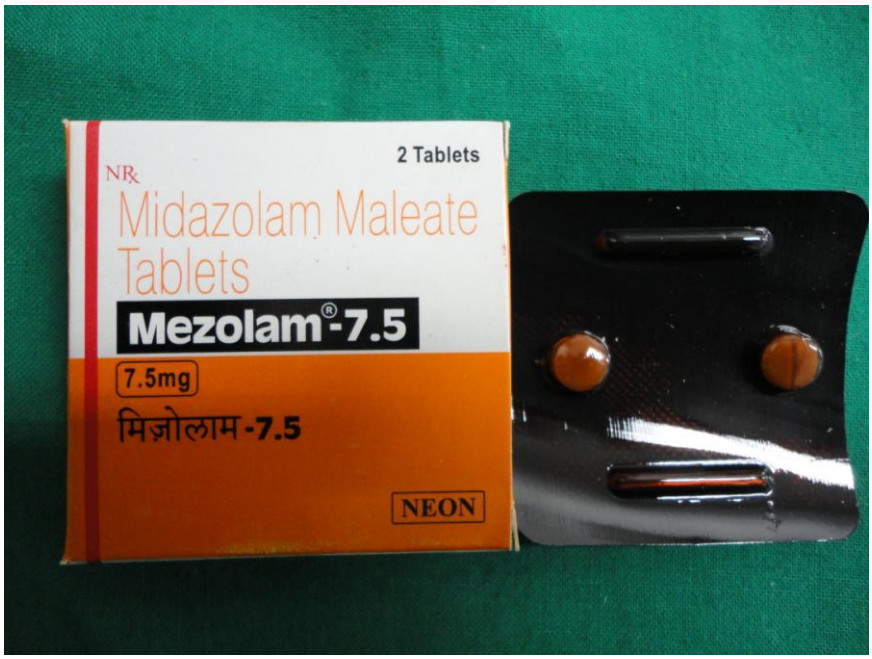
Recall of events during anaesthesia and surgery:Questionnaire.(1 point for recall)

1. What was the last thing you remember before you went to sleep?
2. What was the first thing you remember when you woke up?
3. Can you remember anything in between those two periods?
4. Did you dream during the operation?

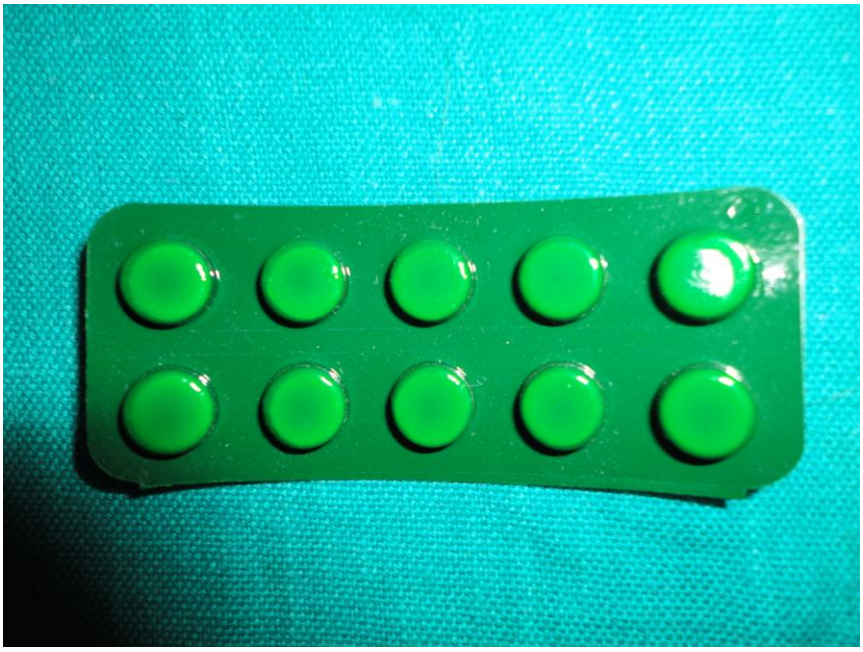
Sedation Scores	**Time Interval**				
	Baseline	**30 Min**	**60 Min**	**Arrival at PACU**	**Discharge from PACU**
0					
1					
2					
3					
4					

VAS Scores	**Time Interval**				
	Baseline	**30 Min**	**60 Min**	**Arrival at PACU**	**Discharge from PACU**
0-100 mm					

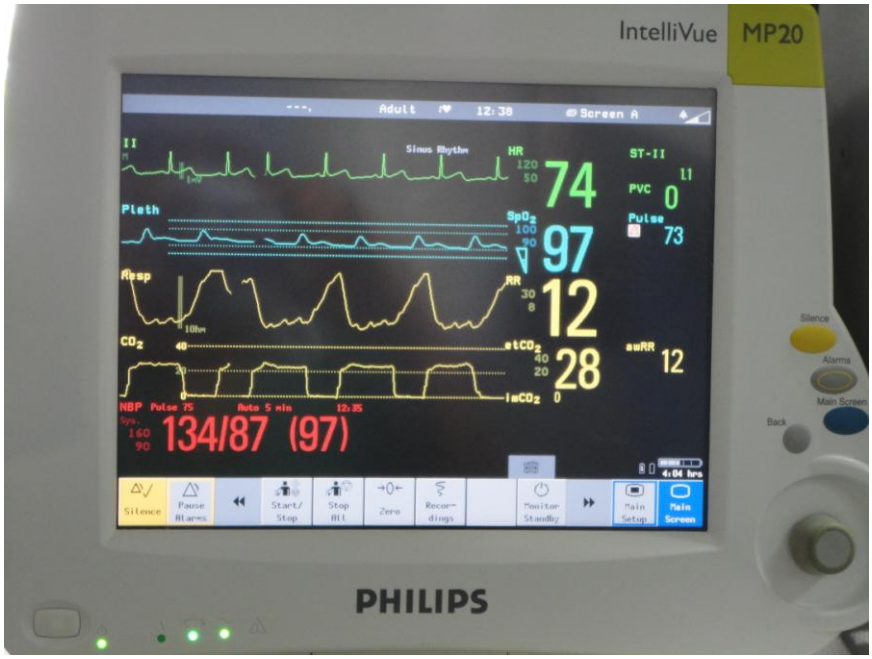
ANNEXURE III – PHOTOGRAPHS



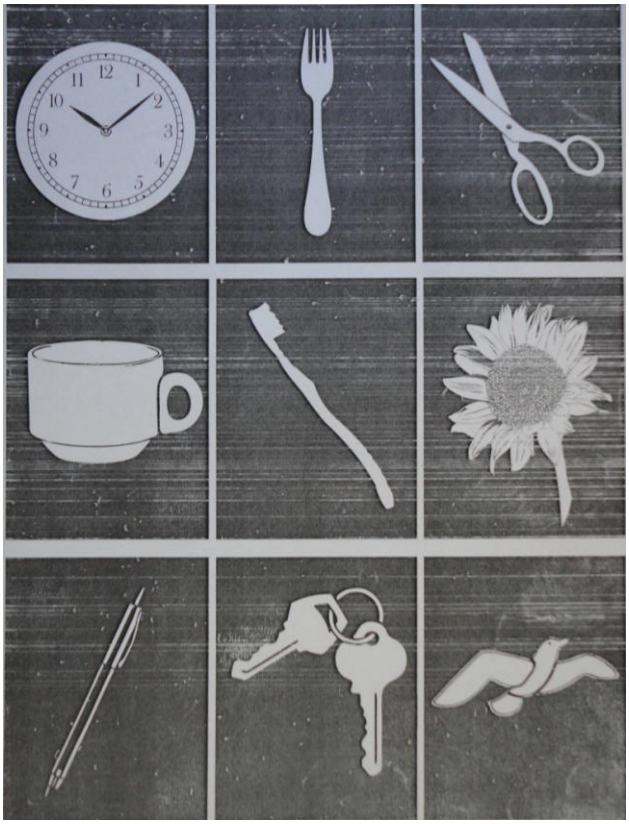
Photograph 1. Tablet Midazolam 7.5 mg



Photograph 2. Tablet Alprazolam 0.5 mg



Photograph 3. Monitoring during general anaesthesia



Picture 4. Target set of familiar pictures used for picture recognition

Photograph 5. Anaesthesia machine

MASTER CHART - GROUP A

Serial number	In Patient Number	Age (Years)	Sex	Weight (Kgs)	Type of Surgery	Duration of surgery (Min)	Memory score	memory questionnaire	VAS scores (mm)					Sedation scores				
									Baseline	30 Min	60 Min	Arrival at PACU	Discharge from PACU	Baseline	30 Min	60 Min	Arrival at PACU	Discharge from PACU
1	391739	45	F	63	laparoscopic appendicectomy	80	3	3	50	40	30	30	30	0	1	1	1	0
2	392098	48	M	68	reduction of fracture radius	70	2	3	50	40	40	40	40	0	1	1	1	0
3	390530	35	M	65	wound debridement and grafting	60	3	4	50	40	30	30	30	0	1	2	1	1
4	391762	47	F	60	fibroadenoma excission	70	3	3	50	40	30	30	30	0	1	1	1	0
5	363284	27	F	64	laparoscopic appendicectomy	70	3	3	50	40	30	20	20	0	1	1	1	0
6	366246	50	M	64	exploratory laparotomy	90	1	1	50	40	30	40	40	0	1	1	1	1
7	360063	32	M	64	debridement of thermal burns	80	2	0	50	40	40	30	40	0	1	1	1	1
8	361887	28	M	62	laparoscopic appendicectomy	70	3	4	50	40	30	30	20	0	1	1	1	0
9	361530	38	M	70	laparoscopic cholecystectomy	80	2	3	50	40	20	20	30	0	1	1	1	0
10	361815	19	F	66	laparoscopic appendicectomy	70	3	3	50	40	40	40	40	0	1	1	1	1
11	361405	50	M	62	duodenoscopy and proceed	60	3	4	50	40	30	30	30	0	1	1	1	0
12	361323	50	M	62	laparoscopic appendicectomy	80	3	3	50	40	30	20	20	0	1	1	0	0
13	362512	50	M	61	open excision of prostate	90	3	3	50	40	40	30	30	0	1	1	0	0
14	368810	30	F	62	debridement of fascitis	60	3	3	50	40	30	30	30	0	1	1	1	1
15	368890	38	M	62	laparoscopy proceed for pain abdomen	70	3	3	50	40	30	20	30	0	1	1	1	0
16	368893	20	F	68	fibroadenoma excission	60	2	3	50	40	40	30	30	0	1	1	1	0
17	368084	45	M	64	Open cholecystectomy	90	3	3	50	40	30	20	30	0	1	1	1	1
18	367887	40	F	69	laparoscopic appendicectomy	70	3	4	50	40	30	20	30	0	1	1	1	1
19	392054	38	F	68	closed reduction of forearm bones	80	3	3	50	40	30	30	30	0	1	1	1	0
20	356339	49	M	62	decompression T12 vertebra	90	3	1	50	40	30	20	20	0	1	1	0	0
21	355609	27	M	61	open reduction, fracture ulna	70	3	4	50	20	20	20	30	0	1	1	0	0
22	357427	45	M	62	K wire fixation of ulna	80	3	4	50	30	20	20	20	0	1	1	1	0
23	354976	40	M	69	decompression T11 vertebra	90	3	4	50	40	30	30	30	0	1	1	0	0
24	355309	50	M	69	decompression of vertebra	90	2	4	50	40	30	40	40	0	1	2	2	1
25	357164	48	M	66	ORIF for fracture ZMC	60	2	2	50	40	30	20	30	0	1	0	0	0
26	359014	45	F	64	appandicectomy	90	3	3	50	40	30	20	20	0	1	1	1	1
27	389565	42	M	64	osteomylitis ulna for debridement	60	3	3	50	40	30	30	30	0	1	1	1	0
28	389910	38	M	68	grafting of left hand	80	3	4	50	40	30	30	30	0	1	1	1	0
29	391133	38	M	64	laparotomy proceed	90	3	3	50	40	30	30	30	0	1	1	1	0
30	391386	35	M	68	endoscopy for ethmoidal polyp	90	3	3	50	40	30	30	30	0	1	1	2	1
31	391396	22		62	laparoscopic appendicectomy	90	2	3	50	40	40	40	40	0	1	2	1	1
32	391389	36	F	68	breast lump excision	70	3	3	50	40	30	30	30	0	1	1	1	0
33	383102	35	M	70	K wire fixation of ulna	80	3	3	50	40	30	30	30	0	1	1	1	0
34	383315	38	M	68	reduction of fracture humerus	80	2	3	50	40	30	30	40	0	1	1	1	1
35	383204	24	F	62	laparoscopic appendicectomy	70	3	3	50	40	40	30	30	0	1	1	1	0
36	363405	50	M	63	endoscopy of shoulder joint	90	3	3	50	40	30	30	40	0	1	1	1	0
37	360281	23	M	62	laparoscopic appendicectomy	80	2	1	50	40	30	40	30	0	1	1	1	1
38	382289	35	F	63	skin grafting upon thigh	80	3	3	50	40	30	30	40	0	1	1	1	1
39	382014	35	F	66	cholecystectomy	90	3	3	50	40	30	30	30	0	1	1	1	1
40	368092	33	M	61	laparoscopic appendicectomy	80	3	2	50	40	30	30	30	0	1	1	1	0
41	362598	43	F	62	laparoscopic appendicectomy	80	3	4	50	40	30	30	30	0	1	1	1	1
42	362564	28	F	61	laparoscopic appendicectomy	80	2	3	50	40	30	30	20	0	1	1	1	0
43	362507	40	F	68	incisional hernia repair	80	2	2	50	40	40	30	30	0	1	1	1	1
44	377949	38	M	63	lipoma excision	70	3	3	50	40	30	30	30	0	1	1	1	0
45	358738	30	F	64	skin grafting of forearm	70	3	3	50	40	30	30	30	0	1	1	1	0
46	377443	21	F	68	fibroadenoma excision	60	1	1	50	40	30	30	40	0	1	2	1	1
47	378785	46	M	68	lipoma excision	70	3	3	50	40	30	20	30	0	1	1	1	0
48	381159	45	M	62	external fixation of ulna	80	3	2	50	40	30	30	30	0	1	1	1	1
49	380659	21	F	61	reduction of fracture humerus	80	3	3	50	40	30	30	30	0	1	1	1	1
50	380815	22	F	62	excision of cervical lymphnodes	60	2	3	50	40	30	30	30	0	1	1	1	0
51	380960	26	M	70	corneal tear suturing	80	1	1	50	40	30	40	40	0	1	2	2	1
52	380718	21	F	62	excision of cervical lymphnodes	60	3	3	50	40	40	30	30	0	1	1	1	1
53	380148	38	F	60	scalp swelling excision	70	1	0	50	40	30	40	40	0	1	1	1	0
54	377473	21	F	60	laparoscopic appendicectomy	70	2	0	50	40	40	30	30	0	1	2	2	1
55	377351	35	F	63	open reduction of fracture humerus	90	1	1	50	40	30	30	30	0	1	2	2	1
56	380722	50	M	61	grafting of left hand	70	1	1	50	40	30	20	30	0	1	1	1	1
57	356972	32	M	70	laparoscopic cholecystectomy	80	2	0	50	40	40	30	40	0	1	2	2	2
58	365711	18	F	62	rhinoplasty	60	1	1	50	40	30	30	30	0	1	1	1	1
59	360063	32	M	62	grafting of electrical burns	80	2	0	50	40	40	30	40	0	1	1	1	1
60	364897	33	F	66	excision of thyroid nodule	80	2	2	50	40	40	40	30	0	1	2	2	1

ANNEXURE IV – KEY TO MASTER CHART

Kg	-	Kilogram
Min	-	Minutes
VAS	-	Visual analog scale
mm	-	Millimeter
PACU	-	Post anaesthesia care unit
M	-	Male
F	-	Female