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Original Research Article

Comparison of Amnesia Produced with Commonly Used Sedative Drugs - A Randomized Study

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Author's Contribution:
MG- Concept and design of the study, aims and objectives **PJ**- prepared the first Draft of manuscript, arranged all the references, developing consent form and this is his own dissertation work; **VC** – Contribute regarding conception or design of study, data collection, interpreted the results and manuscript preparation; **KK**-Coordination, guidance and revision of manuscript **AA**- Coordination, statistical analysis and interpretation and revision of manuscript and article submission

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Abstract
Aims and Objectives: Evaluate the sedative and amnestic drugs in conscious sedation and determine the duration and extent of amnesia, to investigate duration and extend of retrograde amnesia and anterograde amnesia, and, to determine strategies to reduce intra-operative awareness.
Methods: The patients were randomly allocated to receive either Propofol, Midazolam or Ketamine via a continuous infusion in order to achieve a level of sedation (score 4: Ramsay Sedation Scale). Five minutes after the initiation of the sedative infusion, a subarachnoid block was instituted, in order to achieve an adequate block for the proposed surgery.5 minutes prior to receiving the sedative infusion, each patient was shown a picture of a commonly occurring object to assess the possibility of retrograde amnesia. Two more pictures were shown after they reached a sedation score of 4. At the end of the sedative infusion, a fourth picture was shown to the patient.30 minutes after commencing the sedative infusion, a sequence of 5 commonly used words were formed into a sentence and told to the patient, close to her/his ear, by a single observer.
Results: The hemodynamic parameters were more stable in the Ketamine group as compared to the Midazolam or Propofol groups (P=0.00). Ketamine group had the maximum number of patients who could not recognize the anesthetist (P=0.003) or the 1st picture (P=0.005), which was suggestive of retrograde amnesia. As the depth of sedation increased significant amnesia was present for Midazolam group and Propofol group.The hinted recall was

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maximum in Ketamine group and least in Midazolam group (P=0.00) for both visual and auditory information.

KeyWords: Propofol, Ketamine, Midazolam, Amnesia, Retrograde, PTSD, Memory, Recall

1. Introduction:

Amnesia is a crucial component of anesthesia, be it either in general or regional anesthesia. It is known that post-traumatic neurosis caused by intra-operative cognition during general anesthesia is more likely after awareness than when there is no explicit recall. With conscious sedation, only some of the centers in the medullary reticular formation and thalamus are depressed in a dose-dependent manner.[1] Thus, this level of sedation additionally provides the benefit of preservation of protective airway reflexes, especially in monitored anesthesia care.
The objective of this study was to compare popularly used sedative drugs, Propofol, Midazolam and Ketamine given in equi-sedative continuous intravenous infusions; i.e till patients reach a score of '4' of the Ramsay Sedation Scale, for their sedative, amnestic, hemodynamic & recovery characteristics.
The primary objectives were to study the extent of amnesia following the administration of the three amnestic agents and to investigate duration and extent of retrograde amnesia and anterograde amnesia.
The other objectives of this study were to investigate the level of patient satisfaction with the sedative amnestic agent and the time to recovery with the three sedative drugs. The estimation of the incidence of untoward events with each sedative drug was also carried out. With this study, we aim to determine strategies to reduce intra-operative awareness (prevent explicit recall).

2. Materials and Methods

Study design:
This was a prospective, randomized study and was carried out following approval from the institutional ethics committee. The study began after an application to register the trial with CTRI was made. The patients were randomized by using computer-generated random numbers, using an online randomization website. The Study was carried out in the Maharaja Yeshwantrao Holkar Hospital, Indore from April 2015 to August 2016.
There were 50 patients in each group. Thus the study had a total sample size of 150 patients with 50 patients in each of three groups.
The Inclusion criteria for the patients to be involved in the study was i) ASA grade 1 & 2 patients ii)Aged between 18 to 60 years of age iii) Weighing 40 to 80 kilograms iv) Both the genders v)Scheduled for either elective lower limb or lower abdominal surgical procedures, which were anticipated to complete within 2 hours.

The patients who met the following criteria were excluded: i).Patients with a history of allergic reaction to the study drugs ii).Those with significant cardiac, pulmonary, hepatic or renal dysfunction iii). Patients with a history of psychiatric illness iv).Obese patients (BMI> 30 kg/m^2) v). Hypertensive patients vi). Patients with head injury vii) Those with a history of chronic use of sedative drugs, full stomach patients, pregnant patients and epileptic patients.

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Sample Size Estimation & Statistical analysis

The sample size estimation was guided by previous studies.[5,6,15,20] By selecting the level of significance at 5% with a power of 0.84, the sample size per group was calculated to be 38 patients per group. Keeping the possibility of non-normality, the size was further increased to a total of 50 patients per group. The calculations were made with a type I error of 0.05 and a type II error of 0.2. The statistical tests used were Chi-Square Test ($\chi 2$), ANOVA and Tukey Test or Fisher's exact test as appropriate. Associations were measured using Spearman rank correlation (ρ). All analyses were done with SPSS for Windows V11.1. A two-sided P value <0.05 was considered statistically significant.

Methods:

Sedative pre-medication was not given to avoid interference with results. Every patient was pre-medicated with injection glycopyrrolate and injection ondansetron as per our hospital protocol. The patients were initially assessed pre-operatively, where along with the general and systemic examination, baseline measurements of heart rate, mean arterial pressure by a non-invasive sphygmomanometer, pulse oximetry, respiratory rate were made by a single observer.

The patients were blinded to the study drug whereas the anesthetist was not blinded.

If the patients met the inclusion criteria, they were randomly allocated by using a sequence generated by an online randomization website to receive either Propofol 2 mg/ml or Midazolam 0.2 mg/ml or Ketamine 1 mg/ml in 5% dextrose in a 50 ml syringe through a syringe pump. Propofol was initially started at an infusion rate of 4mg/kg/hr and Midazolam started at an initial infusion rate of 0.5mg/kg/hr, Ketamine too was started at an initial infusion rate of 0.5 mg/kg/hr in order to achieve a desired level of sedation of score 4 on the Ramsay Sedation Scale. The time required in minutes to achieve score 4 was noted in each case by a single observer. The infusion rates could later be lowered or raised in order to maintain sedation score 4. Five minutes after the initiation of sedative infusion, a sub-arachnoid block was instituted in the lateral position via a 23 or 25 gauge spinal needle by injecting a sufficient dose of Bupivacaine 0.5% (heavy) (mean dose 15mg±2.5mg) in order to achieve an adequate sensory block for the proposed surgery. Heart rate, mean arterial pressure, was recorded initially at 5-minute intervals for 10 minutes and later at 10-minute intervals till the end of the procedure. All patients were given supplemental oxygen via venturi mask at 4 liters/minute.

Visual Task of Recall of Pictures

5 minutes prior to receiving the sedative infusion, each patient was shown a picture of a commonly occurring object (e.g. Train, dog, tree etc.) to assess the possibility of retrograde amnesia (Called picture 1).The next picture was shown to the patients after they reached a sedation score of 4 (Called picture 2). Around 30 minutes after showing the picture 2, another picture (picture 3), different from the first two pictures, was shown to the patient, for assessing intra-operative recall. Similarly, at the end of the sedative infusion, a fourth picture (picture 4) different from the first three pictures was shown to the patient. Each picture was shown to the patient for at least 30 seconds, during which time the patient was prompted to describe all details he or she sees in the picture.This was done in order to help the patient better remember the pictures shown to them.

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Verbal Task of Recall of Words

30 minutes after commencing the sedative infusion, in order to assess intra-operative recall for auditory stimuli, a sequence of 5 commonly used words were formed into a sentence and told to the patient, close to her/his ear, by a single observer. The 5 worded sentence was repeated twice with a pause of 10 seconds between them.
The verbal task of repeating words was generally more complex than describing pictures for most of the patients. It was therefore not feasible to repeat this as frequently as the pictures.
The sedative infusions were stopped 15 minutes prior to the end of surgery. The total drug used was calculated in milligrams. In the immediate postoperative period, the time taken by the patient to achieve sedation score 2, was recorded as recovery time. Postoperative side effects, if any, such as nausea, vomiting, confusion, delirium, etc.. were noted and treated symptomatically. Nausea and vomiting were treated with ondansetron. For the patients showing signs of confusion or delirium, the infusion was stopped immediately. 4 hours postoperatively, the patients were asked to recall the preoperative and intra-operative pictures and words shown or spoken to him or her.
If they were unable to recall the pictures or words (I.e free recall), the patients were presented with cues, such as words or phrases, to aid recall of previously experienced stimuli.(I.e Hinted recall)

3. Results

Table 1: Recall of all parameters

Recall	Ketamine	midazolam	Propofol	Pearsons chi square test	Asymp. Sig. (2-sided)
Spinal Needle Insertion	78.00%	74.00%	68.00%	1.295	0.523
Anesthetist	70.00%	80.00%	96.00%	11.653	0.003
Picture 1	80.00%	88.00%	100.00%	10.634	0.005
Picture 2	46.00%	18.00%	16.00%	14.386	0.001
Picture 3	34.00%	14.00%	10.00%	10.601	0.001
Picture 4	34.00%	0.00%	34.00%	21.983	0.000

Table 2: Recall on showing a mix of pictures (Hinted Recall)

		Group name		
		Ketamine	Midazolam	Propofol
Recall on showing a mix of pictures	No picture recall	0	2	0
	One picture recall	1	23	14
	Two picture recall	11	18	6
	Three picture recall	14	3	19
	Four picture recall	24	4	11
Total	Count	50	50	50

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Table 3: Side Effects

Side Effects	PG	MG	KG
None	54%	40%	64%
Hypotension	46%	42%	12%
Shivering	0%	10%	18%
Oversedation	0%	12%	0
Bradycardia	12%	0%	0
Hallucination	0%	0%	4%

Patients were distributed equally across the groups in terms of Age and Sex. The duration of the Surgeries was comparable across the three groups as was Duration of Infusion (mean:102 minutes ± 37.8 minutes). There was no statistically significant difference among the duration of infusion for the various groups The patients were comparable across the three groups in all foreseeable confounding factors.

The patients in all three groups were distributed randomly. The mean age for Propofol group was 36.12 and for the Ketamine group was 38.70 while patients in the Midazolam group had a mean of 37.76. The mean of all the 150 patients was 37.53 ± 11.91. By using the ANOVA test 'P' value was calculated to be .551 which was not significant. There was no significant difference amongst the groups as calculated by the Tukey test.

The sex distribution amongst the groups was insignificant, although overall the number of males in the study outnumbered the number of females. Males were 101 and females 49 out of total 150 patients. The Chi-Square test was used to evaluate the distribution. The 'P' value was .674 which was not significant.

HEMODYNAMIC VARIABILITY

The pulse rate showed no significant variation across the three groups throughout, however, the blood pressure showed a statistically significant difference by 30 minutes with Ketamine group having the highest mean blood pressure across the three groups as calculated by application of the ANOVA test (P = 0.000; mean BP 87.54mmHg ± 12.30mmHg). This was even seen at 90 minutes.(P=0.000 mean BP 89.12mmHg ± 9.5mmHg).

SEDATION SCORE

The sedation score was assessed at 5,10,30,60 and 90 minutes after starting the infusions. The score at 5 minutes was statistically significant with maximum sedation being for the Midazolam group and least for Propofol group (P-value = 0.05).The sedation score 10 minutes after starting the infusions was statistically significant with maximum sedation being for the Midazolam group and least for Ketamine Group. (P-value = 0.00). At 30 minutes too sedation was maximum for Midazolam and least for Ketamine group (P value=0.003).The sedation score at 60 and 90 minutes was statistically insignificant with no major difference in sedation score between the three groups.

This progression of sedation score was reflected in time to reach sedation score 4.The average time to reach a Ramsay Score 4 was the least in the Midazolam group (20±7.2 minutes) and maximum in Ketamine group (30±16.31 minutes). This difference was highly significant statistically (P=0.000). The average time to recover to score 2 was the least in Propofol group, 19 ± 7.22 minutes (P=0.001).The Midazolam group and Ketamine Group showed similar times to recovery at close to 32±16.5 minutes for Midazolam and 32.2±11.2 minutes for Ketamine.(P=0.996)

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RECOGNITION OF ANAESTHETIST

The percentage of patients successfully recognizing the anesthetist was most with Propofol group, only 4% of the patients in propofol group could not recognize the anesthetist. Ketamine Group had the most patients who could not recall seeing the anesthetist before (P-value of 0.003). Midazolam too had a significant degree of amnesia with 20% patients being unable to recognize the anesthetist (P Value = 0.05). (Table 1)

There was no significant difference in recall of insertion of the spinal needle among the three groups.

RECALL OF PICTURE 1 (Shown before starting the infusion)

A significant number of patients in the Ketamine group (20%) were unable to recall the picture (Picture 1) that was shown to them immediately before the infusion was started (P-value =0.005).12% of Midazolam group were unable to recall this picture. Whereas all in Propofol group could recall this picture. This was highly significant(P-value =0.005). (Table 1)

RECALL OF PICTURE 2

A significant number of patients in the Midazolam Group (84%) were unable to recall the picture (Picture 2) that was shown to them immediately after they reached a sedation score 4. 82% patients in Propofol Group couldn't recall the picture. However, the number in Ketamine group was only 54% and this difference was statistically significant. (P-value = 0.001).(Table 1)

RECALL OF PICTURE 3

A significant number of patients in the Propofol group(90%) and the Midazolam group (86%) were unable to recall the picture 3, whereas only 66% of the patients in the Ketamine group were unable to recall this picture. (P value= 0.005). (Table 1)

RECALL OF PICTURE 4

Immediately after stopping the infusion showed the highest amnesia was observed in the Midazolam group achieving a 100% amnesia, whereas the Propofol group and Midazolam group had comparable amnesia at 66% each. (P-value = 0.000).(Table 1)

RECALL OF SPOKEN WORDS

The difference was significant statistically with 96% patients in the Midazolam group being unable to recall even one word out of the five as compared to 66% for ketamine and 82% for propofol. No patients in any of the groups could recall all the five words. A total of 34% patients in Ketamine group had some recall while it was only 18% in the Propofol group and 4% in the Midazolam group. This difference was statistically significant with a P-value of 0.001.

RECALL OF PICTURES ON SHOWING A SET OF PICTURES.(Cued Recall)

Patients in the Ketamine group had the maximum recall among the groups with 48% patients correctly identifying all 4 pictures, whereas only 8% recalled all 4 pictures in the Midazolam group and 22% in the Propofol group. This difference was statistically significant with a P-value of 0.00.

(Table 2)

RECALL ON REPEATING A MIX OF WORDS.

The patients in the Midazolam group had the highest degree of amnesia for spoken words with 90% of them being unable to recall even a single word, and none could recall all 5. Whereas in Ketamine group and Propofol group 4% (P-value = 0.000) and 14 % (P =0.001) respectively were able to recall all 5 words. Ketamine Group overall had the highest rate of recall among the three groups and Midazolam group had the lowest. This was statistically significant with a calculated p-value of 0.000.

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SIDE EFFECTS

The side effects observed in the study were peculiar to each group. Although hypotension was most common, especially in the Propofol group and Midazolam group. Ketamine had the least number of side effects overall, although 2 patients had minor hallucinations.

Over-sedation for a prolonged time which required stopping the infusion was a problem in the Midazolam group. (Table 3)

PATIENT SATISFACTION

There was no statistically significant difference in patient satisfaction across the three groups.

COST OF TREATMENT

The average amount of Ketamine used was 60 mg/hr, Midazolam was 5.78 mg/hr and Propofol was 210mg/hr. This meant that sedation with Ketamine cost much less than sedation with the other two agents.

4. Discussion

Amnesia is a topic of great interest as even some sensory perception during general anesthesia can lead to a post-traumatic stress disorder. It obviously is better to completely prevent the perception of all the senses, but it is usually not always possible. Some patients are hemodynamically unstable and can tolerate only a lower dose of anesthetics thus are susceptible to awareness and a traumatic memory. Others usually have some awareness towards the end of the surgery when the plane of anesthesia is deliberately lowered. Therefore amnesia becomes an essential component of anesthesia, regional or general.

Consciousness is a continuum state. On one end is full awareness and at the other lies complete oblivion. It is around the middle of this continuum of consciousness that presents with the most vexing theoretical and standard questions about intra-operative awareness.

A patient who is under a sedative during surgery can have some level of awareness but might not retain a memory of it. The influence of the combination of an epidural or spinal anesthesia with a sedative drug, on the ability to remember is unclear and debatable. It is well documented that negative stimuli can be better remembered in comparison to pleasant ones. This is due to the hormonal changes after a stimulus that affects the amygdala, which in turn affects the ability to remember and recall events[2]. Spinal or epidural anesthesia, and possibly other drugs such as dexmedetomidine, blunt the hormonal responses to noxious stimuli and diminish the influences of the amygdala on memory formation[3].

The percentage of patients who recognized the anesthetist was most with Propofol group while Ketamine Group had the most patients who could not recall seeing the anesthetist before (30% P-Value = 0.003). Midazolam group too had a significant degree of amnesia with 20% (P=0.005) patients being unable to recognize the anesthetist. This is an interesting result as every patient saw and spoke to the anesthetist for at-least 5- 10 minutes before the sedative infusions were started. Thus this could signify that the drugs Ketamine and Midazolam could interfere with the formation of long-term memory or more likely interfere with the recall of events that occurred even before the drugs were administered, at least partially.

Positron emission tomography (PET) studies carried out in humans showed that the encoding as well as retrieval of memory is highly organized within the brain and is region specific. The location and time recall have a mid-brain and left brain foci. For item retrieval, the foci is localized to the right inferior frontal lobe and right anterolateral temporal lobe[4]. The encoding for facial recognition is located in the right hippocampal region. PET studies that evaluated the regional cerebral blood flow (rCBF) in patients, who were sedated with Propofol

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demonstrated a dose-dependent reduction of rCBF in the right frontal lobe as compared in patients who were sedated with thiopental[5,6]. However, temporal lobe blood flow is not significantly reduced at Propofol doses consistent with light sedation[7]. These changes in regional blood flow occurred despite a relative preservation of systemic and cerebral perfusion pressure[8].This could possibly explain the findings of the Propofol group, which had no amnesia for facial recognition, before starting the infusion. Other two drugs most likely interfered with Long-Term Potentiation of the memory of seeing the anesthetist. This was again evident with the recall of picture 1, that was shown just before the infusions were started.

In the Ketamine group, 20% (P-value = 0.005) of the patients were unable to recall the picture that was shown to them immediately before the infusion was started. Whereas all the patients in the Propofol group could recall this picture. Patients in the midazolam also had significant amnesia of picture one (P-value = 0.01). This is suggestive of the existence of an amnesia extending up to a maximum of 10 minutes prior to starting the infusions.

This was supported by a recent study by Liu et al, where they hypothesized that the glycogen synthase kinase (GSK) 3β/β-catenin signaling may play a role in ketamine-induced retrograde amnesia[9].A number of Studies have shown that post-training administration of NMDA antagonists can disrupt retention or consolidation when administered after the acquisition of information (Packard and Teather, 1997; Santini et al., 2001; McDonald et al., 2005)[10-12].

The amnesia for spoken words has been investigated by a variety of word recognition tasks. They have also been used to investigate the phenomenon of indirect memory during anesthesia.The results of many of these studies have been conflicting, showing both positive and negative results[13-16].

In this study both the cued recall of, pictures and words showed that cued recall is highest in the Ketamine group. This hints that Ketamine probably interferes with recall and possibly less with the memory formation.This was supported by a study in 2008 by Chrobak and colleagues[17].They indicated that Ketamine can influence the memory function across various stages, which include encoding, consolidation, and retention of new information. This is through influences on various receptors, ion channels, enzymes, and intracellular signaling systems. They showed that low dose of Ketamine impaired the encoding of "new" information.The study suggested that the strength of the encoded information is weakened in the presence of Ketamine.Specifically, Ketamine disrupted the retrieval of information by promoting proactive interference from previous episodic representations.

Ketamine offers certain benefit over the other two drugs: it has shown some evidence of retrograde amnesia, thus offering a lower incidence of recall of the terrifying memory of spinal needle insertion.It helps maintain the hemodynamics better as compared to the other two groups.And a low dose infusion has been shown to reduce inflammation, and development of chronic pain later by its modulatory effects on the spinal cord[18,19]. Besides Ketamine was the most cost-effective drug, therefore Ketamine sedation could be preferred over other agents especially in amputation surgeries or even other orthopedic surgeries.

5. Conclusion

Ketamine showed some evidence of retrograde amnesia and the least side effects.All the three drugs had their own pros and cons, and probably the best strategy to provide amnesia and sedation is to use these drugs together in order to minimize adverse effects and maximize the benefits.

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An effective strategy would be the usage of a low dose Ketamine infusion throughout the surgery, in order to provide sedation and amnesia in addition to the benefits of lowered postoperative incidence of development of "Chronic Pain Syndrome" in all types of surgeries or "Phantom Limb syndrome" in amputations. This could be supplemented with intermittent boluses of Midazolam to create a more profound amnesia and also completely reduce the risk of even minor hallucinations.

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