ORIGINAL RESEARCH PAPER

Volume-7 | Issue-10 | October-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A COMPARISON OF INDUCTION ANESTHETIC REGIMENS ETOMIDATE VS MIDAZOLAM-FENTANYL COMBINATION IN THE PREVENTION OF AWARENESS DURING GENERAL ANESTHESIA IN CORONARY ARTERY DISEASE PATIENTS POSTED FOR NON CARDIAC SURGERIES.

Anesthesiology

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ABSTRACT

INTRODUCTION: Anaesthesia, although of great help to mankind, can cause untold misery and suffering if not administered properly. Awareness under general anaesthesia is one of them. Patients who experience awareness and recall during anaesthesia describe auditory perceptions, the sensation of paralysis, anxiety, panic, helpless and powerlessness.The present study is done to study the incidence of awareness under general anaesthesia and to study the effect of induction agents etomidate and midazolam-fentanyl combination in the incidence and prevention of awareness during general anesthesia in cardiac patients posted for non cardiac surgeries under general anaesthesia.

METHOD : A clinical study of awareness under general anaesthesia is done at DCMS as prospective, comparative, single blind study which include 100 patients aged between 50 to 75 years undergoing various elective surgical procedures, who were co-operative and could converse intelligently were selected. Except for the surgical condition, they were healthy and were of ASA I ,II and III physical status with history of CAD . They had no history of hearing impairment, difficulty in speaking, psychiatric disorder and history of alcohol or drug dependence. During the preanaesthetic visit all the patients were explained about the study and informed consent was obtained. All the patients were exposed to auditory stimuli like popular music, which was psychologically non-traumatic to the patient, throughout the procedure, using ear phones and a tape recorder. At the end of surgical procedure neuromuscular blockade was antagonised by neostigmine and glycopyrrolate in adequate doses. After reversal of neuromuscular blockade, the lungs were ventilated with oxygen. The patients were asked to open the mouth. If there was no response, laryngoscopy and suction was carried out. The time interval from the time of withdrawal of nitrous oxide till the patient made appropriate response to a verbal request was taken as 'The time to correct response" (TCR).All the patients were interviewed on the same evening of surgery and also on the post-operative day within 24 hours. The following questions were asked and the reply noted.

Awareness under general anaesthesia was taken as the ability of the patient to recall, with or without prompting, any event which occurred between induction of anaesthesia and recovery of consciousness at the end of anaesthesia. Recall of dreams that occurred during anaesthesia was also considered as awareness. In this study, memory recall and 'time to correct response' test were taken into consideration, to study the awareness under anaesthesia.

RESULT : The prospective, comparative, single blind study include 100 patients undergoing various surgical procedures were administered general anaesthesia and the following observations were made. In Group I none of the patients remembered the intubation. Five patients had dreams (Case No. 6 , 17, 23, 39, 45). Five patients said that they hear songs (Case No. 26, 31, 33, 39, 47) and two of them even remembered the singer (Case No. 31, 39). Two patients remembered somebody talking but could not remember the content (Case No. 37, 45). Five patients remembered the intraoperative events vaguely (Case No. 30, 34, 37, 45, 47) and said that they remembered suturing and pain.In the Group II none of the patients remembered any intraoperative events or auditory input. Four patients reported having had dreams intraoperatively (Case No. 22, 24, 26, 47).Inspite of the dreaming, recalling of music, conversation and some intraoperative events, only two patients of the group-I answered that the anaesthesia was unpleasant (Case No. 34, 47).It can be observed from the study that in few patients of group-I dreams, recalling of music, conversation and intraoperative events and unpleasant experience occurred simultaneously. Regular follow-up of the patients who showed awareness was done and they did not have any adverse psychological sequelae. The mean time in seconds of time to correct response (TCR) in the group I and II patients were 42.5 ± 21.1 and 72.6 ± 31.9 respectively. The difference in the mean time is statistically significant ($P<0.05$).The mean time in seconds of time to correct response (TCR) in group – I patients who had awareness and who did not have awareness were 35.8 ± 20.0 and 44.4 ± 22.5 respectively. The difference in the mean value within the group is statistically significant ($P<0.05$) by t-test. The mean time in seconds of time to correct response (TCR) in group – II patients who had awareness and who did not have awareness were 67.8 ± 7.6 and 72.9 ± 33.13 respectively. The difference in the mean value within the Group II, is statistically significant ($P<0.05$) by t-test.

CONCLUSION: From the above study its concluded awareness under anaesthesia is a common problem of nitrous oxide, oxygen and muscle relaxant technique of anaesthesia. The incidence of awareness under general anaesthesia was less in Group-II patients who received fentanyl - midazolam as induction. There was a significantly higher incidence of awareness under anaesthesia in the patients with etomidate induction. In the patients who had awareness under general anaesthesia the time to correct response (TCR) was significantly lesser than those who did not have awareness. Thus TCR test is a simple, valuable and reliable test in assessing awareness under GA. Hence, it is recommended to induce with midazolam-fentanyl, routinely as induction in cardiac patients to decrease the incidence of awareness.

KEYWORDS

Anesthesia Awareness , Midazolam ,Fentanyl,Generalanesthesia,Etomidate, Cardiac Patients

Anaesthesia has helped mankind by abolishing one of its worst enemies ' pain'. Anaesthesia, although of great help to mankind, can cause untold misery and suffering if not administered properly. Awareness under general anaesthesia is one of them. The history of memory for events under anaesthesia is as old as the history of anaesthesia itself [27]. Horace wells failed to demonstrate the anaesthesia properties of nitrous oxide at the Massachusetts General Hospital, Boston in 1845 when the patient complained and remembered feeling pain. One year later, William Thomas Green Morton, at the same hospital succeeded in anaesthetizing Gilbert Abbott, the surgeon was DrJ.C.Warren, with diethyl ether; Abbott later reported that he had been aware of the surgery but had experience no pain.

A significant problem of "awareness under anaesthesia" only appeared

after the introduction of muscle relaxants in anaesthesia practice by Griffith and Johnson in 1942. Dr. Mallision was a firm advocate of the biological product intocostrin. Like his contemporaries he believed in Griffith and Johnson's technique of light anaesthesia and spontaneous respiration with partial curarisation. Contrasting this technique, full paralysis of diaphragm and controlled ventilation was advocated by Liverpool School, which was also called 'The Liverpool Technique'.

Awareness during anaesthesia is frightening experience. Patients who experience awareness and recall during anaesthesia describe auditory perceptions, the sensation of paralysis, anxiety, panic, helpless and powerlessness . The psychological sequelae of awareness are sleep disturbances, nightmares, anxiety and panic attacks, flashbacks, avoidance of medical care, posttraumatic stress disorder. Although most patients of awareness do not file complaints, some do litigate seeking compensation for the suffering.

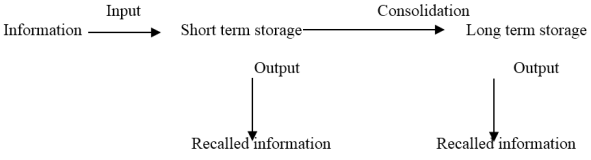
AIMS AND OBJECTIVES

1. To study the incidence of awareness under general anaesthesia.
2. To study the effect of etomidate vs midazolam-fentanyl combination in the prevention of awareness during general anesthesia in cardiac patients posted for non cardiac surgeries.
3. To compare the groups (Group I & Group II).

Group I induced with 0.5 mg/kg etomidate iv over 60 seconds
Group II induced with injection midazolam(0.2mg/kg)+fentanyl 2mcg/kg/dose.

PHYSIOLOGY OF MEMORY PROCESS

One of the early speculations concerning the establishment of this memory trace is generally attributed to Muller and Pilzeker 1900.



The simplified two-storey theory [8,44] postulates that short-term memory is retained in unstable form, whereas long term memory is retained in a consolidate "engram" – a stable, physical memory trace in the brain. The engram follows a more gradual pattern of growth and decay than the short term trace. The growth and decay curves may depends to a great extent on initial strength of the information.

ANAESTHESIA AND MEMORY PROCESS

Amnesia for the events occurring during surgical operations is a desirable feature of general anaesthesia. But it is not always attained. Evidence from research on memory suggest that anaesthetic amnesia results from

1. Attenuation of sensory transmission.
2. Impairment of the ensuing memory-consolidation process.

In a few patients, however, auditory information of high emotional content, coinciding with a lightening of anaesthesia, results in memory consolidation sufficient to permit unpleasant recall, spontaneously or under hypnosis.

Information in input, short term storage and recall

General anaesthesia does not imply a complete block of neural function. The auditory system of cat[46] and the visual system of the monkey, [19] remain functional at planes that depress the reticular formation to the level of 'unconsciousness'. Anaesthesia raises sensory thresholds [1,9,20,49] and reduces the late components of sensory evoked potentials, [1,4,6,37,53.] Thus the net input from a given external stimulus to the memory processing system is presumably attenuated by anaesthesia, resulting in formation of a weak engram which rapidly decays to below the threshold level required for recall. Patients anaesthetised with ether to stage III, plane II were conscious and cooperative but were afterwards amnesic for the residual pain is consistent with this interpretation.

Memory consolidation, long term storage and recall

Memory consolidation becomes invulnerable to weak amnesic treatment about a minute after information input. [39,54] An hour later only near lethal treatments (deep anaesthesia, strong electroconvulsive shock, high dose of chemoconvulsants) disrupt consolidation. Anaesthetic amnesia is probably not due to depressed transmission alone, however because during ether or barbiturate anaesthesia in animals, painful stimulu still evoke electrical responses in the cerebral cortex,[4] (although not in reticular system) indicating functional transmission. Therefore, impaired consolidation presumably contributed to subsequent loss of recall.

A plausible interpretation of incomplete amnesia is that while light anaesthesia attenuates sensory transmission and impairs memory consolidation during its vulnerable early stage, the combined effect may not always suffice for amnesia.

Induction effects interact with anaesthetic effects upon memory. The incidence of unpleasant recall in obstetric patients dropped from 21.1 to 3.1 percent in patients given narcotic Induction within six hours preoperatively, [70] when a tranquilizer (diazepam) replaced the narcotic, the incidence of unpleasant recall rose to 38.5 percent.[64] Diazepam alone (0.24 $mg.kg^{-1}$) administered intravenously impaired recall for at least 30 minutes in volunteers.

The evidence for the formation of memory tracing is still controversial. Nevertheless, there is theoretical rationale for the evidence that such formation occasionally occurs under certain circumstances. "Surgical anaesthesia" is not a unique state with a single immutable effect upon memory process. On the contrary, anaesthetic amnesia is a probabilistic phenomenon.

The major factors that contribute to a high probability of amnesia are uninterrupted maintenance of anaesthesia and absence of auditory input of high emotional content. When transient lightening of anaesthetic level coincides with conversation frightening to a patient, the probability of memory reconsolidation and later recall is increased.

MATERIAL AND METHODS

A clinical study of awareness under general anaesthesia was undertaken in Deccan College of Medical Sciences, Owasi Hospital Research Centre between November 2017 and September 2018 after obtaining clearance from ethical committee. Single blinded randomized trial was done .

100 patients aged between 50 to 75 with history of CAD years undergoing various elective surgical procedures, who were co-operative and could converse intelligently were selected. They were of ASA 1 , II and III physical status. They had no history of hearing impairment, difficulty in speaking, psychiatric disorder and history of alcohol or drug dependence.

During the preanaesthetic visit all the patients were explained about the study and informed consent was obtained. According to the Induction, they received, they were grouped as group I and group II of 50 each.

Group I induced with 0.5 mg/kg etomidate iv over 60 seconds
Group II induced with injection midazolam(0.2mg/kg)+fentanyl 2mcg/kg/dose.

Technique

Multi-channel monitor with ECG, pulseoximeter (SPO2), ETCO2 and noninvasive blood pressure functions was connected to the patient. Immediately before induction, pulse rate and blood pressure were recorded and taken as baseline.

All the patients were induced . The patients were maintained on 67% nitrous oxide in oxygen, sevoflurane 1MAC and veccronium 0.08 mg.kg-1 I.V. and were ventilated with closed's circuit. All the patients received fentanyl 1 mics/kg/hr mg intravenously for analgesia maintainence. Throughout the anaesthetic procedure, flow rates of gases i.e., nitrous oxide and oxygen were not altered. Muscle relaxant was repeated at the first sign of attempts at respiration. Pulse rate, blood pressure and SPO2 were monitored throughout the procedure.

All the patients were exposed to auditory stimuli like popular music, which was psychologically non-traumatic to the patient, throughout the procedure, using ear phones and a tape recorder.

At the end of surgical procedure neuromuscular blockade was antagonised by neostigmine and atropine in adequate doses. After

reversal of neuromuscular blockade, nitrous oxide was cut off and the lungs were ventilated with oxygen. The patients were asked to open the mouth. If there was no response, laryngoscopy and suction was carried out. This was repeated at 15 seconds intervals.

The time interval from the time of withdrawal of nitrous oxide till the patient made appropriate response to a verbal request was taken as 'The time to correct response" (TCR).

All the patients were interviewed on the same evening of surgery and also on the post-operative day within 24 hours. The following questions were asked and the reply noted.

1. What was the last thing you remembered before you went to sleep?
2. What was the first thing you remembered happening on waking?
3. Whether you had any dreams, if yes, specify.
4. Had you any other experience or memory while you were asleep?
5. Was there any recollection of any events during the operation?
6. Whether you remembered something going down your throat?
7. Whether you remembered music being played?
8. Whether you remembered any conversation during the operation?
9. Whether the whole episode was pleasant or unpleasant?
10. What was the worst thing about your operation?

Awareness under general anaesthesia was taken as the ability of the patient to recall, with or without prompting, any event which occurred between induction of anaesthesia and recovery of consciousness at the end of anaesthesia. Recall of dreams that occurred during anaesthesia was also considered as awareness.

In this study, memory recall and 'time to correct response' test were taken into consideration, to study the awareness under anaesthesia.

STATISTICALANALYSIS

The descriptive statistics like Mean, Standard Deviation & Standard error were calculated and presented for both the groups. The difference in mean values between the groups and wherever necessary within the groups were calculated by the means of students T-Test

Cross tables were prepared to see the association between categories and it was tested statistically by the means of chi-square test and the P value being p=0.05.

RESULTS

In the present study 100 patients undergoing various surgical procedures were administered general anaesthesia and the following observations were made.

TABLE 1: Age and Sex Distribution

Age in years	Group I n= 50			Group II n=50		
	Male	Female	Total (%)	Male	Female	Total (%)
50-60	5	8	26	14	5	38
61-70	5	14	38	8	8	32
>71	4	14	36	4	11	30
Mean age in years	33.5 ± 8.6			30.6 ± 9.1		

(P>0.05) Table I shows that majority of patients were in the age group of 61-70 years.

TABLE II: Type of Surgery

Surgical Procedures	Group - I	Group – II
G.J./ truncalVagotomy and G.J.	5	6
Appendicectomy	5	8
Laparotomy	4	2
Cholecystectomy	14	8
Hysterectomy	8	1
Ovariotomy	2	-
Fibroadenoma excision	-	1
Hernia repair	2	5
Fracture ORIF/ Orthopaedic surgery	2	1
Submandibular / parotid excision	-	1
Trendelenberg operation	-	2
Pyelolithotomy	-	-
Pilonidal sinus excision	-	1
Lymphatic cyst excision	-	1
Jaboulay's procedure	-	1
Cleft lip repair	-	1
Mastoid exploration	-	1
Gynaecomastia excision	-	2
Hydatid cyst excision	-	2
LSCS	8	6

TABLE III: Duration of Anaesthesia

Times in minutes	No. of Cases	
	Group I	Group II
0-60	14	16
61-120	31	24
>120	5	10

Table III shows that in majority of the cases the duration of anaesthesia lasted for 1 – 2 hours.

Table IV Incidence of Awareness according to recall

Groups	Remembrance of act of intubation	Dreaming		Conversation/Music heard		Intra-Operative events remembered		Unpleasant experience	
	No. of Cases	No. of cases	%	No. of cases	%	No of Cases	%	No.of Cases	%
I	0	5 (Case no. 6,17, 23, 39, 45)	10	7(Case no. 26, 31, 33, 37, 39, 45, 47)	12	5(Case no. 30, 34, 37, 45, 47)	10	2(Case no. 34, 47)	4
II	0	4 (Case No. 22, 24, 26, 47)	8	0	0	0	0	0	0

Table IV shows the incidence of awareness in both the groups of patients.

Table IV

In Group I none of the patients remembered the intubation. Five patients had dreams (Case No. 6 , 17, 23, 39, 45). Five patients said that they hear songs (Case No. 26, 31, 33, 39, 47) and two of them even remembered the singer (Case No. 31, 39). Two patients remembered somebody talking but could not remember the content (Case No. 37, 45). Five patients remembered the intraoperative events vaguely (Case No. 30, 34, 37, 45, 47) and said that they remembered suturing and pain.

In the Group II none of the patients remembered any intraoperative events or auditory input. Four patients reported having had dreams introperatively (Case No. 22, 24, 26, 47).

Inspite of the dreaming, recalling of music, conversation and some intraoperative events, only two patients of the group-I answered that the anaesthesia was unpleasant (Case No. 34, 47).

It can be observed from the table that in few patients of group-I dreams, recalling of music, conversation and intraoperative events and unpleasant experience occurred simultaneously.

Regular follow-up of the patients who showed awareness was done and they did not have any adverse psychological sequelae.

TABLE V (a): Table showing the mean values of time to correct response (in secs) in Group I and Group II patients.

	Mean time (in secs)
Group I	42.5 ± 21.1
Group II	72.6 ± 31.9

(T-test) (P<0.05)

The mean time in seconds of time to correct response (TCR) in the group I and II patients were 42.5 ± 21.1 and 72.6 ± 31.9 respectively. The difference in the mean time is statistically significant (P<0.05).

Table V(b): Table showing the mean values of time to correct response (secs) within the

Group I patients who had awareness and who did not have awareness.

Awareness	No. of Cases	Mean Time (in secs)
Present	12	35.8 ± 20.0
Absent	38	44.4 ± 22.5

The mean time in seconds of time to correct response (TCR) in group – I patients who had awareness and who did not have awareness were 35.8 ± 20.0 and 44.4 ± 22.5 respectively. The difference in the mean value within the group is statistically significant (P<0.05) by t-test.

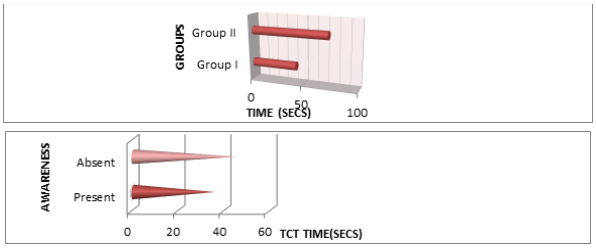
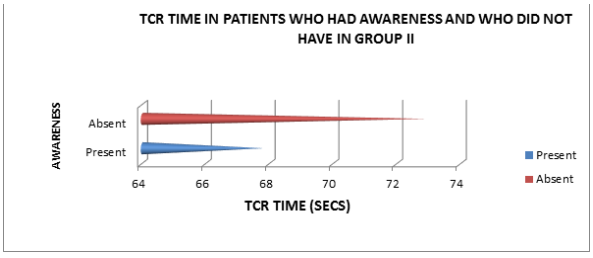


TABLE V (c) : Table showing the mean values of time to correct response (in secs) within the

Group II patients who had awareness and who did not have awareness.

Awareness	No. of Cases	Mean Time (in secs)
Present	4	67.8 ± 7.6
Absent	46	72.9 ± 33.13

The mean time in seconds of time to correct response (TCR) in group – II patients who had awareness and who did not have awareness were 67.8 ± 7.6 and 72.9 ± 33.13 respectively. The difference in the mean value within the



Group II, is statistically significant (P<0.05) by t-test.

DISCUSSIONS

By definition, general anaesthesia is a state of unconsciousness accompanied by loss of sensation without interference with vital functions. One truly does not expect a patient who is unconscious under anaesthesia to have awareness. Awareness was not normally encountered when volatile anaesthetic agents were used with the patient breathing spontaneously. The problem of awareness was first encountered with the introduction of muscle relaxant and pulmonary ventilation (Winter Bottom 1950). This technique became very popular with most anesthesiologists of its distinct advantage of having a patient in lighter planes of anaesthesia with prompt recovery of protective reflexes and consciousness immediately after reversal of neuromuscular blockade at the end of anaesthesia. At the same time, the incidence of awareness during general anaesthesia also increased. The implications of awareness under general anaesthesia also increased. The implications of awareness under general anaesthesia are many. The patient has a unpleasant experience which may result in post traumatic stress disorder like sleep disturbances, nightmares and daytime anxiety. There is also a medico-legal aspect leading to claims for compensation.

Problems due to awareness have been widely published in the literature and there has been considerable publicity of the same in the press and electronic mass media and many workers have utilized various means and techniques for detecting awareness during anaesthesia. Yet there has been no satisfactory means of investigating it.

Nowadays there are various monitors to measure the depth of anaesthesia and to know whether the patient is aware under general anaesthesia.

1. EEG – Monitor
It measures the spontaneous electrical activity of the brain produced by the inhibitory and excitatory potentials in the superficial cortex. These are very small and need to be amplified. These are not easy to interpret.
2. EEG – Derived parameters
Computer assisted analysis facilitates data compression for easier interpretation. These are quite expensive and are not 100% sensitive or specific.
3. Others like
a. Positron emission tomography.
b. Superconductive quantum interference devices (SQUID).
c. Ocular microtremor monitoring (OMT).

These are not widely used, are expensive and are still in experimental sages. These monitors are yet to gain wide acceptance.

Clinical signs suggestive of awareness are generally motor and autonomous. Eyelid motion, swallowing, increased spontaneous respiratory activity, coughing, facial grimacing and extremity or head motions are signs often assumed to indicate inadequate amnesia. Hypertension, tachycardia, mydriasis, tearing, sweating and salivation indicate too light a level of anaesthesia. When a muscle relaxant is used these signs may not be present even though there is awareness under general anaesthesia.

Factors cited as contributing to awareness.

Inadequate anaesthetic technique.
- No Induction.
- Ultrashort acting intravenous induction agent.
- Excessive neuromuscular blockade.
- Difficult or prolonged intubation.
- Equipment failure.
- ASA Group – IV and Group – V.
- Obstetric procedures.
- Morbid obesity.
- Cardiac surgery.
- Bronchoscopy.
- Pharmacologic autonomic blockade.
- Increased anaesthetic requirement.

In the present study, these factors which contribute to awareness were avoided as far as possible.

Memory for the intra-operative events is considered as a sign of awareness. Memory can be further divided into implicit and explicit.

Explicit memory is one where the patient remembers the event and a consciously recall it.

Implicit memory refers to changes in performance or behavior, that are produced by prior experiences to tests that do not require any intentional or conscious recollection of these experiences.27

Study of implicit memory needs the patients to be intelligent and very cooperative to do the tasks to be tested. All out patients were not so intelligent enough. However the test of explicit memory is simple and gives a reliable method of testing the occurrence of awareness under general anaesthesia, hence it was used in our study.

In our study 100 patients were divided into two groups of 50 each.Group I induced with 0.5 mg/kg etomidate iv over 60 seconds . Group II induced with injection midazolam(0.2mg/kg)+fentanyl 2mcg/kg/dose.

The difficulty in defining awareness makes it difficult to compare studies of the incidence of awareness. Most previous studies have not clearly stated their definition of awareness.

In our study, in Group-I patients the incidence of unpleasant experience was slightly higher i.e., 4% when compared to above study, where as in Group - II patients there was no incidence of unpleasant experience.

In our patients who showed awareness in the two groups, there were no signs suggestive of lighter planes of anaesthesia like tachycardia, hypertension, lacrimation or sweating. According to Russell IF. et al. 1993, 56 individually or in aggregate, physiological variables seemed of little value in predicting the consistency of patient's awareness under general anaesthesia. We did not employ isolated forearm technique, as Breckenridge (1981)7 has questioned its validity and as it is less sensitive in detecting the light planes of anaesthesia.In the study of awareness using 'time to correct response' (TCT) test, Cormack R.S. 1979 13 reported a mean TCT time of 48 and 114 seconds, after morphine and lorazepamInduction respectively. In our

study the mean TCR was significantly lesser in Group-I patients (42.5 seconds) than Group-II patients 72.6 sec (P<0.05). Even within the group-I and II patients, the TCR time was significantly lesser in patients who had awareness than those who did not have awareness under general anaesthesia (P<0.05).

CONCLUSION

From the above study the following were concluded.

Awareness under anaesthesia is a common problem of nitrous oxide, oxygen and muscle relaxant technique of anaesthesia. The incidence of awareness under general anaesthesia was less in Group-II patients who received midazolam+fentanyl as Induction .There was a significantly higher incidence of awareness under anaesthesia in the patients who received etomidate as Induction .In the patients who had awareness under general anaesthesia the time to correct response (TCR) was significantly lesser than those who did not have awareness. Thus TCR test is a simple, valuable and reliable test in assessing awareness under GA.Hence, it is recommended to use combination of midazolam + fentanylroutinely for ASA II and III cardiac patients for non cardiac surgeries to decrease the incidence of awareness.

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