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Research Article

A Prospective, Randomised, Double Blind Clinical Study of Comparing Hemodynamic Effects and Intraocular Pressure Changes Effect of Etomidate and Midazolam during Monitored Anaesthesia Care in Patients Having Hypertension or Coronary Artery Disease Undergoing Cataract Surgery

Dr. Dipal Vadodariya[1], Dr. Lopa Trivedi[2]* and Dr. Harish Trivedi[3]

[1]Resident Doctor, Department of Anaesthesiology, Government Medical College & Sir Takhtsinhji General Hospital, Gujarat, India
[2]Associate Professor, Department of Anaesthesiology, Government Medical College & Sir Takhtsinhji General Hospital, Bhavnagar, Gujarat, India
[3]Associate Professor, Department of Ophthalmology, Government Medical College & Sir Takhtsinhji General Hospital, Bhavnagar, Gujarat, India

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Abstract: Background & Objectives: As most of the patients posted for cataract surgery belongs to geriatric age group, hypertension and coronary artery diseases (CAD) are more common. Most of the surgeries are performed under local anaesthesia and patients are conscious. This may cause an exaggerated neuroendocrine stress response which is detrimental to patients with compromised cardiac conditions. The aim of our study was to evaluate the hemodynamic and intraocular pressure effects of etomidate in comparison to midazolam during monitored anaesthesia care (MAC) in hypertensive and CAD patients undergoing cataract surgery. **Methods:** 60 patients posted for cataract surgery under MAC, were randomized into two groups (each of 30): Group E patients were given inj. etomidate 0.1 mg/kg dose and Group M patients were given inj. midazolam 0.03 mg/kg. Both drug were diluted up to 10ml of NS. Ramsay sedation score (RSS) was kept at 3. HR, SBP, DBP, MAP, SpO_2, respiratory rate, intraocular pressure, RSS, and complications were recorded at specific time interval till the end of surgery. **Results:** Mean onset of time for sedation in group E was significantly shorter than group M. Group E produced significant decrease in intraocular pressure than group M. The decrease in HR, SBP, DBP, and MAP were comparable in both groups but the decrease was significant while comparing to baseline. **Conclusion:** Etomidate achieved adequate depth of sedation in shorter time and produced a significant reduction in intraocular pressure when compared with midazolam. Both drug caused comparable decreased in hemodynamic variables which was within permissible limit.

Keywords: Monitored anaesthesia care, cataract surgery, hypertensive & coronary artery disease patient, etomidate, midazolam, hemodynamic effects, intraocular pressure changes.

INTRODUCTION

Cataract surgery is one of the most commonly performed surgical procedures in today's ageing world (Ronald D Miller). As most of the patients posted for cataract surgery belongs to geriatric age group, hypertension or coronary artery disease are more common.

Pain, fear and anxiety are common during ocular surgery because most of the surgeries are performed under local anaesthesia and patients are conscious. This can compromise intraoperative cooperativeness of the patients. More importantly, they may cause an exaggerated neuroendocrine stress response which may have untoward effects like hypertension, tachycardia, ischemic strain on the heart; hyperventilation and acute panic attacks. These effects are detrimental to elderly patients having compromised cardiac conditions. To increase the comfort of the patients and success of procedure conscious sedation is the primary requirement (Woo, J. H. *et al.*, 2009). So anaesthesiologist may be called upon to provide monitored anaesthesia care (MAC) to these patients.

According to the American Society of Anaesiologist (ASA), a monitored anaesthetic care is planned procedure during which the patient undergoes local anaesthesia together with sedation and analgesia (Anaesthesia and resuscitation unit, 2005). Monitored anaesthetic care includes preoperative assessment and optimisation, intraoperative and postoperative care.

***Corresponding Author:** Dr. Lopa Trivedi Email: dipalvadodariya.27[at] gmail.com

Throughout the procedure, the anaesthesiologist: (1) administers sedatives, analgesics, anaesthetic agents, or other medications as necessary to ensure patient safety and comfort; (2) monitors and evaluates vital functions continuously; and (3) maintains the patient's airway and manages other clinical problems that may arise (Lui, K. C., & Lam, A. 2002). In addition, MAC is being increasingly utilised for out-patient surgical procedures (e.g. cosmetic surgery, cataract surgery, cystoscopy, placement of deep intravenous lines, and vascular shunts) (Sa Rego MM *et al.,* 2000). As procedures performed under local anaesthesia with MAC usually have a shorter recovery time compared with procedures undertaken under general or regional anaesthesia, MAC will have an increasingly important place in clinical practice, especially for economic reasons (White, P. F., & Negus, J. B. 1991).

In cataract surgery, conscious sedation is indicated to reduce discomfort during block administration and surgery with added advantages of hemodynamic stability together with enhanced patient cooperation and satisfaction. The properties of ideal sedative agent for ophthalmic procedure should have rapid onset, short duration, nontoxic, non-accumulating and minimal side effects. The drugs used for sedation can be classified into benzodiazepine, intravenous induction agents, narcotic, analgesic and alpha adrenal receptor agonist (Woo, J. H. *et al.,* 2009).

Conventionally, midazolam has been widely used for MAC because of its faster onset and shorter duration of action (Adams, D., & Dervay, K. 2012; Chan, K. K. L., & Ho, H. F. 2008). Etomidate, an imidazole derivative can be used as a sedative agent (Forman, S. A. 2011). Etomidate was reformulated using lipid emulsion and reintroduced in 2007 in India (Karki, G. *et al.,* 2014). The rapid onset of sedation and rapid recovery time may lead to more rapid discharge and potentially increased patient satisfaction (Adams, D., & Dervay, K. 2012). In addition, etomidate does not inhibit sympathetic tone or myocardial function (Latson, T. W. *et al.,* 1992; & Gelissen, H. P. *et al.,* 1996), and produces minimal blood pressure and heart rate changes in patients, including those with valvular or ischemic heart disease (Scorgie, B. 1983; Du Cailar, J. *et al.,* 1976; & Ebert, T. J. *et al.,* 1992). The mention properties of etomidate makes it an attractive alternative to benzodiazepine being used for MAC.

Based on these facts, we decided to undertake the present study for comparing the hemodynamic and intraocular pressure effects of etomidate and midazolam during MAC in cataract surgery under local anaesthesia in hypertensive and coronary artery disease patients.

MATERIAL AND METHODS

The aim of our study were to monitor parameters like changes in intraocular pressure, hemodynamic variables, onset time of sedation, sedation score, patient's & surgeon`s satisfaction, incidence of complications in cataract surgery during MAC for comparison of etomidate and midazolam in respect of above mentioned parameters**.**

After obtaining approval from the Institutional review board (IRB No.554/2015) and written informed consent, this prospective, randomized, double blind, clinical study was carried out in Dept. of Anaesthesiology, Govt. Medical College & Sir T. Hospital Bhavnagar, Gujarat during 2015-16. 60 patients with hypertension and/or coronary artery disease, aged 40 to 80 years, ASA Physical status II and III, scheduled for elective cataract surgery under Monitored anaesthesia were enrolled in this study. Patient with alcohol or drug addiction, neuropsychiatric disease, severe respiratory insufficiency, history of drug allergy, sedative drug use within 24 hours before the surgery or difficult airway were excluded. Patients were randomized into following two groups of 30 each by computer generated random number sequence method. Group E (n=30) - Patient were given inj. etomidate 0.1mg/kg diluted with normal saline up to 10ml was given over 30s. Group M (n=30) - Patient were given inj. midazolam 0.03 mg/kg diluted with normal saline up to 10ml was given over 30s.

Preoperative Preparation

All patients were kept nil by mouth (NBM) for 6 hrs. Patients were explained about the need of sedation, major steps of conscious sedation and operative procedure in local language and informed written consent was obtained. Syringe was prepared by an anaesthesiologist, not participating in the study with 0.1mg/kg etomidate or 0.03mg/kg midazolam diluted up to 10ml with normal saline. The syringe was covered well with opaque white adhesive tape and labelled with enrolment number of patient according to randomization list, so it could not differentiated by external appearance. Syringe was handover to attending anaesthesiologist (unaware about the content of the drug), who was responsible for monitoring the patient intra-operatively.

In preanaesthetic preparation room, standard monitoring was established for heart rate (ECG), systolic blood pressure; diastolic blood pressure and mean arterial pressure (NIBP), peripheral arterial saturation (pulse oxymeter) and baseline vital parameters was recorded. Sedation was graded by Ramsay sedation score (RSS).

Intravenous line was secured and patients were premedicated with Inj. ondensetron 0.08 mg/kg and Inj. ranitidine 1 mg/kg i.v. Intraocular pressure was measured by Schiotz tonometry.

RAMSAY SEDATION SCORE

SCORE	LEVEL OF SEDATION
1	Nervous, agitated and/or restless
2	Cooperative, oriented, quiet patient
3	Only obeying orders
4	Sleeping, hitting the glabella, and responding to high voice suddenly
5	Sleeping, hitting the glabella, and responding to high voice slowly
6	No response to any of the stimulation

In Operation Theatre

As per assigned group sedative drug was given. Oxygen was administered with a nasal cannula at a rate of at least 4L/min. Onset of action of sedation for drug was recorded (time of giving sedative drug up to the time when Ramsey sedation score become 3). Intraocular pressure was recorded by an ophthalmologist after achieved adequate sedation (when Ramsey sedation score 3 achieved), and then ophthalmologist has given peribulbar block. Ramsay sedation score, HR, SBP, DBP, MAP, Respiratory rate, SpO_2 were measured and recorded at 1, 3, 5, 10, 15, 20, 30, 40,50, 60min and till the end of surgery after giving study drug. Periodic assessment of the level of sedation done at scheduled time in order to maintain contact with the patient and to prevent respiratory or hemodynamic side effects. If anytime during surgery Ramsay sedation score become < 3, titrated dose of etomidate 0.05mg/kg and midazolam 0.01mg/kg was given. We had recorded total study drug dose and complications if any. Bradycardia was defined as fall in pulse rate below 60 beats per minute and treated with inj. Atropine 0.6 mg i.v. bolus. Mean arterial pressure 20%on either side of baseline was considered significant and treated accordingly. After recovery, patient's satisfaction score and Surgeon's satisfaction score was recorded between 1 to 3 (1- poor, 2- good, 3- excellent).

Statistical Analysis

The data obtained in the study for various parameters were presented in the tabulated and graphical form. Using statistical software (graph pad Instat3.0 software) mean and standard deviation was calculated for all the quantitative variables. Intra group comparison was made using the Repeated measures ANOVA and inter group comparison among the different groups were done using unpaired t - test. Inter group comparison of qualitative data were done by Chi square test. *p* value <0.05 was considered statistically significant.

OBSERVATION AND RESULTS

Demographic profile in terms of age, sex, weight and ASA physical status were comparable in two groups. Duration of surgery was also comparable in two groups.

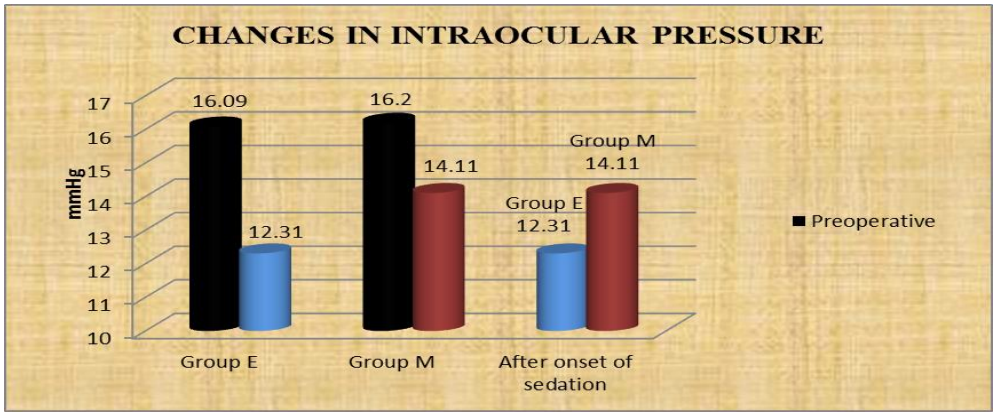
DEMOGRAFIC PROFILE OF PATIENTS

Patient Characteristics	Group E (Mean±SD)	Group M (Mean±SD)	*p* Value
Age (Years)	62.96±7.47	61.83±8.69	0.7783
Gender (M/F)	13,17	10,20	>0.05
Weight (Kg)	55.50±10.91	57.50±9.38	0.4498
ASA Physical Status (II/III)	22,8	22,8	>0.05
Duration of Surgery (min)	45.66±7.74	43.33±6.60	0.2142

Pre-operative intraocular pressure was comparable in two groups. Both group caused extremely significant decrease in intraocular pressure from pre-operative value after onset of sedation **(*p*<0.0001)**. On comparison of group E with group M, Group E produced statistically significant decrease in Intraocular pressure than Group M. (Table-1)

Table 1: Changes in Intraoculr Pressure

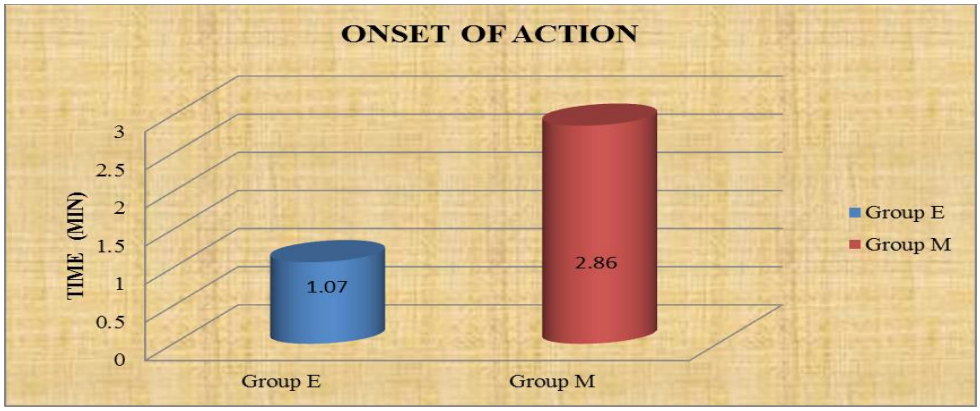
Intraocular Pressure	Group E	Intragroup	Group M	Intragroup	Inter group
	Mean±SD	*p* value	Mean±SD	*p* value	*p* value
Preoperative	16.09±1.82		16.20±1.92		0.9584
After onset of action	12.31±3.08	<0.0001	14.11±2.00	<0.0001	0.0079



On comparison of group E with group M, Group E produced statistically extremely significant faster onset of action of sedation than Group M. (P<0.0001) (Table-2).

Table 2: Onset Time of Sedation

	Group E	**Group M**	
	Mean±SD	**Mean±SD**	**Inter group *p* value**
Onset time of sedation	1.07±0.38	2.86±0.68	<0.0001

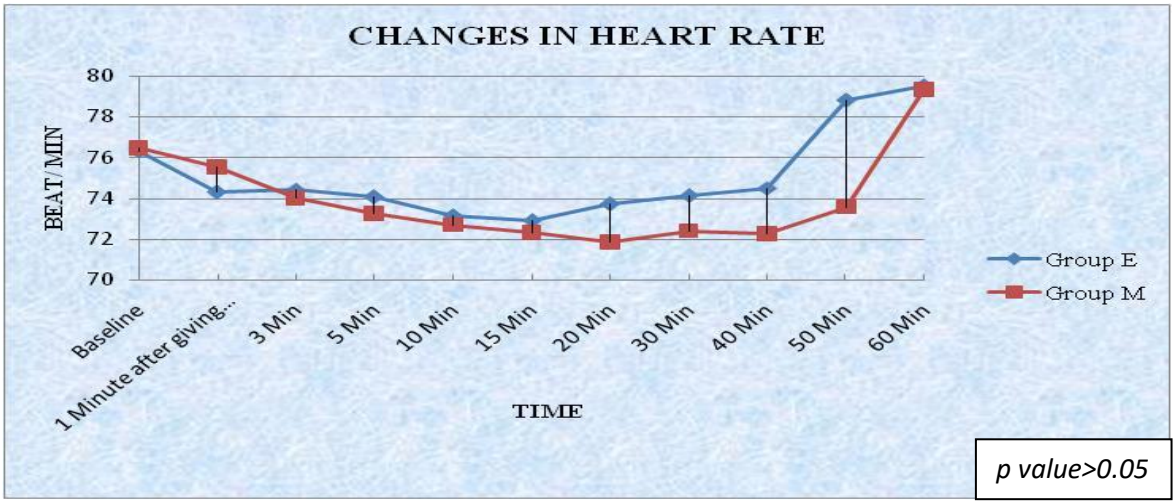


As compared to Group M, there was statistically significant higher sedation score found in Group E within 3 minute after giving sedation **(**Table-3**)**. After 3 minute sedation score remain comparable in both groups. Sedation score reached baseline within 40 minutes after giving sedation.

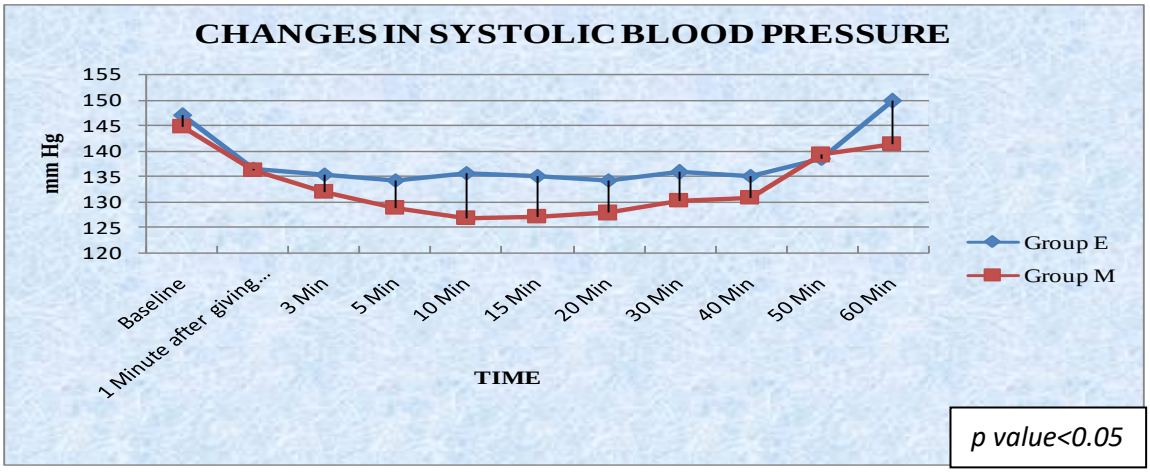
Table 3: Changes in Sedation Score

Time	**Group E**		**Group M**		**Inter group *p* Value**
	Mean±SD	**Intragroup *p* Value**	**Mean±SD**	**Intragroup *p* Value**	
Baseline	1.63±0.49		1.7±0.46		0.5914
1 Min after sedation	2.7	<0.001	2	>0.05	<0.05
3 Min	3.2±0.40	<0.001	2.63±0.49	<0.001	0.0008
5 Min	3.03	<0.001	3	<0.001	>0.05
10 Min	3	<0.001	2.93	<0.001	>0.05
15 Min	2.96±0.18	<0.001	2.93±0.36	<0.001	>0.999
20 Min	2.93	<0.001	3	<0.001	>0.05
30 Min	2.83±0.37	<0.001	2.93±0.25	<0.001	0.4887
40 Min	2.4±0.49	>0.05	2.26±0.52	>0.05	0.419
50 Min	2.16±0.57	<0.05	2.28±0.48	>0.05	0.7622
60 Min	2.2±0.44	>0.05	2.33±0.57	>0.05	0.8772

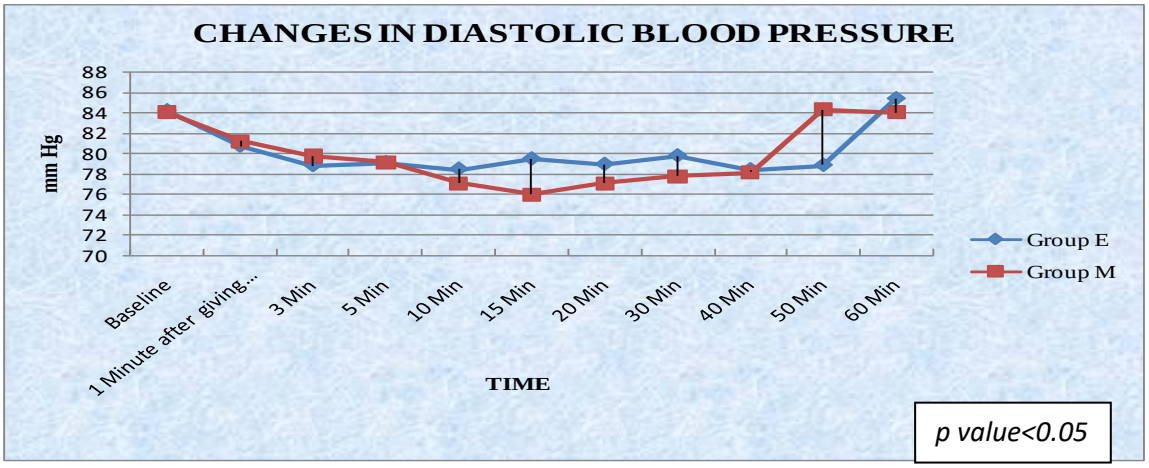
Baseline HR was comparable in each group, and both groups produced comparable decrease in HR. None of the patient in both groups develops Bradycardia.



Baseline SBP was comparable in each group. On comparison of group E with group M, group M produced statistically significant decrease in SBP at 5 minute, than after decreased in SBP was comparable.



DBP was comparable in each group, and both groups produced comparable decrease in diastolic blood pressure. MAP was comparable in each group, and both groups caused comparable decrease in mean arterial pressure.



SpO_2 and respiratory rate remained stable and comparable to baseline in the two groups throughout the study period. Patient's and surgeon's mean satisfaction score was comparable in each group and not significant statistically significant. Three patients in Etomidate group developed myoclonus which was resolved spontaneously within 30 second and 1 patient developed respiratory depression. No other complication was observed in two groups throughout the study period. Etomidate group, four patients required supplementation of drug. The mean time was 25 minute for drug supplementation. Midazolam group, three patients required supplementation of drug. The mean time was 30 minute for drug supplementation.

DISCUSSION

During surgery under local anaesthesia most patients experience periods of hemodynamic instability, which healthy individuals can tolerate, but are usually catastrophic in hypertensive patients due to the wide pressure fluctuation and sympathetic hyperactivity, and increases the risk of cardiovascular complications during the anaesthetic-surgical procedure (Daşkaya, H. *et al.*, 2014; & Singh, R. *et al.*, 2010). Patients may experience anxiety when ophthalmic procedure going on in fear of pain and discomfort. Etomidate and midazolam both cause decrease in intraocular pressure (Oji, E. O., & Holdcroft, A. N. I. T. A. 1979; Fragen, R. J., & Hauch, T. 1981; & Dursteler, B. B., & Wightman, J. M. 2000). In the present study etomidate produced more decrease in intraocular pressure than midazolam. Till date no study was conducted, which had compare the effect of etomidate and midazolam on intraocular pressure changes. So, further studies needed to prove the superiority of etomidate than midazolam in intraocular pressure changes. In present study Ramsay sedation score was used to evaluate desirable sedation. This scale is widely used by several authors in studies on anaesthesiology and intensive care, has proven to be an established method in assessment of sedation quality (Ramsay, M. A. E. *et al.*, 1974; De Jonghe, B. *et al.*, 2000; & Watson, B. D., & Kane-Gill, S. L. 2004). Most of study used etomidate 0.1 mg/kg and midazolam 0.03mg/kg for procedural sedation and had concluded that etomidate achieved adequate depth of sedation in shorter time than midazolam (Sa Rego MM *et al.*, 2000; Dickinson, R. *et al.*, 2001; Hum, L. *et al.*, 1997; Ruth, W. J. *et al.*, 2001; Vinson, D. R., & Bradbury, D. R. 2002; Hunt, G. S. *et al.*, 2005; & Burton, J. H. *et al.*, 2002).We have similar findings in present study that desirable sedation score was achieved more rapidly with etomidate (1.07±0.38 minute) than midazolam (2.86±0.68 minute).While searching the literature, it was found that etomidate offers superior hemodynamic stability than other anaesthetic agents (Scorgie, B. 1983; Daşkaya, H. *et al.*, 2014; Singh, R. *et al.*, 2010; Moffat, A., & Cullen, P. M. 1995; Aghadavoudi, O. *et al.*, 2013; & Gooding, J. M. *et al.*, 1979). Midazolam produces decrease in systemic blood pressure and decrease in systemic vascular resistance. No changes in heart rate, cardiac output and index, stroke volume and index. Thus, midazolam has favourable cardiocirculatory effects, so it is safe in cardiac patients with coronary obstruction and congestive heart failure (Du Cailar, J. *et al.*, 1976; Ebert, T. J. *et al.*, 1992; Forster, A. *et al.*, 1981; Lebowitz, P. W. *et al.*, 1982; & Marty, J. *et al.*, 1986). In present study etomidate and midazolam caused decrease in hemodynamic parameters which were within permissible limits and comparable. Respiratory rate and oxygen saturation remained stable and comparable in both groups. Patient's satisfaction and surgeon's satisfaction was similar in both groups. 3 patients required supplementation of etomidate and 4 patients required midazolam supplementation. Etomidate was reported to produce myoclonic reaction (a period of involuntary twitching of muscles), especially at higher doses when it was used for rapid sequence intubation. This reaction could be perceived as increased agitation or a seizure (Anaesthesia and resuscitation unit. 2005; Lui, K. C., & Lam, A. 2002; Sa Rego MM *et al.*, 2000; White, P. F., & Negus, J. B. 1991; & Adams, D., & Dervay, K. 2012). 3 patients developed myoclonus who received etomidate and 1 patient developed respiratory depression. Complications in all patients disappeared spontaneously within 30 seconds before starting of surgery so it did not interrupt the operative field and did not produced discomfort to patients. No other complications were seen in both groups.

CONCLUSION

From present study, it is concluded that etomidate achieved adequate depth of sedation in shorter time and produced a significant reduction in intraocular pressure compared with midazolam. Etomidate and midazolam both caused comparable decrease in hemodynamic variables which was within permissible limit.

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