Midazolam and etomidate for induction of anaesthesia in ophthalmic surgery

ABSTRACT

Objectives: To assess the effect of midazolam 0.02 mg/kg administered with etomidate on the incidence of myoclonus and the dose requirement for etomidate to induce general anaesthesia.

Design: Double blind randomised control trial.

Setting: Two urban teaching hospitals in Durban, Kwa Zulu Natal (KZN).

Patients: 60 patients older than 60 years of age undergoing intraocular surgery.

Outcome measures: Etomidate dose required for loss of verbal contact (dose V) and loss of eyelash reflex (dose E). Myoclonus assessed by means of a three-point scale (0-nil; 1-mild; 2-severe) 30 sec after the last dose of etomidate. Duration of recovery from cessation of anaesthesia to first response to verbal command.

Results: No significant difference in myoclonus or dose requirement for etomidate could be demonstrated. There was no difference in haemodynamic variation between the groups and recovery time was not prolonged.

Conclusion: Midazolam 0.02 mg/kg given with etomidate for induction of anaesthesia does not reduce myoclonus or dose requirement for etomidate. Further studies may be undertaken to assess the usefulness of larger doses of midazolam for co-induction or oral premedication with midazolam.

Patients requiring intraocular surgery are often elderly with co-existing cardiovascular disease. General anaesthesia (GA) may be avoided in the majority of these patients by the use of local anaesthesia but a proportion will still require GA for longer operations such as retinal detachment repair, to prevent coughing or sudden movement in less co-operative patients or at the patient’s request.

Etomidate would be a useful drug for induction of anaesthesia in these patients due to its neutral effect on haemodynamics. Unfortunately etomidate administration may be associated with the development of myoclonus in 23 to 36% of patients which may be severe.

Midazolam is a short acting benzodiazepine which has been used successfully with a number of other induction agents to reduce the dose of these drugs required for induction of GA, a technique known as co-induction. Diazepam has been used to reduce myoclonus induced by etomidate but it is a long acting benzodiazepine which may prolong recovery from general anaesthesia. The dose of midazolam required for effective co-induction with thiopentone is only 0.02 mg/kg and may be even lower in elderly patients. The use of a combination of a small dose of midazolam with etomidate to induce anaesthesia has not been described previously but appears logical as midazolam should not only reduce the dose of etomidate required for induction but should also act directly to suppress myoclonus. The haemodynamic stability of the etomidate induction should be maintained and recovery should be unaffected.

This study was thus undertaken to assess the effect of co-induction with midazolam (0.02 mg/kg) and etomidate on the dose of etomidate required, incidence of myoclonus, haemodynamic stability and recovery time in patients requiring intraocular surgery under GA.

METHODS

Following approval by the University of Natal Medical Faculty ethics committee sixty patients presenting to one of two metropolitan hospitals for intraocular surgery under GA gave informed consent to participate in the study. Patients on long term benzodiazepine or psychotropic drug therapy as well as those with a history of adverse reactions to benzodiazepines or etomidate were excluded. Patients were enrolled on the evening before surgery and were given promethazine 0.5 - 1 mg/kg as night sedation at 2200. No premedication was given on the morning of surgery.

On arrival in theatre monitoring (including ECG, non-invasive blood pressure and pulse oximetry) was applied and intravenous access established. Oxygen (100%) was given by facemask via a circle absorber system before induction.

Patients were randomly allocated to one of two groups. Group M patients received midazolam 0.02 mg/kg in 10ml normal saline and group S patients 10ml of saline 2 minutes before induction of
GA. Medication was prepared in a double blind fashion. Two minutes after administration of study medication etomidate 0.1 mg/kg was administered. Further doses of 0.025 mg/kg were given every 20 sec until loss of verbal contact with the patient (dose V) and repeated until loss of the eyelash reflex (dose E). Total doses were corrected for patients’ weights and recorded in mg/kg. Following the administration of the final dose of etomidate patients were observed for 30 sec for the presence of myoclonus which was graded according to a three point scale (Table I).

Patients were then given alfentanil 10-20 µg/kg, vecuronium 0.1 mg/kg and the 100% oxygen changed to isoflurane 1-3% with 50-70% nitrous oxide in oxygen. Ventilation was manually assisted until establishment of neuromuscular block. Patients were then intubated and mechanically ventilated to normocapnia as measured by sidestream capnography. Fentanyl 1-3 µg/kg was given incrementally for analgesia. Pulse and blood pressure were recorded on arrival in theatre as a baseline, immediately after intubation and at 5-minute intervals for the first hour after intubation.

On completion of surgery anaesthetic gas administration was stopped and patients ventilated with 100% oxygen. Residual neuromuscular block was antagonised with neostigmine 2.5 mg and glycopyrrolate 0.5 mg. The time at which anaesthetic gas administration was stopped and the time of the patient’s first response to verbal command were noted and the duration of recovery (T awake) calculated. The duration of anaesthesia from induction to cessation of anaesthetic gas administration was also calculated.

The mean values obtained from the two groups for the induction doses of etomidate: dose V and dose E and T awake were analysed by means of the unpaired Student’s T test. The incidence of myoclonus in the groups was analysed by means of the Mantel-Haenszel Chi-square test. Differences in the continuous variables (pulse and blood pressure) were analysed using repeated measures analysis of variance. Statistical significance was taken at the 5% (p = 0.05) level.

### RESULTS

The two groups were comparable in terms of age, sex distribution and weight (Table II). There were no significant differences in blood pressure and pulse rate between the groups.

The dose of etomidate per kilogram body weight required for induction was less in patients given midazolam [dose V (0.14 mg (0.044) (mean (SD)) and dose E (0.18 mg (0.059))] compared with those given saline [dose V - 0.15 mg (0.049); dose E 0.20 mg (0.06)] but the differences were not statistically significant [p = 0.14 (dose V) and p = 0.20 (dose E)].

Myoclonus was reduced in patients given midazolam with 14 patients given midazolam experiencing no myoclonus compared with 8 given saline. Three patients given midazolam had severe myoclonus compared with 6 given saline (Table III). These differences were, however, not statistically significant (p = 0.09).

The duration of surgery, T awake and dose of fentanyl required for analgesia did not differ significantly between the groups (Table IV).

### DISCUSSION

Myoclonus is an annoying side effect associated with induction of anaesthesia with etomidate, which may result in reluctance to use the drug despite its neutral haemodynamic effects.1 The incidence of myoclonus in the saline treated patients in this study of 73% (Table III) is higher than described by Giese (23%) or Fragen (36%).2,3 The reason for this is uncertain but demonstrates the significance of the problem in our setting.

Unfortunately a significant reduction in incidence of myoclonus by co-induction with midazolam 0.02 mg/kg could not be demonstrated by this study. The dose of etomidate required for induction of GA was also unaffected. A non-significant trend towards suppression of myoclonus and dose reduction was seen which might become significant if a larger dose of midazolam is used. Fentanyl has been used at induction to reduce the incidence of myoclonus from 20 to 3%.2 The administration of fentanyl and midazolam together with etomidate may eliminate myoclonus.

The dose of midazolam chosen (0.02 mg/kg), while less than 10% of the ED 50 for midazolam used as a sole induction agent, had proven effective in a previous study of midazolam/thiopental co-induction.7 Thiopental, however, does not cause myoclonus so only the hypnotic rather than the anticonvulsant efficacy of midazolam was addressed. The same low dose was used in our study to minimise the potential haemodynamic disturbances, which may be seen with midazolam4 and to minimise the prolongation of recovery. The study group comprised older patients [mean age >60yrs (Table II)] who have been shown to have an increased sensitivity to the hypnotic effects of midazolam.5

The fact that haemodynamic stability was maintained and T awake was not prolonged by co-induction with midazolam...
0.02 mg/kg would seem to justify the investigation of a larger dose of midazolam for co-induction with etomidate. A dose of 0.04 mg/kg would still be less than 20% of the ED 50 for midazolam used for induction so haemodynamic effects should be minimal. The duration of surgery was between 78 and 84 minutes (Table IV) which would allow sufficient time for recovery from the hypnotic effects of a larger dose of midazolam so that T awake should also be unaffected.

An oral formulation of midazolam is available in this country and is used extensively as premedication. The effect of oral premedication with midazolam prior to administration of etomidate has not been described and may be another method of reducing myoclonus.

CONCLUSION

This study has demonstrated that co-induction with midazolam 0.02 mg/kg and etomidate resulted in a non-significant tendency to reduction of myoclonus and dose requirements for etomidate. Haemodynamic stability was maintained and recovery was not prolonged with this dose of midazolam. Further study to assess the usefulness of midazolam given in a higher dose or as oral premedication to reduce myoclonus after administration of etomidate may be undertaken.

References


Two-Year Clinical / Research Fellowships

- 50% clinical with Department of Anesthesiology.
- 50% research with Outcomes Research® Institute (www.or.org).
  - Stipends approximately $42,000/year US.
  - 20 weekdays/year vacation; 10 days/year meetings.
  - Personal health, life, and malpractice insurance.
  - $5,000/year for approved educational activities.

Requirements

- ECFMG certificate (i.e., passed all steps of the USMLE).
  - Completed anesthesia residency.

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