The use of oral midazolam for perioperative anxiolysis of healthy patients undergoing Mohs surgery: Conclusions from randomized controlled and prospective studies

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Background: Anxiety can complicate any outpatient procedure by causing elevation in blood pressure and heart rate with resultant increase in intraoperative and postoperative bleeding. Anxiety may also reduce patient satisfaction with the surgical experience. Midazolam is an efficacious short-acting benzodiazepine with an excellent safety record. However, little experience is documented on the use of midazolam in outpatient dermatologic surgery.

Objective: To establish the safety and efficacy of oral midazolam in healthy patients undergoing Mohs micrographic surgery.

Methods: Patients undergoing outpatient Mohs surgery were randomized in a double-blind, placebo-controlled study of single-dose midazolam for efficacy and safety in producing anxiolysis of short duration. A subpopulation of patients was evaluated prospectively in a nonrandomized arm of the study. Data on vital signs, anxiety, adverse events, and overall satisfaction were collected and compared using analysis of covariance model.

Results: Forty-four patients were randomized and 31 patients were enrolled in the prospective arm. Socioeconomic and surgical characteristics were similar among the groups. At 60 minutes, there was a clinically and statistically significant reduction in anxiety and alertness in both randomized and prospective arms. There were no major adverse events. Patients in all 3 groups were equally satisfied with their experience.

Limitations: Few patients with high perioperative anxiety were willing to participate in a randomized controlled trial of anxiolytic medication.

Conclusions: Midazolam is safe and efficacious in perioperative anxiolysis for healthy patients undergoing outpatient Mohs micrographic surgery. Midazolam offers the benefits of amnesia, reduced alertness, and reduced blood pressure with no clinically significant adverse effects. (J Am Acad Dermatol 2011;64:310-22.)

Key words: anxiety; anxiolysis; BCC; hypoxia; midazolam; Mohs surgery; SCC; visual analog scale.

INTRODUCTION

Mohs micrographic surgery (MMS) has become the cornerstone treatment of high-risk nonmelanoma skin cancers (NMSCs) as well as those skin cancers requiring tissue preservation for reconstructive purposes.[1-3] MMS is usually an outpatient procedure performed with the patient under local anesthesia and no sedation. The procedure is inherently time consuming, with the mean cumulative time for MMS and reconstruction often exceeding 2 hours.

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Understandably, some patients undergoing MMS for facial skin cancer are anxious about the process. The anxiety may adversely impact patients' experience of the surgery, resulting in abnormalities of cardiovascular physiology, which can increase the risk of bleeding, and may cause a delay in seeking appropriate treatment for other NMSCs.

An ideal pharmacologic agent to reduce anxiety and induce amnesia in patients undergoing outpatient MMS for NMSC would need to be easily administered and have fast onset (within minutes), a wide safety margin, and a short elimination half-life ($t_{1/2}$). Midazolam has these attributes: it is a short-acting (elimination $t_{1/2}$, 1.5-3 hours) imidazobenzodiazepine with hypnotic and amnestic properties.[4] As do other benzodiazepines, midazolam has anxiolytic, sedative, anticonvulsant, and muscle relaxant effects that are dose dependent.[5,6] Midazolam is predominantly administered as an intravenous or intramuscular medication. However, oral midazolam has enjoyed success as a sedative in outpatient gastrointestinal and dental procedures. When administered orally, midazolam undergoes significant first-pass metabolism. The onset of action is first manifested as drowsiness at 15 minutes after administration, with psychomotor effects peaking at 60 minutes as deep sleep, which return to baseline at 120 minutes.[7,8] Midazolam is a pregnancy category D drug. Patients with renal failure have a higher percentage of unbound midazolam as well as markedly decreased renal clearance of the drug, thus extending the duration of action up to 4-fold.[6,8] Midazolam metabolism is affected by drugs influencing P450-3A4 activity and, possibly, by hepatic dysfunction.[6,9-15] Similar to other benzodiazepines, midazolam elimination $t_{1/2}$ is significantly prolonged (mean, 33%) in the elderly.[16]

Midazolam is a safe medication when administered as a single oral dose or in small increments at 2-hour intervals. Serious adverse events reported with midazolam use particularly occurred with intravenous administration in combination with other drugs, typically an opioid, in the setting of conscious sedation or intubation.[17] However, administered as a single agent, midazolam does not produce significant respiratory depression or hypotension.[18] Desaturation occurring with midazolam is transient and responds to verbal stimuli and oxygen supplementation.[18-20] Other serious adverse events are exceedingly rare and are mostly case reports: cardiac arrhythmias, allergic reaction, and disinhibition.[21-25] More commonly reported are nausea, vomiting, cough, and hiccough.[26,27]

CAPSULE SUMMARY

- Oral midazolam offers significant reduction of perioperative anxiety in patient undergoing outpatient Mohs surgery.
- Oral midazolam is also associated with decrease in alertness.
- When used as a single agent, oral midazolam is safe in healthy outpatient Mohs surgery patients with 1.9% incidence of minor respiratory complications and no major or clinically significant adverse events.

To investigate safety and efficacy of oral midazolam in the setting of outpatient MMS, a randomized, double-blind, placebo-controlled study of a single-dose was conducted. In addition, patients who were not eligible to participate in the randomized arm or who refused to participate in the randomized study were enrolled in a prospective, weight-adjusted dose study. The primary outcome measure was the anxiety score at 60 minutes, as assessed by the patient using a 10-point visual analog scale. An additional primary outcome was the adverse event rate, with the intent of establishing equivalency between the two randomized groups.

METHODS

Study design

The protocol and consent form were approved by Mayo Clinic Institutional Review Board (IRB). The study protocol adhered to the ethical guidelines of the 1975 Declaration of Helsinki. The study was registered with http://clinicaltrials.gov.

Eligible patients, 18 years of age and older with two or more sites of biopsy-confirmed squamous cell or basal cell carcinomas limited to head and neck regions requiring MMS in the Department of Dermatology at Mayo Clinic (Rochester, MN) were screened for participation. Patients with a prior history of allergy to midazolam or any of the syrup components, history of hypersensitivity to other benzodiazepines, congestive heart failure (American Heart Association Class III and IV), renal failure requiring hemodialysis, end-stage liver failure, chronic alcoholism or alcohol intoxication within 24 hours of surgery, untreated or uncontrolled open angle glaucoma, uncontrolled hypertension, history of psychoses or affective disorders, neuromuscular disorders such as myasthenia gravis, chronic obstructive pulmonary disease were excluded. Also excluded were patients taking medications interfering with renal excretion or microsomal metabolism unless the last dose was taken 5 or more half-lives[28] before