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ORIGINAL RESEARCH

A retrospective evaluation of the efficacy of midazolam and ketamine as premedication for paediatric patients undergoing elective surgery

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Background: Preoperative anxiety is common in paediatric patients and is associated with negative postoperative outcomes. Sedative premedication may alleviate some of this anxiety. A new sedation protocol using midazolam and ketamine in combination was instituted at our tertiary hospital. We aimed to evaluate the efficacy and the side effect profile of this regimen.

Methods: We conducted a retrospective review of paediatric surgical patients who received oral midazolam (0.25 mg/kg) together with ketamine (3 mg/kg) as premedication, prior to induction of anaesthesia for elective surgery. The Watcha scale was used to assess preoperative and postoperative behaviour. Premedication efficacy was assessed using the Wilson sedation scale together with the 4-point anxiety scale. We further compared the incidence of significant preoperative anxiety with the incidence from a previous study.

Results: We included 146 patients in our study. There was optimal sedation (Wilson sedation score = 1/2) in 47.9% of the patients (CI 39.9–56.1) with failed sedation (Wilson sedation score = 0) in 34.9% (CI 27.6–43.1) and over-sedation (Wilson sedation score = 3/4) in 17.1% (CI 11.8–24.2) of the patients. Optimal anxiolysis (4-point anxiety scale = 1) was achieved in 76.0% of the patients (CI 68.4–82.3). Failed anxiolysis (4-point anxiety scale = 2/3/4) occurred in 23.3% of the patients (CI 17.7–31.6). The majority of patients had no side effects (79.5%; CI 72.1–85.3). For those who experienced side effects, the most common was hypersalivation (12.3%; CI 7.9–18.8). The incidence of postoperative delirium was 3.4% (CI 1.4–8.0) and there was significantly less anxiety compared to our previous regimen (5.5%; CI 2.7–10.6 versus 13.5%; $p = 0.007$).

Conclusion: The combination of midazolam and ketamine appears effective in providing safe sedation and reducing preoperative anxiety. Side effects occurred in up to a fifth of patients; predominantly hypersalivation. The combination of midazolam and ketamine for premedication should be considered for ASA I–II patients without contraindications undergoing elective surgery.

Keywords: paediatric anaesthesia, premedication, midazolam, ketamine, efficacy, side effects

Introduction

Many children experience significant stress and anxiety prior to surgery. There is a strong association between this preoperative anxiety and adverse postoperative outcomes, such as emergence delirium and negative behavioural changes which include bed wetting, sleep disturbance, separation anxiety and poor appetite. These may persist for months following surgery.[1] Sedative premedication is a well-established technique used to alleviate anxiety in these children, and the use of midazolam and ketamine holds great promise. The combination of these drugs allows a lower dose to be used than if these were used individually, potentially resulting in fewer adverse effects.[2] A recent systematic review suggested that trials using combinations of midazolam (0.25 to 0.3 $mg.kg^{-1}$) and ketamine (2 to 3 $mg.kg^{-1}$) provided higher quality sedation with a similar or better side-effect profile than midazolam 0.5 $mg.kg^{-1}$ alone, without prolonging recovery time.[3] The optimal dose, as well as the incidence of adverse events when using these combinations, must still be elucidated.

Different techniques have been employed to alleviate preoperative anxiety in paediatric patients. These include sedative premedication, parental presence at induction and various other behavioural interventions.[4] Sedative premedication is the most well-established technique and a number of drugs have been advocated.[4] Recent reports have suggested that the anxiolytic properties of midazolam together with the sedative-analgesic properties of ketamine make this combination a favourable premedication in the paediatric population,[5-8] and that this is superior to oral midazolam or ketamine alone.[8,9] Rabie[10] demonstrated that the combination of oral midazolam and ketamine premedication produced more calm, awake and quiet children who are easily separated from parents, readily accepted the mask and with decreased postoperative opioid requirements. Funk et al.[5] showed that the increased success rate did not come at the cost of increasing side effects or prolonging recovery.

We undertook a retrospective review to determine: (i) the efficacy of combined oral midazolam and ketamine (MIKE) when used as premedication in paediatric patients aged 2–8 years, undergoing elective surgery at Grey's Hospital (a tertiary hospital in KwaZulu-Natal, South Africa), and (ii) the incidence of preoperative and postoperative adverse effects following the use of MIKE as premedication.

Methods

We conducted a single-centre, retrospective analysis of the Paediatric Anaesthesia Database at Grey's Hospital in Pietermaritzburg, KwaZulu-Natal (KZN), South Africa. The database consists of quality improvement data routinely completed by anaesthetists and recovery nursing staff and is approved by the relevant ethics committees (BE086/18). Institutional approval was obtained for this study.

Patient selection

All patients between ages 2–8 years (weight < 30 kg, ASA I–II) who received MIKE premedication (midazolam 0.25 mg/kg to a maximum of 7.5 mg, with ketamine 3 mg/kg mixed with sucrose) and who were undergoing elective surgery scheduled to be 30 minutes or more, were included in the study. We included patients who underwent surgery between 1 November 2016 and 20 March 2019. Premedication was administered in the theatre complex in a monitored setting. Patients with a compromised airway or with pre-existing neurology (e.g. Down's syndrome or cerebral palsy) were not given premedication and patients who did not swallow the entire premedication were excluded from the analysis.

We extracted patient demographics, parental presence and surgical procedure from the database. We also assessed the baseline behavioural score in the ward using the Watcha scale (Table I) as it is easy to use and has good sensitivity and specificity in comparison to other scores in the assessment of emergence delirium.[11] We also used the Watcha scale to assess behaviour immediately postoperatively. Pre-induction behaviour was assessed using the Wilson sedation score[12] and the 4-point anxiety scale (Table I). These scales are used at our institution because they are intuitive and easy to use, and the Wilson sedation score shows good inter-rater reliability.[13]

We also extracted data related to the anaesthetic technique, duration and time to emergence, as well as recovery room events, interventions and adverse effects. We defined the study endpoints as follows:

- Optimal sedation: a child who was assessed as drowsy, eyes closed but arousable to commands (Wilson sedation score = 1 or 2)
- Failed sedation: a child who was awake and orientated (Wilson sedation score = 0)
- Over-sedation: a child who could only be aroused by mild physical stimulation or a child who was not arousable (Wilson sedation score = 3 or 4)
- Optimal anxiolysis: a child who was calm and cooperative (4-point anxiety scale = 1)
- Failed anxiolysis: a child who was apprehensive but withdrawn, crying, agitated or difficult to control (4-point anxiety scale = 2, 3 or 4).

We further aimed to compare the incidence of significant preoperative anxiety with the incidence from a previous study in our unit that predominantly used trimeprazine and did not employ MIKE premedication.[14]

Statistical analysis

Baseline patient characteristics were reported as mean (standard deviation [SD]) for continuous normally distributed variables, median (interquartile range [IQR]) for data not normally distributed and count (per cent) for categorical variables. Categorical data were analysed using the chi-square test. For all analysis a p-value < 0.05 defined statistical significance. The sample size was determined by the number of eligible patients in the database.

Results

We included 146 patients in the analysis. Median age was 4 (IQR 3–6). Male patients constituted 73.3% (107/146) of the sample. Most patients were calm at the preoperative visit (78.6%) or crying but consolable (11.7%). Eleven patients were either agitated or inconsolable (7.6%). Most patients (55.9%) took the premedication with ease, while 44.1% had to be persuaded.

A parent was present at 95% of the inductions (138/146). Types of surgery included general surgery (55%), orthopaedics (37%), ENT, plastic surgery and ophthalmology (2% each) and maxillofacial surgery (1%). The median time from administration of premedication to induction of general anaesthesia was 40 minutes (IQR 30–55 minutes).

Almost half of the patients reached optimal sedation (47.9%; CI 39.9–56.1; 70/146), while failed sedation occurred in 34.9% (CI 27.6–43.1; 51/146) and over-sedation occurred in 17.1% (CI 11.8–24.2; 25/146) of the patients. Six of the over-sedated patients were unrousable to mild physical stimulation. All of these patients followed an uncomplicated postoperative course without requiring extended monitoring. Most patients reached optimal anxiolysis (76.0%; CI 68.4–82.3; 111/146), while 23.3%

Table I: Clinical behavioural, sedation and anxiety scales

Score	Watcha behavioural scale	Wilson sedation scale	The 4-point anxiety scale
0	Asleep	Fully awake and oriented	
1	Calm	Drowsy	Calm, sleepy
2	Crying, can be consoled	Eyes closed but rousable to command	Apprehensive, but withdrawn from surroundings
3	Crying, cannot be consoled	Eyes closed but rousable to mild physical stimulation (earlobe tug)	Crying
4	Agitated and thrashing around	Eyes closed but unarousable to mild physical stimulation	Agitated, difficult to control

(CI 17.7–31.6; 34/146) experienced failed anxiolysis. Of those patients with failed anxiolysis, 27 appeared apprehensive or withdrawn, while seven were crying or anxious and one was agitated or difficult to control. Most patients experienced no pre-induction side effects (79.5%; CI 72.1–85.3; 116/146). About one-fifth experienced side effects (20.5%; CI 14.7–27.9; 30/146), with the most common being hypersalivation (12.3%; CI 7.9–18.8; 18/146). Paradoxical reactions occurred in 7/146 patients while the remainder (5/146) were not specified.

Mean duration of anaesthesia was less than one hour in 41.3% and less than two hours in 87.6% of the cases. The majority used sevoflurane for induction (88.9%) and continued a volatile maintenance strategy. Only 5% used a ketamine anaesthetic for maintenance of anaesthesia. Opioids were used in 55.5% of cases. The median time to emergence was 10 minutes (IQR 5–18). The Watcha scale scores of patients on arrival in recovery were as follows: asleep (79.3%; 115/145), calm (16.5%; 24/145), crying but consolable (2.1%; 3/145), crying but inconsolable (2.1%; 3/145) and agitated (1.4%; 2/145). Postoperative delirium was thus present in 3.4% of patients (5/145). Postoperative delirium did not require specific treatment in any of the patients.

Most patients had no side effects in recovery (76.0%; 111/146), with drowsiness (10.3%; 15/146) and hypersalivation being the most common (8.9%; 13/146) in patients who did experience side effects. There were six unspecified side effects. One patient had hypoventilation and airway obstruction and required brief stimulation and neck extension to alleviate the incident. The median time to discharge from recovery was 39.5 minutes (IQR 30–50).

We further compared the incidence of significant preoperative anxiety (4-point anxiety score = 3 or 4) with the incidence from a previous study in our unit that did not use MIKE premedication (Watcha score > 2).[14] There was significantly less anxiety (5.5%; CI 2.7–10.6; 8/146 versus 13.5%; CI 11.3–15.8; 125/928; a difference of 8.0%; CI 2.6–11.6; $p = 0.007$) with a similar incidence of postoperative delirium (3.4%; CI 1.4–8.0; 5/146 versus 3.4%; CI 2.4–4.8; 32/928; a difference of 0.02%; CI -4.43–2.41; $p = 0.988$).

Discussion

This study showed that MIKE was able to provide good anxiolysis and sedation, with reduced preoperative anxiety compared to our previous protocols that made use of trimeprazine (Vallergan Forte). There were no significant preoperative side effects and only one serious postoperative complication.

It is common for anaesthetists to encounter uncooperative children for induction of anaesthesia, causing distress for the patient, parents and the perioperative team.[1] Stress in the child is driven by the unfamiliarity of the hospital, the procedure and the anaesthesia; and this stress is compounded by separation from the parents. Reducing this agitation may reduce the complications associated with a difficult anaesthetic induction, such as enuresis, anxiety and postoperative behavioural changes (including separation anxiety, sleep disturbances and alteration in appetite).[1,4] The reduction of preoperative anxiety may also impact the incidence of emergence delirium.[15] Sedative premedication forms one part of a broader strategy, which must also include aspects such as behavioural interventions and possibly parental presence at induction.[4] In some cases, sedative premedication may be inadvisable and non-pharmacological methods are essential in the reduction of psychological trauma to the patient.[16]

Ketamine is a phencyclidine derivative and N-methyl-D-aspartate receptor antagonist, which produces dissociative sedation, and has amnesic, analgesic and sedative effects, usually with retention of protective airway reflexes.[17] It produces a dose-dependent cataleptic state. It may be associated with psychotomimetic effects (hallucinations or nightmares), which are thought to be ameliorated by co-administration with midazolam.[18] Midazolam is a short-acting benzodiazepine acting on gamma-aminobutyric acid (GABA) receptors and has amnesic, anxiolytic and sedative properties. It has minimal cardiovascular and respiratory depressant effect when used for oral premedication at recommended doses (0.4–0.8 mg/kg^{-1}).[18] The intravenous formulation is unpalatable and is mixed with sucrose to allow for voluntary oral administration in children. A palatable oral formulation using cyclodextrin has recently been approved in Europe, but is not yet available in South Africa.[19] By combining ketamine with midazolam, the drugs can be used at lower doses than if used individually, with an improved side effect profile.[2]

Current South African paediatric sedation guidelines do not cover premedication.[17] International guidelines mention MIKE premedication, but do not mention specific dosage ranges to guide practitioners.[20] While recent reports have supported the use of MIKE premedication; these studies have been limited in application by different dosing, timing and outcomes measured across the studies.[5-10] A recent systematic review analysed ten randomised controlled trials that tested MIKE versus midazolam alone.[14] Trials using high (> 4 mg/kg^{-1}) doses of ketamine reported prolonged recovery times and higher complication rates. Trials using intermediate (3–4 mg/kg^{-1}) doses of ketamine reported similar complication rates to those using midazolam alone. Low-dose regimens (midazolam ≤ 0.3 mg/kg^{-1} and ketamine ≤ 3 mg/kg^{-1}) had better side effect profiles and provided better sedation than midazolam (0.5 mg/kg^{-1}) alone.

We showed a decrease in the incidence of significant preoperative agitation compared to a previous study from our unit (5.4% versus 13.5%; $p = 0.007$).[14] This comparison should be interpreted with caution, as we used different scales between the two studies and the initial study did not have the same inclusion criteria as our current study. Additionally, the premedication regimen was not standardised and the incidence of parental presence was not captured in the previous study. However, it is standard practice at our institution to have a parent present in the theatre at the time of induction and as this practice has not changed, it is unlikely to be a confounder. Another problem common to most premedication research is the inconsistent

use of different premedication scales. However, despite the difference in score definitions, they all capture the progression from a high level of anxiety to a low level of anxiety. This becomes particularly true when scores are combined to create broad categories of "anxious" or "not anxious" or "agitated" or "not agitated". In our analysis, we compared the highest level of anxiety ("significant anxiety") from each scale. This provides a valid rationale for conducting comparisons between studies using different sedation scores. The incidence of postoperative delirium was identical.

One child suffered from postoperative apnoea and hypoventilation in recovery, without long-term sequelae. This is not uncommon in the immediate postoperative period but may have been compounded by the use of MIKE. The incidence of apnoea is hard to quantify, but studies using capnography as a monitor have suggested that hypoventilation or apnoea occurs in up to 45% of paediatric patients in recovery, with oxygen desaturations occurring in almost a fifth of patients, with 9% of patients requiring intervention.[21] We did not monitor the patients in our study with capnography, suggesting the incidence of hypoventilation may have been higher, but an intervention was required in only 1/146 patients (0.7%). This is comparable to studies where capnography is not used to monitor for hypoventilation and apnoea.[22]

We omitted one ineligible child from our primary analysis who inadvertently received MIKE premedication. This child presented with upper airway obstruction due to the human papillomavirus and was categorised as ASA III. The child received MIKE and the case was complicated by preoperative hypoventilation and upper airway obstruction. Although these complications were present prior to receiving the premedication, it is possible that MIKE premedication compounded this problem. The case proceeded uneventfully and there were no further adverse events. However, this case highlights the fact that premedication should be used cautiously, if at all, in patients with increased postoperative risk of airway obstruction.

Almost 80% of patients had no pre-induction side effects, with the most common side effect in the rest of the patients being hypersalivation. Our complication rates were similar to studies using equivalent regimens.[2,23,24] More than three-quarters of patients had no side effects in recovery. Over-sedation occurred in 17% of the patients (25/146) and most of these patients were rousable to mild physical stimulation. Only six patients were assessed as unrousable to mild physical stimulation. None of these patients suffered complications related to respiratory depression in the preoperative or postoperative period. We administered the premedication in the theatre complex in a monitored setting and caution is advisable outside of this context.

The primary limitation of this study is its retrospective nature. Although the use of the scoring systems and the administration of the premedication are standardised within the unit, we were not able to exclude variation in these factors as possible confounders. We were also unable to extract the number of patients who refused premedication. Comparison with results from other studies is made difficult by the lack of standardisation of sedation assessment tools, varying dosing of premedication and differing population composition. We have also examined healthy paediatric patients (ASA I–II) with no airway obstruction or pre-existing neurology presenting for elective surgery. Thus, caution should be applied in using MIKE outside of these parameters.

Conclusion

We have shown that MIKE premedication reduces preoperative anxiety and provides good sedation in healthy paediatric patients scheduled for elective surgery. Side effects occur in approximately one-fifth of patients and are mostly limited to hypersalivation. Further research should look at expanding the use of MIKE to different populations and aiming to reduce the side effect profile of the existing regimen.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

Ethical approval for the study was obtained from the University of KwaZulu-Natal Bio-Medical Ethics Committee (BE452/14). There was no requirement for written consent, as this was a low risk observational study. Institutional approval was obtained for this study from Grey's Hospital as well as the KZN Department of Health (KZ_201812_017).

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