Midazolam for urethral catheterisation in female infants with suspected urinary tract infection: a case-control study

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Received 20 October 2012
Revised 4 December 2012
Accepted 14 January 2013
Published Online First 22 February 2013

ABSTRACT

Objectives Based on the 2010 Israeli Medical Association recommendations, young children with suspected urinary tract infection (UTI) are mildly sedated with oral or intranasal midazolam to reduce the distress associated with urethral catheterisation (UC). The primary objective of this study was to examine the rate of urine culture contamination (UCC) in infants who underwent UC with and without sedation. Other objectives were to evaluate serious adverse events and emergency department (ED) length of stay.

Methods A retrospective case-control study was conducted in a paediatric ED.

Results Two cohorts of patients who underwent UC were compared, 164 female infants who were sedated with midazolam (case subjects) and 173 who were not (controls). Cases and controls had a mean temperature of 38.3°C and 38.2°C, respectively. One hundred and forty-one patients were treated with oral midazolam and 23 received the drug intranasally. Cases and controls had a UCC rate of 20/164 (12%) and 45/173 (26%), respectively. Compared with controls, cases had lower odds of UCC (OR=0.39, 95% CI 0.21 to 0.73).Serious adverse events related to midazolam were not recorded. Case subjects and controls had a mean ED length of stay of 2.96 h and 2.50 h, respectively. The difference between the groups was statistically significant ($p<0.014$, 95% CI 0.10 to 0.90 for difference between means).

Conclusions In this cohort of febrile infants, sedation with oral or intranasal midazolam reduced the risk of culture contamination during UC without causing serious adverse events. However, patients who were treated with sedation had longer length of stay in the ED.

INTRODUCTION

Urinary tract infection (UTI) is one of the most common serious bacterial infections in young infants, especially females.[1] Urethral catheterisation (UC) is considered the preferred technique for obtaining urine for culture in febrile infants with suspected UTI. This technique is less invasive and less painful than supra-pubic aspiration (SPA); however UC samples are more likely to be contaminated than samples obtained by SPA.[1–4] Previous studies revealed that UC might be a distressing procedure for young children. For this reason, treatment with midazolam prior to voiding cystourethrography is now considered the standard of care.[5–7]

In order to reduce the level of anxiety experienced by children undergoing invasive procedures, such as UC in the emergency department (ED), the Israeli Medical Association (IMA) issued guidelines recommending the use of oral or intranasal midazolam.[8] Consequently, in the paediatric ED of Rambam Health Care Campus (RHCC), patients between the ages of 4 months and 24 months have been sedated with midazolam for UC relatively frequently. Based on the ED protocol, if the child is older than 4 months of age, has an American Society of Anaesthesiologists (ASA) physical status classification of ≤2, and has been fasting for >1 h, the patient and his/her caregivers are offered the option of oral midazolam by the treating physician. If the oral route fails, midazolam is given intranasally.[8] If caregivers refuse to have their child treated, the procedure will be performed with no sedation.[8] The impression of experienced physicians at the paediatric ED of RHCC was that midazolam reduces fear and distress, and enables proper restraint during catheterisation, and is a clean technique.

The main objective of our study was to determine whether infants who were treated with midazolam for UC had lower rates of urine culture contamination (UCC) compared with those who did not. Other objectives were to evaluate serious adverse events related to midazolam and ED length of stay with and without midazolam.

METHODS

Study design and subjects

A retrospective case-control study was conducted in the paediatric ED of RHCC in Haifa, Israel. We extracted the medical records and identified all patients aged 4–24 months who had UC as part of the evaluation for UTI between 1 January 2011 and 31 December 2011.

Two cohorts of patients who underwent UC were compared; females who were sedated with oral or intranasal midazolam (case subjects), and females who had no treatment (controls). The study was approved by the RHCC ethics committee.

Variables

The following variables were extracted from the electronic patient files of the hospital's database: demographics (age, weight, gender), degree of fever at ED presentation as measured by the triage nurse, presence of vesicoureteral reflux or any other congenital urinary tract malformation, ED length of stay (total time from initial assessment by the emergency physician until discharge), and urine cultures results (positive culture, negative culture, contaminated culture). A positive urine culture was defined as $\geq 10^4$ colony-forming unit per millilitre (cfu/ml)

To cite: Shavit I, Feraru L, Miron D, *et al*. *Emerg Med J* 2014;**31**:278–280.

of a urinary pathogen. UCC was defined as the presence of more than two pathogens at greater than or equal to 10^4 cfu/ml, or non-pathogenic bacteria. For each case subject, the following parameters were also recorded: mode of midazolam administration (oral/intranasal), dosage in milligrams per kilogram (mg/kg), and any severe adverse event due to midazolam. According to departmental policy, the nurse responsible for the patient recorded any serious adverse event related to midazolam. Department protocol defines a serious adverse event as 'apnoea, aspiration, hypoxia (saturation of 90% or less), or admission to the hospital due to midazolam-related adverse reaction'.

Outcome measures

The primary outcome measure of the study was the rate of UCC.

The secondary outcome measure of the study was the presence of any serious adverse event.

The third outcome measure of the study was the mean ED length of stay.

Statistical analysis

A χ^2 test was used to assess differences between categorical variables, and a Student t test was used for the analysis of differences in the means of continuous variables. All statistics were calculated using StatsDirect statistical software (V.2.6.6, StatsDirect Limited, Cheshire, UK).

RESULTS

Demographic characteristics

During the study period, 417 infants underwent UC for UTI (figure 1). Twenty-one patients had a urinary tract malformation and were excluded from the study. Of the 396 eligible subjects, 337 were females and 59 were males. The case group included 164 female infants with a mean age of 17.5±6.1 months and a mean weight of 10.4±1.8 kg. The control group had 173 female infants with a mean age of 15.2±6.7 months and a mean weight of 9.9±1.6 kg. Case subjects and controls had a mean rectal temperature of 38.3±1.19°C and 38.2±1.20°C, respectively.

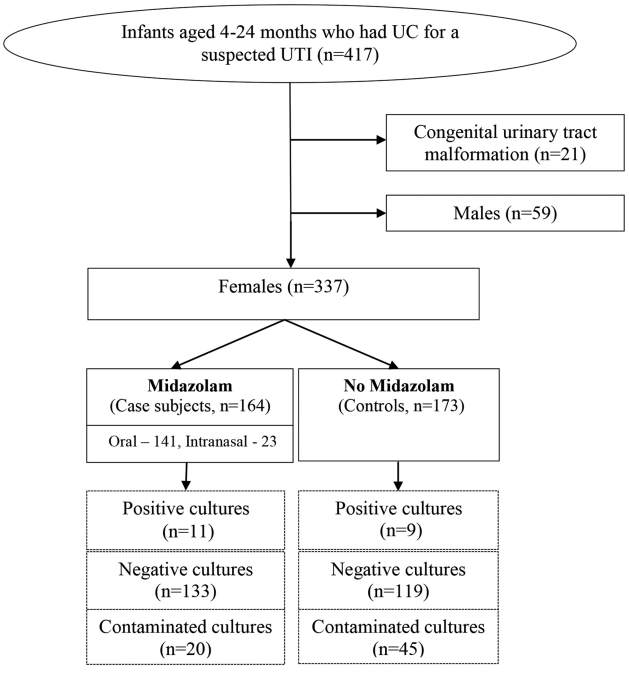

Figure 1 Comparison between patients who were sedated with midazolam and patients who had no treatment. UC, Urethral catheterisation; UTI, Urinary tract infection.

Of the 164 case subjects, 141 were treated with oral midazolam and 23 received the drug via the intranasal route. Mean oral and intranasal doses of midazolam were 0.65 mg/kg and 0.5 mg/kg, respectively.

Urine cultures and contamination rate

Case subjects and controls had 11 and 9 positive samples, respectively, with no statistical difference between the groups (p=0.65, 95% CI 0.5 to 3.2 for difference between means). Cultures yielded three types of bacteria: 15 *Escherichia coli*, 4 *Klebsiella pneumoniae*, and 1 *Proteus mirabilis*. One of the samples of the control group yielded a mixed growth of *E coli* and *P mirabilis*.

Cases and controls had a UCC rate of 20/164 (12%) and 45/173 (26%), respectively.

Cases had significantly lower odds of culture contamination compared with controls (OR=0.39, 95% CI 0.21 to 0.73). Three of the 65 culture contaminations yielded non-pathogenic bacteria. These patients did not develop symptoms of clinical disease.

Serious adverse events

Serious adverse events related to midazolam were not recorded in 161 cases. This information was missing in three cases.

ED length of stay

Case subjects and controls had a mean ED length of stay of 2.96±0.69 h and 2.50±1.07 h, respectively. The difference between the groups was statistically significant (p<0.014, 95% CI 0.10 to 0.90 for difference between means). The range of length of stay was 1.16–5.25 h for the case subjects, and 0.41–4.63 h for the controls.

DISCUSSION

We found that female infants who were sedated with oral or intranasal midazolam had lower odds for UCC compared with those who were not sedated. The rate of contamination with midazolam was 12% compared with 26% in the non-midazolam group. Both groups had a similar rate of positive cultures. This is the first study to investigate the impact of sedation on the risk of culture contamination due to UC in children with suspected UTI.

Reducing the rate of UCC has clinical importance because, compared with SPA, obtaining a urine sample by catheterisation brings a higher risk for contamination, which may lead to unnecessary antibiotics pending final identification of the organism.[4 9]

These findings could be explained by the anxiolytic and sedative effects of midazolam; it can be assumed that sedation enabled proper restraint of the patient during the procedure, and was a clean catheterisation technique. Of note, is that IMA protocol recommends relatively high doses of oral midazolam (0.75 mg/kg, with a maximal dose of 10 mg) or intranasal midazolam (0.5 mg/kg, with a maximal dose of 5 mg).[8] The mean oral and intranasal doses of midazolam in our study were 0.65 and 0.5 mg/kg, respectively.

Importantly, despite the fact that most study patients were febrile, no serious adverse reactions were recorded. Data from

recent studies indicate that oral midazolam is safe and effective for paediatric patients undergoing stressful procedures.[8 10 11] Our findings support these data. It is important to note however, that only patients who were older than 4 months of age, with an ASA score of 2 or less and a fasting time of more than 1 h, were treated with midazolam.

We found that sedation prolonged the patient's length of stay. Case subjects had a mean ED length of stay of 2.96 h as opposed to controls who a mean ED length of stay of 2.5 h (27.6 min longer). This finding is consistent with a previous study that reported 17.1 min prolongation of mean length of stay when oral midazolam was used in the ED.[12] In settings where there is heavy pressure to ensure optimal flow of ED patients this could be a potential impediment to the use of midazolam prior to UC.

Our study has limitations inherent in a retrospective chart review. First, data regarding midazolam's adverse reactions did not allow evaluation of non-severe adverse events, such as vomiting or oversedation. Second, the study sample came from a single centre, and some relevant information, such as parent satisfaction with the procedure, could not be obtained from the records. Third, according to hospital data, approximately 90% of the UC in the 4–24-months age range are performed on female infants; for this reason, we included only females in the analysis.

Despite these limitations, we believe that this study provides valid information on the value of oral and intranasal sedation in febrile children in the ED.

CONCLUSIONS

The findings of this study suggest that sedation with oral or intranasal midazolam reduces the risk for UCC during UC in young female infants with suspected UTI. However, ED length of stay was increased.

This study supports recent evidence demonstrating that young children can be safely treated with midazolam for stressful ED procedures. We believe that our findings contribute to the quest to reduce pain and distress experienced by children in the ED. Prospective studies are needed to determine if sedation with oral or intranasal midazolam is a safe and effective therapeutic option for these patients.

Contributors IS conceived the idea for the study, analysed the data, conducted the statistical analysis, and drafted the manuscript. LF collected and analysed the data. DM critically reviewed the article. GW critically reviewed the article and the literature. IS has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests None.

Ethics approval Rambam Health Care Campus Ethics committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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Emerg Med J 2014 31: 278-280 originally published online February 22, 2013
doi: 10.1136/emermed-2012-202088