

Use of sedative drugs at reducing the side effects of voiding cystourethrography in children

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Background: Imaging of the kidneys and urinary tract has a significant and critical role for diagnosis of genitourinary system diseases. Although technological progress goes toward less invasive approaches, some of the current methods are still invasive and annoying. Voiding cystourethrography (VCUG) is the best and most accurate method for diagnosis and grading of vesicoureteral reflux. VCUG is a distressful procedure that gives serious anxiety and pain in a large proportion of children and fear for parents; therefore, using effective sedative drugs with the least side effects is necessary and should be considered. **Materials and Methods:** In this review article, importance and efficacy of different drugs before catheterization VCUG be compared in the base of literature survey on EMBASE, PubMed, and Cochrane source. **Results:** We found that the treatment should be based on nonpharmacological and pharmacological methods; nonpharmacological treatment includes the psychological preparation before procedures as a safety precaution with little or no risk modality, as well as reassuring support. The presence of parents during painful procedures cannot alleviate children distress. Pharmacological methods include oral midazolam (0.5 mg/kg) and intranasal use (0.2 mg/kg) that had been used 10 min before the procedure can effect on anterograde amnesia and sedation without considerable effect on accuracy and grade of reflux. Nitric oxide has a shorter recovery time versus midazolam but has a potential risk for deep sedation and may interfere with the child's voiding phase. **Conclusion:** In summary, oral midazolam of 0.5–0.6 mg/kg or 0.2 mg/kg intranasal is acceptable drug that can be used before VCUG.

Key words: Children, cystourethrography, midazolam, sedative

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INTRODUCTION

Voiding cystourethrography (VCUG) is the gold standard for diagnosis and grading of vesicoureteral reflux and other bladder problems as parts of evaluation of the lower and upper urinary tract that mainly used in small infant and children. It is an invasive procedure that should be done in radiology ward by insertion of a catheter, filling bladder with radiopaque material, and after then, the conscious child should be asked to void spontaneously.^[1] There are two types of cystography: traditional or VCUG and direct radioisotopes cystogram both required to catheterization, and VCUG is necessary for male children at the first investigation.^[2-5]

METHODS

In this review article, we evaluate the importance of distress and find the appropriate modalities that can help children, parents, and staff during VCUG performance by comparison of published literatures in EMBASE, PubMed, and Cochrane sources to catch existing research work on sedation in VCUG and related drugs, such as midazolam, nitric oxide, propofol, and chloral hydrate.

Voiding cystourethrography and sedation

Distress is a more comprehensive term beyond of just pain stimulus. Incidence of serious distress may occur in 61%–71% of cases during VCUG that may occur in different stages from entering room, catheterization, filling of bladder, voiding, and leaving room.^[6] It is

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important that medical team talk to families and parents in advance about the procedure and small booklets containing the necessary information should be accessible for them.^[7] Anxiety and stress in children candidated for cystography can be very intense that affect other family members, especially parents. These procedures can create considerable anxiety that may impair the patient's diagnosis and treatment. The lack of pain and anxiety control, properly interferes with the diagnosis and treatment, can also expose children to the risk of depression and other mental disorders in long term.^[8] To manage pain and anxiety in children, several regulations have been introduced, including behavioral therapy, psychotherapy such as hypnotherapy and relaxation, general anesthesia, and the use of sedative drugs (including benzodiazepines and nitric oxide). There are two decades that studies tried seriously to use an ideal drug for sedation, pain, and anxiety control before procedure; this drug should be fast onset action, effective with short recovery time with minimal side effects, safe, and easy to use by medical staff.^[9]

Role of parental presence during procedure as an adjuvant to nonpharmacologic therapy

A systematic reviews tried to assess the effects of parental presence in the pediatric treatment room on child, parent, and health professional that show parental presence may not have a clear, direct influence on child distress, and behavioral outcomes.^[10] In other study, it has been shown that the physicians and nurses in the study population tended to prefer parents not to be present during procedures as the level of procedure invasiveness increased.^[11]

Nonpharmacological methods

There are no validated prediction tool exists for VCUG distress occurrence in children. Nonpharmacological interventions may range between simple educational^[12] and more structured play therapy sessions^[13,14] and hypnoses.^[15] Preparation, distraction, and reassurance before, during, and after the procedure are likely to reduce the distress of the procedure with little or no risk.^[16-18]

Pharmacological treatment

It includes sedative, antianxiety, and analgesic medications and anesthetics.

Sedating drugs

For a successful cystography procedure, some degree of children consciousness for voiding phase is essential; therefore, patient's consciousness level should be evaluated regularly as much as they should obey orders and tip of advice.

Midazolam

It has been discussed in several references that the use of benzodiazepine drugs will be effective in reducing

psychological impacts of invasive diagnostic procedures, which are especially important in children.^[19] Midazolam belongs to the family of benzodiazepine with antianxiety and sedative effects. It has a rapid onset and short duration of action so that it is commonly used in children and adults to perform diagnostic and therapeutic procedures. It creates anterograde amnesia, so it can prevent undesirable remembrance when a process is painful for the patient.^[20,21]

This drug is used for premedication in different forms, such as intravenous, intramuscular, sublingual, oral, and intranasal. The half-life of midazolam is about 2 h. A half-life of more than 7 h has also been reported due to genetic dissimilarities of different persons. The action mechanism of midazolam is similar to diazepam (resonance opening chloride channels in gamma-aminobutyric acid neurotransmitters, hyperpolarization of the membrane cells, and neuronal stimulates resistance).

Midazolam is metabolized in the liver. Several metabolites are produced during the hydroxylation, and its major metabolite (1-hydroxymethyl midazolam) that is a less active metabolite than midazolam is excreted in urine mainly as conjugated with glucuronide.^[22]

Several studies have examined the effect of midazolam. Two studies applied oral midazolam with the dose of 0.5 mg/kg and 0.6 mg/kg. The maximum dose given was 15 mg, 15–30 min before the procedure.^[23,24] In another study, the dose of intranasal (0.2 mg/kg) was used 5 min before the procedure.^[25] All studies above showed a significant distress reduction with midazolam in the group under study, although in one study, complications such as paradoxical agitation were reported in <5% of children for whom flumazenil was used as antidote of midazolam.^[26] One of the benefits of midazolam investigated by who Bozkurt compared the effects of high-dose intranasal midazolam (0.5 mg/kg) with placebo group in VCUG and shows there are no differences between the two groups in terms of the degree of reflux.^[27]

Nitric oxide

Nitric oxide is a powerful painkiller that is the central antagonist of the N-methyl-D-aspartate receptor complex, which is an advantage compared to midazolam. In one study, nitric oxide concentration of 50% was compared with the oral midazolam, in 24 children. No significant difference between midazolam and nitric oxide was reported. However, the urination time in nitric oxide was longer (15 min vs. 2.7 min). Nitric oxide had also a shorter recovery time (29 min vs. 63 min [$P < 0.001$]) than midazolam.^[23]

Chloral hydrate

In one study with three case groups, chloral hydrate is compared with oral midazolam and placebo with dose of

25 mg/kg. No statistically significant difference was found in stress reduction. However, this result may be due to the low dose or low sample size of the study.^[28]

Propofol

In one study, low-dose propofol was used under the supervision of an anesthesiologist. This study showed that propofol reduces the ability of the child to urinate completely and may interfere in the diagnosis of reflux.^[29]

Opiates

There is no study on examination of opiates in VCUG. However, in one study, an intranasal form of fentanyl was used for severe pain of children at emergency department. Opiates may also interfere with bladder function.

Local anesthetics

Lidocaine gel reduces pain during catheterization in VCUG, so it is recommended.^[30]

The effect of sedation on children postoperative behaviors

The effect of pain experience on newborn and infant well be known; consequences in the short term include altered patterns of behavior, and changes in physiological parameters and in long-term may have an altered response to pain. Alleviating potentially painful or stressful events may lead to a better medical and neurodevelopmental outcome.^[31]

In older children, it has been shown that the development of adverse postoperative phenomena, such as emergence delirium and postoperative behavioral changes, is related to levels of preoperative anxiety.^[32]

The minimum time interval between administration of oral midazolam and separation of children from their parents which has been studied shows that midazolam administered orally produces significant anterograde amnesia when given as early as 10 min before a surgical procedure.^[33]

Another study shows that behavioral change after a procedure in children is unknown; in spite of using midazolam, sleep pattern changes in children who received midazolam before surgery show that they were awake significantly less during the night compared to control group who did not received midazolam. This study recommends more study for children postoperative behavioral changes.^[34]

The effect of sedation on cystographic results

It has been shown that midazolam in high dose (0.5 mg/kg) and low dose (0.2 mg/kg) has not effect on difference in reflux grading in Stokland *et al.* study while Herd *et al.* show that the use of midazolam may under grade reflux as

much as one grade in half of cases.^[24,25] While in other study, high-dose intranasal midazolam (0.5 mg/kg) compared with placebo group and showed there are no differences between the two groups in terms of the degree of reflux.^[27]

CONCLUSIONS

In summary, sedation reduces distress during VCUG, and midazolam is the drug that has been studied the most and determined to be safe. With the dose of 0.5–0.6 mg oral (maximum 15 mg) or 0.2 mg/kg intranasal, it is effective without serious adverse effect. It seems that midazolam is shown not to interfere with detection of reflux and grading it prominently while other anesthetic agents have potential risk for deep sedation and may interfere with the child's voiding phase; we believe it is better that each guideline must be designed based on culture and religious markers of a society, but the use of midazolam in a sweet by oral or nasal way ranged from 5 to 30 min before catheterization with the use of nonpharmacologic modalities and local sedation besides professional personnel in a warm atmosphere, all results in VCUG which can decrease distress for children, parents, and medical staff during procedure and postoperative behavioral disorders.

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Conflicts of interest

The authors have no conflicts of interest.

AUTHORS' CONTRIBUTION

- YR contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work
- AA contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work
- AA contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work
- SS contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work
- MN contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work
- MB contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work
- AA contributed in the conception of the work, revising the draft, approval of the final version of the manuscript,

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- AA contributed in the design of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work
- RR contributed in the conception and design of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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