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# Sedation with Intravenous Pethidine and Midazolam for Renal Biopsies in Paediatric Patients in a Regional Hospital: A Retrospective Study

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**Abstract** A retrospective study was conducted to investigate the effectiveness and safety of a sedation protocol with pethidine and midazolam for ultrasound-guided percutaneous renal biopsy in 64 paediatric cases in a regional hospital from 1 July 1998 to 30 June 2005. Forty-nine (77%) patients were successfully sedated with pethidine and midazolam (group A). The mean dose of pethidine for group A patients was 0.56 mg/kg while that of midazolam was 0.21 mg/kg. Fifteen (23%) patients required ketamine in addition to pethidine and midazolam (group B). Both age (student's t test, $p<0.0001$) and sex (chi square test, $p<0.025$) were statistical significantly associated with the use of ketamine using univariate analysis. Group B patients (range 2-14 y.o., mean = 6.6 y.o.) were younger ($p<0.05$) than group A patients (range 3-18.5 y.o., mean age = 11.6 y.o.). The percentages of transient oxygen desaturation were 2% for group A and 13.3% for group B, this difference was not statistically significant (Fisher's exact test, $p=0.134$). In conclusion, the combination of intravenous pethidine and midazolam was an effective and safe sedation protocol for ultrasound-guided percutaneous renal biopsy in children.

**Key words** Children; Renal biopsy; Sedation

## Introduction

Ultrasound-guided percutaneous renal biopsy is widely used to diagnose renal pathology.[1] In paediatric patients, this procedure is technically challenging as the size of kidney is smaller. In addition, the kidney is more mobile and it is always difficult to maintain a child in a static position.

The purpose of sedation for invasive procedure is to control pain, alleviate anxiety, and prevention of any motion that may affect the procedure to be performed successfully. It also provides an appropriate degree of memory loss or decreased awareness after the procedure.[2] General anaesthesia, lytic cocktail or combination of midazolam and ketamine is used for renal biopsy in small children.[1] 'Lytic cocktail' is a combination of meperidine (pethidine), promethazine and chlorpromazine. However, the rate of therapeutic failure and the rate of life-threatening adverse events, including respiratory depression and mortality, are high.[3,4] Since the dosage of lytic cocktail cannot be titrated easily, it is an unfavourable and undesirable method for paediatric sedation.[4] Alternative sedatives and analgesics should be considered as commented by the American Academy of Pediatrics.[4] The combination of midazolam and ketamine is also used for procedural sedation. Ketamine induces sedation, analgesia and amnesia while midazolam

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controls those psychic events associated with the use of ketamine. However ketamine does not have any antidote. In contrast, the combination of pethidine and midazolam is effective and safe in many invasive procedures like bone marrow aspirations, incision and drainage, lumbar puncture and thoracocentesis.[5] However pethidine's sedative effect may take few hours to be worn off. Moreover, there are antidotes available in case of overdose.

Pethidine is a synthetic narcotic. It is commonly used as a pre-medication for painful procedure or as a treatment for post-operative pain. It can produce prompt but short-lasting analgesia which can last for three to four hours. It causes less constipation when compared with morphine. Pethidine, in case of overdose, causes respiratory depression and gastrointestinal immobility which can be reversed by naloxone.[6]

Midazolam is a benzodiazepine. It has the advantages of rapid onset of action of one to five minutes and short duration of action lasting around one to two hours when given intravenously. It has the desirable side effect of retrograde and antegrade amnesia. Midazolam, in case of overdose, causes respiratory depression which can be reversed by flumazenil, a competitive antagonist.[6]

In our literature search, we found that there had been no universally adopted sedation protocol for ultrasound-guided percutaneous renal biopsy in paediatric population worldwide. We adopted the combination of intravenous pethidine and midazolam as the sedation protocol. Intravenous ketamine would be added if the above sedation failed. As the absorption rate of intramuscular injection of pethidine is variable, we only included those patients who were given intravenous pethidine. The aim of this study was to explore the effectiveness and safety of this sedation protocol in paediatric ultrasound-guided percutaneous renal biopsy.

## Methods

### *Patients*

A retrospective review was conducted in patients who were admitted for ultrasound-guided percutaneous renal biopsy under sedation to the Department of Paediatrics and Adolescent Medicine, Alice Ho Miu Ling Nethersole Hospital, Hong Kong, from 1 July 1998 to 30 June 2005. Patient records for all children were retrieved and studied. Only cases using the combination of intravenous pethidine and midazolam with ketamine added when necessary were included in our study.

### *Protocol*

As suggested by the American Academy of Pediatrics, our patients were kept nil by mouth for at least four hours prior the procedure.[7] An intravenous access was placed *in-situ*. Intravenous pethidine was injected to all patients. Immediately before the injection of lignocaine as local anaesthesia, intravenous midazolam was given. The dose of midazolam was titrated to the desired effect. Intravenous ketamine was added when the above regimen was inadequate according to individual's clinical decision.

All renal biopsies were performed by the same two doctors. The adequacy of sedation was assessed by the chief doctor. The assistant doctor monitored the cardiopulmonary status of the patient and assisted in the procedure if required. Both doctors were well trained in paediatric airway management and resuscitation skills.

The patients were monitored continuously by pulse oximetry (audible and visual signals). Electrocardiographic monitoring was also used. The heart rate and oxygen saturation were recorded. The blood pressure was measured by Dinamap and the respiratory rate was monitored regularly. The occurrence of vomiting was also reported. Oxygen, suction equipment, resuscitation gears and antidotes including naloxone and flumazenil were readily available. All biopsies were done under ultrasound-guidance with an automatic biopsy device (Temno). After the procedure, the patient's ventilatory status, oxygen saturation, haemodynamic variables and level of consciousness, were closely monitored by the nurses until the patients had fully recovered from the sedatives.

The effectiveness and safety of this sedation protocol were analysed. The characteristics of patients and the dosage of sedatives used were compared between the group that required only pethidine and midazolam (group A) and the other group that required ketamine in addition to pethidine and midazolam (group B). Complications including oxygen desaturation, change in heart rate, blood pressure and respiratory rate and the occurrence of vomiting were studied. Level of oxygen desaturation has not been defined by the American Academy of Pediatrics Sedation Guidelines. We defined desaturation as $SaO_2$ less than 90% as this was the level considered to be of clinical significance.[8] The characteristics of patients having oxygen desaturation and the dosage of sedatives used were compared with patient who did not have oxygen desaturation.

### *Statistical Analysis*

Student's t tests were used for analysing continuous variables and chi-square tests were used for analysing

categorical variables. Fisher's exact test was used to evaluate categorical variables when appropriate. A *p*-value of less than 0.05 was considered statistically significant.

## Results

The flow chart of patients included in our study was shown in Figure 1. A total of sixty-four cases were included in the study according to the set criteria over the seven-year study period. All biopsies were done on native kidneys. The mean age of patients was 10.4 years old (ranged 2-18.5). Table 1 showed the characteristics of both groups.

All children were assessed by doctors for fitness of sedation and the baseline vital signs were recorded prior the procedure. They were classified as class I, II and III according to the American Society of Anethesiologists (ASA) physical status classification.[7] All the patients classified as ASA class III had stable cardiopulmonary status.

In our study, 49 (77%) patients could be well sedated with only pethidine and midazolam with the procedure of ultrasound guided percutaneous renal biopsy completed. Mean pethidine and first dose midazolam doses were 0.57 mg/kg (0.4-0.97) and 0.18 mg/kg (0.05-0.32) respectively. From Table 1, we see that there was no difference in the dosages of pethidine (student's t test, $p$=0.31) and the first dose midazolam (student's t test, $p$=0.30) used for both

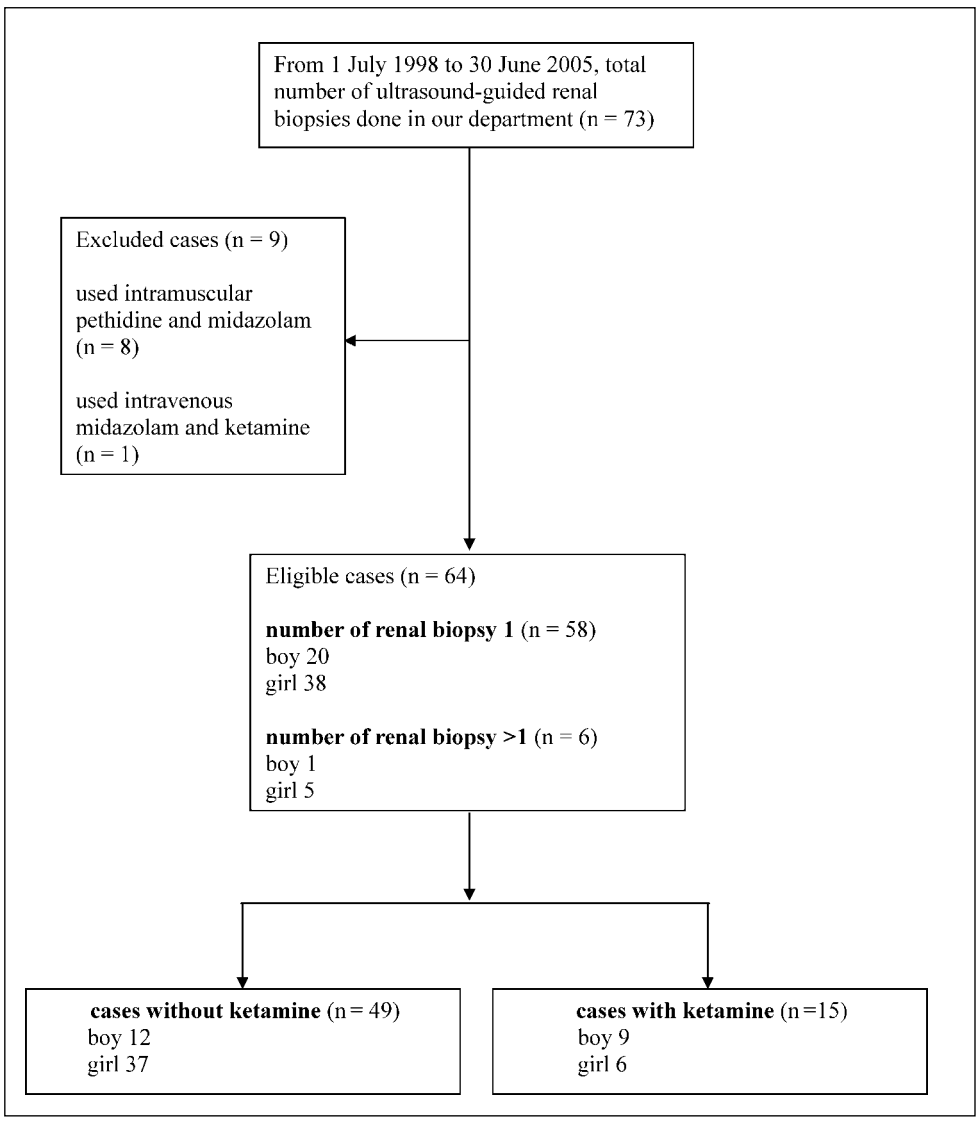


**Figure 1** Flow chart of patients included in our study.

groups. Group B patients were significantly younger than group A (student's t test, $p<0.0001$). Females were more likely to fall into group A (chi square test, $p<0.025$). Total dose of midazolam was significantly higher in group B (student's t test, $p<0.0001$).

In this study, no major complication was documented in the case notes. All patients did not require antidotes or resuscitation. They had stable heart rate, blood pressure and respiratory rate after the sedatives were administered. No vomiting was reported as well. Although the percentages of transient oxygen desaturation were 2% for group A and 13.3% for group B, this difference did not reach statistically significant level (Fisher's exact test, p=0.134). Table 2 illustrated the characteristics of these patients.

Sedative-analgesic dosage used in patients with or without transient oxygen desaturation was compared in Table 3. Among those patients who did not require ketamine, the only one patient with transient oxygen desaturation received a relatively high dose of pethidine (0.8 mg/kg) while the two patients with desaturation belonging to the ketamine group also received a relatively

**Table 1** Characteristics of study groups

| | **Group A (n = 49)** | **Group B (n = 15)** | ***p*-value** |
|---|---|---|---|
| Females % (n) | 76% (37) | 40% (6) | <0.025* |
| Age (years) | 11.6 ± 3.8 | 6.6 ± 3.7 | <0.0001* |
| Pethidine dose (mg/kg) | 0.56 ± 0.14 | 0.61 ± 0.21 | 0.31 |
| First dose midazolam (mg/kg) | 0.18 ± 0.06 | 0.20 ± 0.05 | 0.30 |
| Total dose of midazolam (mg/kg) | 0.21 ± 0.11 | 0.39 ± 0.10 | <0.0001* |

All data were expressed as means ± standard deviation.

SD=standard deviation, *=statistical significance ($p$ <0.05), n=number of cases

**Table 2** Characteristics of patients having transient oxygen desaturation

| | **Patient 1** | **Patient 2** | **Patient 3** |
|---|---|---|---|
| Sex/ Age (years) | M/6.2 | M/13.7 | M/14 |
| ASA Class | I | I | III |
| Midazolam dose (mg/kg)* | 0.34 | 0.20 | 0.36 |
| Pethidine dose (mg/kg) | 0.80 | 0.80 | 0.60 |
| Ketamine dose (mg/kg) | 1.00 | Nil | 0.49 |
| Reason for renal biopsy | Microscopic haematuria | Microscopic haematuria | Nephrotic syndrome, gross haematuria, hypertension, renal function impairment |

*=total equivalent dose of midazolam used

**Table 3** Comparison of sedative-analgesic dosage used in patients with or without oxygen desaturation

| | **Patients without ketamine (n = 49)** | | **Patients with ketamine (n = 15)** | |
|---|---|---|---|---|
| | **without oxygen desaturation (n = 48)** | **with oxygen desaturation (n = 1)** | **without oxygen desaturation (n = 13)** | **with oxygen desaturation (n = 2)** |
| Pethidine dose (mg/kg) | 0.55 ± 0.14 | 0.80 | 0.59 ± 0.10 | 0.70 |
| Midazolam dose (mg/kg)* | 0.21 ± 0.10 | 0.20 | 0.40 ± 0.10 | 0.35 |
| Ketamine dose (mg/kg) | Nil | Nil | 0.61 ± 0.22 | 0.75 |

Data in the study groups were expressed as mean ± standard deviation.

SD=standard deviation; n=number of cases; *=total equivalent dose of midazolam used

high mean dose of 0.7 mg/kg. Note that the total midazolam dose used was, however, similar in both groups.

## Discussion

There was no consensus of sedation protocol for paediatric ultrasound-guided percutaneous renal biopsies. We have shown that the combination of intravenous pethidine and midazolam was an effective and safe sedation protocol for this purpose.

In Hong Kong, the Co-ordinating Committees in Paediatrics, Radiology and Anaesthesiology (COC) has formulated a set of guidelines for sedating children for diagnostic and therapeutic procedures in year 2000.[6]

In the COC guidelines for sedation in painful short procedures, e.g. biopsies with or without image guidance, patient should be given midazolam 0.1-0.2 mg/kg intravenously (for sedation and amnesia) together with local anaesthetic. The alternative is to give pethidine 0.5 mg/kg intravenously, and if no respiratory depression is observed in 5 minutes, midazolam is added intravenously. The dose of midazolam is carefully titrated at 0.025 mg/kg boluses up to a maximum of 0.2 mg/kg. The third choice is ketamine. The dose of ketamine is 0.5-1 mg/kg with additional bolus doses of 0.25-0.5 mg/kg up to a maximum total dose of 2 mg/kg over 20 minutes for difficult patients. Ketamine may be given intramuscularly at 2-4 mg/kg. Atropine 0.01-0.02 mg/kg may be given intravenously or intramuscularly to reduce salivation.

According to the COC guidelines, one of the three options for sedating children who undergo painful short procedures is using only intravenous pethidine and midazolam. In our study, 77% of the cases complied with the guidelines in this aspect and the mean dose of pethidine used in these forty-nine patients was comparable to that recommended in the COC guidelines. In addition, the COC guidelines stipulated that the maximum dose of midazolam should be 0.2 mg/kg. There were only 47% of the cases under our study fulfilled this recommendation.

Our result showed that nearly half of our patients could not be well sedated with pethidine and a midazolam dose of ≤0.2 mg/kg. This may prompt to a review in the COC guidelines for painful short procedure. The higher dose required could be due to different pharmacogenomics in different people. Other non-pharmacological methods, e.g. cuddling and distraction for gaining patient co-operation should not be overlooked.[9] In particular, our patients were not routinely advised on sleep deprivation before the procedure. This could attribute to the higher sedation requirement. Sleep deprivation can result in better sedation.[9] Furthermore, if topical anaesthetic, EMLA (2.5% lignocaine and 2.5% prilocaine in a cream base) was added at the puncture site, it was possible that less amount of sedatives-analgesics would be needed by our patients.[2,9]

In general, more difficulties will be accounted to gain co-operation from younger children. In Riavis's study, all patients aged 5 years or less required at least two doses of ketamine.[10] It was also shown in our study that younger patients required more sedatives, ketamine. Further study should be done to establish the best sedation regimen, either intravenous ketamine alone or combination of midazolam and ketamine or combination of pethidine, midazolam and ketamine, for younger children.

The safety profile for our sedation protocol was comparable to Riavis's study which used intravenous benzodiazepine and ketamine for renal biopsies. Riavis's study quoted a 10% of cases suffered from transient oxygen desaturation while our result showed that 13.3% cases using ketamine had mild oxygen desaturation.[10]

In all cases having transient oxygen desaturation, they had good response to oxygen supplement. It was noted that the complication occurred irrespective of the doses of sedatives used. In fact, the dosage of sedatives used were within normal recommended range, except one patient was given a higher dose of intravenous ketamine (1 mg/kg) which was the dose for induction in general anaesthesia.

Where there is combination of sedative and analgesic treatment, there would be predilection to cause respiratory depression and airway obstruction. The Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists formulated by the American Society of Anesthesiologists emphasized the need to appropriately reduce the dose of each component as well as the need to continually monitor respiratory function.[11] It was possible that this patient had received a higher dosage of ketamine, in addition to pethidine and midazolam, and was complicated with oxygen desaturation.

In our study, close monitoring of patients by pulse oximetry with standby oxygen supplement are mandatory for the safety precaution in procedural sedation. These findings were consistent with the recommendations in American Academy of Pediatrics and the American Society of Anesthesiologists.[7,11] Special caution in administering several sedatives together should be warranted as well.

Our result suggested that for younger children, pethidine

and midazolam would probably be insufficient for sedation, and ketamine would need to be added. Thus, in order to avoid the additive effects of respiratory depression of pethidine and ketamine, the former might as well be omitted in the younger age group. However, further studies may be needed to evaluate this protocol and to find out the age threshold for using ketamine-added or ketamine-only protocol.

There were several limitations for this study. The duration of biopsy, details of sedation (including onset, level, endpoint, recovery time and duration of sedation) and details of side effects like presence of unpleasant psychic events and amnesia induced by midazolam during recovery were all not assessed in this study because the details were not well recorded in the case notes. Such information would be helpful in further assessing the effectiveness and safety of our sedation protocol.

## Conclusions

Our study demonstrated that the combination of intravenous pethidine and midazolam was an effective and safe sedation protocol for ultrasound-guided percutaneous renal biopsy in children. Further research should examine the age threshold for adding ketamine in the sedation and whether ketamine-only is an effective method in performing short painful procedure in children.

## References

1. Gauthier BG, Mahadeo RS, Trachtman H. Techniques for percutaneous renal biopsies. Pediatr Nephrol 1993;7:457-63.
2. Krauss B, Green SM. Sedation and analgesia for procedures in children. N Engl J Med 2000;342:938-45.
3. Snodgrass WR, Dodge WF. Lytic/"DPT" cocktail: time for rational and safe alternatives. Pediatr Clin North Am 1989;36: 1285-91.
4. Reappraisal of lytic cocktail/demerol, phenergan, and thorazine (DPT) for the sedation of children. American Academy of Pediatrics Committee on Drugs. Pediatrics 1995;95:598-602.
5. I Chan LY, Tan CL. Use of intravenous midazolam for sedation in children undergoing ward procedures. J Singapore Paediatr Soc 1992;34:30-3.
6. Guidelines for sedating children for diagnostic and therapeutic procedures. The Coordinating Committees in Paediatrics, Radiology and Anaesthesiology, Hong Kong, 2000.
7. American Academy of Pediatrics Committee on Drugs: Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures. Pediatrics 1992;89(6 Pt 1):1110-5.
8. Yam KL, Yau FT. Pilot study in evaluation the side effects of chloral hydrate sedation in children. HK J Paediatr (new series) 2002;7:214-9.
9. Cote CJ. Sedation for the pediatric patient. A review. Pediatr Clin North Am 1994;41:31-58.
10. Riavis M, Laux-End R, Carvajal-Busslinger MI, Tschäppeler H, Bianchetti MG. Sedation with intravenous benzodiazepine and ketamine for renal biopsies. Pediatr Nephrol 1998;12:147-8.
11. American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology 2002;96:1004-17.