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# Comparison of propofol and ketamine-midazolam for cystoscopy: A randomized trial with clinical economic analyses

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**Abstract**

*Objectives*: We compared the duration and quality of recovery and the cost of anesthesia between propofol and ketamine-midazolam for cystoscopy as a model to explain the decision in a tertiary care, government hospital in a developing country. *Methods*: This is a randomized, double-blind trial. Forty-eight male patients were randomized to receive propofol or ketamine-midazolam. Recovery was evaluated by a series of clinical tests, modified P deletion and Stroop color tests, and the time to discharge. Patients' pain score, satisfaction score and willingness to pay were evaluated. Direct medical cost from the perspective of health care provider was calculated. Cost-effectiveness and cost-benefit analyses were done. *Results*: Although clinical recovery was not different, both psychomotor tests showed that patients in the propofol group recovered significantly faster. They were able to stand, walk and meet the discharge criteria faster ($P < 0.05$) and had fewer side effects. However, pain and satisfaction scores and the willingness to pay were not different. For each patient, propofol cost 12.31 US dollars more but the patient recovered 44.8 min faster than with ketamine-midazolam. When this faster recovery time was changed into monetary units, propofol did not save money but cost 9.03 US dollars per patient more than ketamine-midazolam. Patients' expectation and salary scales can affect decision-making. 

*Keywords:* Clinical economic analysis; Ambulatory anesthesia; Propofol and ketamine

## 1. Introduction

Pain and discomfort during cystoscopy, a very common procedure to diagnose and treat diseases in the lower urinary tract, can be alleviated using local, regional and various general anesthesia regimens. Total intravenous general anesthesia is one suitable choice; but among the intravenous drugs, propofol claims fast and clearer recovery, whereas the cheaper drug, ketamine, has a longer elimination half-life and recovery. An anesthesiologist acting as the agent of the patient may want to use the newer drug. However, effectiveness information may not be enough for him to decide which drug is more suitable for his patients in his environment and budget.

We proposed to compare propofol and ketamine-midazolam in cystoscopy patients not only in an effectiveness study but also cost-effectiveness and cost-benefit analyses. Recovery was assessed by clinical tests, psychomotor tests, and the time until the patients were eligible for discharge. We also compared the patients' pain, satisfaction, and willingness to pay between the two techniques.

## 2. Materials and methods

This is a randomized, double blind trial. The permission to study was granted by the Hospital Committee on Human Rights Related to Research Involving Human. Inclusion criteria were male patients who were to have cystoscopy, had no or mild systemic diseases, had nothing per oral for 6 h, had no premedication and gave their informed consent. Exclusion criteria were patients who could not cooperate, had psychological or motor power problems or who were expected to have a procedure which lasted more than half an hour.

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Lidocaine jelly (10 ml) was applied into the urethra in lithotomy position in all patients. Five minutes afterwards the patients received:

1. Group 1 ($n = 24$): intravenous propofol 2 mg/kg then 40–60 mg incremental dose when the patients showed sign of need, e.g. movement, facial expression. Lidocaine 20 mg was given together with the first 100 mg of propofol to decrease the pain on injection [1].
2. Group 2 ($n = 24$): intravenous ketamine 0.5 mg/kg plus midazolam 0.04 mg/kg then ketamine 0.25 mg/kg incremental dose when they showed the same sign of need.

Cardiovascular and respiratory functions were monitored using automated blood pressure, pulse rate and pulse oximetry (Colin BX-5) and electrocardiogram. One anesthesiologist, who was not blinded to the drugs, gave all anesthesia. The airway was manually supported when there was sign of airway obstruction and oxygen supplement (2 l/min) via nasal cannular was given when the hemoglobin oxygen saturation fell below 92%.

In the recovery room, recovery was evaluated with a series of clinical tests, two psychomotor tests, and discharge criteria as follows:

1. Clinical recovery tests. The time from the end of anesthesia to the time the patient could open his eyes when called, tell his name and date of birth, lift his head for more than 5 s, sit and then stand and walk 3 m unaided were recorded.
2. Modified P deletion test [2]. The patient was asked to select one particular letter of the alphabet from a list of random alphabet letters. This test was applied every 10 min until he could choose correctly within ± 10% of preanesthesia baseline value. We modified the test by using local language and made sure that they were large enough for our patients to read. Different sets of alphabets were used to prevent patients from remembering the sequence.
3. Stroop color test. The patient was asked to call out the color (blue, red or green) of markers. The test was applied every 10 min until he could reach ± 10% of the preanesthesia baseline value.
4. Time to discharge. This was the time from the end of anesthesia until the patient fulfilled all the previous clinical criteria, had stable cardiovascular and respiratory status, drank water with no nausea or vomiting, and was able to dress and walk about unaided.

These tests were evaluated by two trained investigators who were blinded to the drugs given, in similar lights and under the same environment for both groups. They were sequenced so that patients were allowed time to complete each test and proceed through more difficult tests until they were eligible for discharge. Postoperative side effects (nausea, vomiting, vertigo, headache and bad dream) were recorded.

Before discharge the patient was asked to evaluate pain during the procedure by a visual analogue scale (VAS); zero meant no pain at all and 10 meant the worst severe pain imaginable. Satisfaction towards anesthetic technique was also assessed by VAS, zero meant not satisfied at all and 10 meant fully satisfied. His 'willingness to pay' was assessed by gradually increasing the amount of money from 20 US dollars, the normal charge for cystoscopy under local anesthesia. The patient was asked to indicate the highest price that he would be willing to pay for cystoscopy under the anesthetic technique he just had, if he were to have cystoscopy again.

The direct medical cost from the health care provider's perspective consisted of personnel cost, equipment cost, drug and consumable item cost [3]. Personnel cost in the operating room (OR) was calculated by multiplying the mean salary per minute of an anesthesiologist (1995 salary scales of all in the department) by the duration of anesthesia. Personnel cost in the recovery room (RR) was calculated by multiplying the mean salary of a nurse by the time the patients spent in RR to fulfil the discharge criteria. The actual amount of drugs and time that monitoring equipment was used were recorded both in OR and RR. The cost per minute of monitoring equipment was deducted from the equivalent annual cost, assuming that all equipment was used for 8 h daily for 270 days per year. The equivalent annual cost was calculated from the purchase price divided by an annuity factor [4]. This factor came from a table that correlated the equipment's expected years of life (according to the American Hospital Association [5]) and the discount rate of 7%. Drugs and consumable item cost were the purchase cost of the Department of Anesthesiology of a government, tertiary care, teaching hospital in Bangkok, Thailand.

In cost-effectiveness analysis, the incremental cost-effectiveness ratio was the difference in anesthesia costs divided by the difference in effectiveness (recovery) between the two techniques. In cost-benefit analysis, effectiveness was translated into a monetary unit [3]. If the more expensive drug resulted in shorter recovery room stay, then net benefit equalled the difference between the saving in RR cost and the cost difference in OR.

### 2.1. Statistical analyses

Analysis of data was with SPSS/PC. The distributions of data were tested with Kolmogorov–Smirnov Goodness of Fit; variables with normal distribution were compared using Student $t$-test; continuous, non-normal distributions were compared using Mann–Whitney $U$-Wilcoxon Rank Sum test. Discrete variables were compared using $\chi^2$ test. $P < 0.05$ was taken as indicating statistical significance.

Table 1
Patients' characteristics were not significantly different

| | Propofol ($n=24$) | Ketamine-midazolam ($n=24$) |
|---|---|---|
| Age (years) | 45.9 ± 13.3 | 54.9 ± 10.6 |
| ASA I/II (%) | 83/17 | 58/42 |
| Had previous cystoscopy (%) | 71 | 83 |
| Anesthesia duration (min) | 7.6 ± 6.0 | 9.7 ± 6.0 |
| Procedure | | |
| Cystoscopy | 10 | 11 |
| Cystoscopy and others | 14 | 13 |
| Income (dollars/month) | 210 ± 311 | 390 ± 451 |

## 3. Results

Patients in both groups had comparable ages, physical status according to American Society of Anesthesiologists (ASA) classification, experience of having previous cystoscopy, duration of anesthesia and type of operation (Table 1). The mean incomes of patients had a very large standard deviation and were not significantly different.

The clinical tests showed that the time for both groups to open eyes, tell their names and dates of birth, lift their heads and sit were not different. However, it took the ketamine-midazolam group significantly longer ($P<0.05$) to be able to stand, walk and meet the discharge criteria. Modified P deletion test and Stroop color test confirmed that patients in the propofol group recovered significantly faster ($P<0.05$), as shown in Table 2.

VAS pain scores, VAS satisfaction scores, and the maximum amount of money the patients were willing to pay for propofol and ketamine-midazolam were not significantly different between the two groups (Table 3).

Table 2
Clinical recovery tests, psychomotor tests, and the time to discharge

| Time to | Propofol (min) | Ketamine-midazolam (min) |
|---|---|---|
| Eye opening | 7.83 ± 3.99 | 5.67 ± 9.98 |
| Telling his name | 8.21 ± 4.06 | 6.38 ± 10.14 |
| Recall of birth date | 8.83 ± 4.08 | 7.63 ± 10.27 |
| Lift his head > 5 s | 10.46 ± 4.38 | 8.79 ± 9.97 |
| Sitting unaided | 15.38 ± 5.28 | 29.52 ± 25.32 |
| Standing unaided | 28.17 ± 9.04* | 45.54 ± 37.47 |
| Walking 3 m unaided | 31.58 ± 10.84* | 72.50 ± 53.29 |
| Modified P-deletion test | 23.13 ± 8.70* | 44.17 ± 22.83 |
| Stroop color test | 23.33 ± 7.89* | 43.29 ± 19.34 |
| Time to discharge | 48.04 ± 15.36* | 92.88 ± 47.92 |

* $P<0.05$.

Table 3
Pain scores, satisfaction scores and willingness to pay (mean ± S.D.) were not different. The number of patients who had vertigo and headache were different

| | Propofol | Ketamine-midazolam |
|---|---|---|
| VAS pain score | 0.2 ± 0.6 | 0.2 ± 0.5 |
| VAS satisfaction score | 9.2 ± 1.1 | 8.8 ± 1.6 |
| Patients' willingness to pay (dollars) | 47 ± 37 | 56 ± 50 |
| Pain on injection of i.v. drugs | 2 | 0 |
| Need of airway support | 4 | 4 |
| Need of oxygen supplement | 5 | 3 |
| Movement during cystoscopy | 8 | 8 |
| Awareness during anesthesia | 0 | 0 |
| Nausea, vomiting | 1 | 3 |
| Vertigo | 1 | 9* |
| Headache | 0 | 16* |
| Bad dream | 0 | 1 |

* $P<0.05$.

The mean hemoglobin oxygen saturation ($S_pO_2$) in both groups was not below 92% and an equal number of patients needed manual airway support. The number of patients who had an $S_pO_2$ drop to 92% and needed oxygen supplement was not significantly different and both groups responded well to standard treatment. Postoperative vertigo and headache were significantly more common in the ketamine-midazolam group.

Intraoperative cardiovascular changes differed between the two groups. Systolic blood pressure decreased by more than 20% of baseline in seven patients in the propofol group and increased by more than 20% of baseline in six patients in the ketamine-midazolam group. Eight patients in each group had their heart rate increase more than 20% of baseline. No treatment was needed.

The mean total doses of propofol and ketamine given were 227.5 mg and 40.5 mg respectively. Anesthesia cost in the OR in the propofol group was 2.7 times higher than the ketamine-midazolam group (19.63 vs 7.32 dollars per patient), as shown in Table 4. This difference was due to cost differences between propofol and ketamine. But because the propofol group recovered faster, their cost in the RR was lower than the ketamine-midazolam group (3.51 vs 6.80 dollars per patient).

The time until the patients were eligible for discharge was a practical, meaningful outcome to evaluate recovery. In cost-effectiveness analysis, the incremental cost-effectiveness ratio was the difference in anesthesia costs divided by the difference in time to discharge between the two techniques, or $(19.63-7.32)/(92.8-48.0)$ dollars/min. This meant that, for each cystoscopy patient, if we chose propofol we would spend 12.31 dollars more but the patient would recover 44.8 min faster than if we chose ketamine-midazolam.

Table 4
Direct medical costs of anesthesia and recovery in US dollars

| | Propofol | Ketamine-midazolam |
|---|---|---|
| In the operating room | | |
| Anesthesiologist | 0.64 | 0.81 |
| Equipment cost | 0.22 | 0.28 |
| Propofol or ketamine | 14.10 | 1.25 |
| Midazolam, other drugs and items | 4.67 | 4.98 |
| Total anesthesia cost | 19.63 | 7.32 |
| In the recovery room | | |
| Nurse anesthetist | 3.01 | 5.83 |
| Equipment cost | 0.50 | 0.97 |
| Total recovery cost | 3.51 | 6.80 |
| Total direct medical cost | 23.15 | 14.12 |

Propofol group spent 7.6 min in OR and 48 min in RR. Ketamine-midazolam group spent 9.7 min in OR and 92 min in RR.

In cost-benefit analysis, effectiveness was translated into monetary units. From the health care provider perspective, the net benefit equalled the difference between total direct medical costs of the two techniques. When the anesthesia cost and recovery cost were added together, propofol cost more than ketamine-midazolam (23.15 vs 14.12 dollars per patient), a difference of 9.03 dollars. This meant that the saving in RR was less than the saving from choosing ketamine-midazolam in OR.

## 4. Discussion

Anesthesia in different countries varies due to differences in health systems, reimbursement systems and the expectation of the population. Newer drugs are valuable additions to the anesthesiologist's armamentarium but the cost of these agents is obviously higher than the drugs they were designed to replace [6]. Developing countries have shortages in anesthesia manpower, equipment and drugs. Because of the long waiting lists, minor surgeries are done under local anesthesia by the surgeon [7]. These ambulatory surgeries under local anesthesia are well accepted by health care providers because time between cases is minimized, anesthetic complications are avoided, post-anesthesia care is not needed, and additionally because of cost savings.

However, some procedures, i.e. gastroscopy, cystoscopy, can be painful and humiliating from the patients' point of view, even when local anesthetics has been applied. In our previous study [8] patients who received cystoscopy under local anesthesia by surgeons had a mean VAS pain score of $4.8 \pm 2.2$, and mean VAS satisfaction score of $6.7 \pm 2.1$. If they were to have this procedure again, only 39% preferred local to general anesthesia. The bad experience can have a long lasting impact when the patients refuse to come for follow up, which this group usually needs, and can result in late diagnoses and treatment.

Propofol (2,6-diisopropylphenol) has been used in short procedures [9] and its effectiveness was compared with other intravenous drugs, i.e. thiopentone [10,11], opioids [12], benzodiazepine [13,14], inhalation agents [15–17] and other combination of drugs [18]. New opioids such as alfentanil have been used to supplement propofol anesthesia [12,19] but is in itself expensive. Midazolam has been compared with propofol [14] but it had to be antagonized by flumazenil which would have markedly increased the costs had the costs been assessed. Ketamine has been available longer and it costs less. Given intravenously, this drug resulted in a dissociative anesthesia state and had an analgesic effect, even at the dose of 0.2–0.75 mg/kg [20]. Patients were often drowsy in the recovery room and midazolam was given to prevent any emergence phenomenon. That recovery from propofol was faster than from ketamine has been shown in one study in pediatric patients undergoing cardiac catheterization [21] but the costs were not compared. Isoflurane has been shown to have faster recovery than propofol [22] but the recovery assessed by Digit Symbol Substitution Test at as early as 1 h in the recovery room was not different. In that study, 75% of all patients were discharged on the first postoperative day and 25% stayed in hospital for two nights, mainly for social reasons. 'Recovery' and 'time to discharge' should be defined and measured objectively so that the results of the study could be understood.

We have shown that propofol resulted in faster recovery and fewer side effects than ketamine-midazolam. The opportunity cost of a long RR stay is that the bed is not available for other patients. Propofol has a low incidence of nausea and vomiting [23–25]. These side effects were found to delay discharge by an average of 24 min and substantially increased the costs incurred by an outpatient surgical center [26]. It would be very difficult, if not impossible, to change headache, vertigo or a bad dream into a monetary unit, apart from counting the cost of drugs given to treat the symptoms, which we did. These adverse symptoms could be considered intangible costs but they were recognized by the longer time to discharge in the ketamine-midazolam group.

This study can be a model for other investigative procedures and minor surgeries, in this country and other countries with the same budget problems. The incremental direct medical cost of propofol over ketamine-midazolam per one patient was 9.03 dollars, but if all cystoscopies in the country were to receive propofol anesthesia, the increase in cost would be significant. Culture and expectation may have affected the measurement. Although recovery time and side effects were different, satisfaction towards anesthesia in the two groups was high and not different. This may be because their pain scores were not different and the patients were never exposed to the alternative drug. Our patients confirmed their satisfaction of intravenous anesthesia when they gave the figure for their willingness to pay 2–3 times higher than the amount they used to pay for cystoscopy under local anesthesia. 'Who pays' will affect the final decision whether an intravenous anesthesia service should be started and which drug should be used. For this cystoscopy the patients did not have to pay the amount they said they were willing to. The amount had a wide standard deviation, as had the mean income. We have not proved whether they would change their preference if they were to pay out of pocket in the future. However, the costs incurred by the department were lower than the amount the patients were willing to pay. So if the cost of care is affordable by the patient or a third party, the hospital may want to offer the service.

Around the world, governments are attacking spending deficits. No country can afford the health care that is available [27]. Improving the quality of anesthesia may not have a major impact on survival. Research with efficacy or effectiveness of drugs as main outcomes is sometimes only partially useful. New drugs and technology are assumed to be more effective, but economic analyses, using regional cost and effectiveness/benefit can lend an insight into the clinical practice and help in decision-making. These techniques have clearly entered anesthesia literature [28–30] and anesthesiologists have to understand their advantages and limitations.

The result of economic analysis varies across countries. Long recovery times will affect the total cost in hospitals with high personnel cost more than what occurred in our hospital. A UK study reported the cost of a recovery room nurse at 16.96 US dollars/h [30] compared to our cost of recovery room nurse of 3.77 dollars/h (estimating 1 British pound = 40 Thai baht and 1 US dollar = 25 Thai baht, exchange rate in 1995). If UK personnel costs were used in our study, choosing propofol would result in a saving of 0.84 dollars per patient. In this scenario, the anesthesiologist cost would also increase but the duration of anesthesia was not much different between the two groups and would have less impact than personnel costs during recovery. Drug costs also vary and change with time. A change in monetary exchange rates greatly affects all commodities and decisions.

We concluded that propofol was more effective, resulting in faster and higher-quality recovery than ketamine-midazolam, even though pain and satisfaction scores evaluated by the patients were not different. However, when we translated the shorter recovery room stay into a monetary unit, from the perspective of a health care provider, propofol was not more cost-beneficial than ketamine-midazolam. This is the common scenario in developing countries where drug cost is high and personnel cost is low. Varying personnel cost could shift the cost-beneficial analysis and propofol could become more cost-beneficial, as in countries with high salary scales. Although we found that clinical economic analyses helped us gain insights into the medical practice, there were still some technical problems and some clinical outcomes that could not be translated into monetary units.

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