A study on comparison between recovery pattern after total intravenous anaesthesia using thiopentone sodium, ketamine hydrochloride and propofol for short surgical cases

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Abstract

Aim & Objectives: The aim of the present study is to compare the recovery pattern after total intravenous anaesthesia using thiopentone sodium, ketamine hydrochloride and propofol for short surgical cases.

Methodology: The randomized controlled trial was a comparison between three groups of adult patients each receiving thiopentone sodium, ketamine hydrochloride or propofol as the anaesthetic agent. Analysis of variance (ANOVA) was applied to all the variables. Barring four parameters the tests of homogeneity were round to be significantly different for the three drugs respectively. Hence it was decided to go for non-parametric tests.

Results: In the present study, recovery of consciousness, cognitive and fine motor functions with thiopentone sodium was slower than with propofol but earlier than with ketamine hydrochloride. Recovery of cognitive and motor functions was slowest with ketamine hydrochloride. Recovery of gross motor activities like sitting, standing and walking was earliest with propofol and equivocal between thiopentone sodium and ketamine hydrochloride.

Conclusion: Thus, propofol has the best recovery profile when compared with thiopentone sodium and ketamine hydrochloride for short surgical cases.

Keywords: Surgical cases, thiopentone, ketamine hydrochloride, cognitive, consciousness

Introduction

From the first demonstration of inhalation anaesthesia by W.T.G. Morton on 16th October 1846, recovery from anaesthesia has always been a worry for all the anaesthesiologists. The quest for a new anaesthetic agent with quick and complete recovery profile is still ongoing. With the advent of "Day Care Surgery", and the move from major to less invasive procedures, recovery from anaesthesia has assumed a new importance. Day care surgery has many advantages like it reduces the inconvenience to the patient, is more economical and reduces the rate of infection and sepsis. It also is beneficial to the hospital as it reduces the occupancy of hospital beds and thus the hospital can provide better patient care and for an increased number of patients. In United Kingdom, almost 50% of the elective procedures are on the day-stay basis and in USA the number is still higher at 60%-70%. Operations lasting for 2-3 hours are now acceptable day case procedures. Anaesthetic agents mainly impair the cognitive and motor functions in the post-operative period. This results in the delay in discharge of the patient from the post anaesthesia care unit. Also, post-operative morbidity is equally important. Complications are related to physical status, anaesthetic technique and the surgical procedure. Post-operative nausea and vomiting, pain and general debility are important causes of unplanned admission after day surgery and prolonged stays. Short stays as for day surgeries are only acceptable if the patient can return home safely and comfortably, with minimal side effects from anaesthesia and surgery.

Many drugs like thiopentone, ketamine, propofol, midazolam, fentanyl, isoflurane, desflurane, sevoflurane, etc. have been used for day care surgery. The purpose of the present study is to compare the recovery profile after total i travenous anaesthesia using the commonest anaesthetic agents namely, thiopentone sodium, ketamine hydrochloride and...
propofol. The object is to study the impairment of mainly the cognitive and motor functions caused by these drugs.

Thiopentone sodium
Thiobarbiturates were first described in 1903 but were not explored further due to fatal experiments in dogs. It is a derivative of barbituric acid. It has a sulphur atom at C2 instead of oxygen in phenobarbitone. It is used in the form of sodium salt. Commercial preparation contains 6% anhydrous sodium carbonate by weight, which prevents precipitation of free acid by atmospheric carbon dioxide. It is manufactured in nitrogen medium. Enhancement of the synaptic actions of inhibitory neurotransmitters and Blockade of the synaptic actions of excitatory neurotransmitters
Gamma aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the central nervous system. GABA receptor is a chloride ion channel composed of at least 5 subunits with specific sites of action for GABA, barbiturates, benzodiazepines and other molecules”.

Ketamine hydrochloride
Ketamine was first synthesized by Stevens in 1962 and first used in humans by Corsena & Domino in 1965. It was released for clinical use in 1970. It is a phencyclidine derivative that produces dissociative anaesthesia, which is evidenced as dissociation between the thalamocortical and limbic system. Ketamine interacts with N-methyl D-aspartate (NMDA) receptors, opioid receptors, monoaminergic receptors, muscarinic receptors and voltage sensitive calcium channels

Propofol
As propofol is insoluble in water it was first prepared with Cremophor EL as base. But because of anaphylactoid reactions to Cremophor EL, the drug was reformulated as an emulsion. It binds to beta sub-unit of GABA<sub>A</sub> receptors and potentiates the GABA induced transmembrane chloride conductance, causing hyperpolarisation of post-synaptic cell membrane and functional inhibition of post-synaptic neuron. The aim of my study is to compare the recovery pattern after total intravenous anaesthesia using thiopentone sodium, ketamine hydrochloride and propofol for short surgical cases.

Materials and Methods
After taking institutional approval a randomized controlled study was conducted. The patients were randomly divided in three groups.

Group I: Patients receiving thiopentone sodium 5 mg/kg and 25 mg top-up when needed.
Group II: Patients receiving ketamine hydrochloride 2mg/kg and 10 mg top-up when needed.
Group III: Patients receiving propofol2mg/kg and 10 mg top-up when needed.
The person administering the drug was blinded to the drug being used (Randomized double-blind pattern).

Selection of patients
All patients were female from age group 20-40 years undergoing tubectomy and belonging to American Society of Anaesthesiologists Group I physical status. Patients were randomly selected in each group. All patients with cardiac or respiratory diseases were deleted from the study.

Sample size
The sample contained 60 patients in total with each group consisting of 20 patients.

Consent
A written informed consent was taken from each patient for surgery and participation in this study. The patients were pre-operatively explained the aim and procedure of the study and the tests which would be performed later.

Pre-operative preparation:
Anaesthesia machine and equipments were checked and kept ready. A good intravenous access was secured.

Premedication:
All patients were premedicated with:
- Tablet Ranitidine 150mg bedtime on previous night and 6:00 am on the day of surgery.
- Tablet Metoclopramide 10mg at 6:00 am on the day of surgery.
- Injection Midazolam hydrochloride 1 mg intravenous, 5 minutes before induction of anaesthesia to prevent awareness under anaesthesia.
- Injection Butorphanol tartarate 0.04 mg/kg intravenous 5 minutes before induction of anaesthesia for providing intra-operative as well as post-operative analgesia.

Anaesthesia:
Group I: Patients were induced with injection Thiopentone sodium 5mg/kg intravenous and maintained with intermittent doses of 25mg as and when required.
Group II: Patients were induced with injection Ketamine hydrochloride 2mg/kg intravenous and maintained with intermittent doses of 10 mg as and when required.
Group III: Patients were induced with injection Propofol 2mg/kg intravenous and maintained with intermittent doses of 10 mg as and when required.

All patients were supplemented with oxygen by Hudson's mask at a flow rate of 8L/min and maintained on spontaneous respiration. Patients were adequately hydrated.

Monitoring:
Pulse rate, blood pressure, Oxygen saturation and ECG were monitored continuously throughout the intra-operative period. Post-operatively, Oxygen saturation and pulse rate were monitored continuously and blood pressure was monitored every fifteen minutes.

Tests
They were divided into three parts.

Early Tests: Early tests were performed in the operating room itself, every minute after the last dose of the anaesthetic was given. They constituted of the time taken after the last dose of the anaesthetic drug to elicit:
- Response to pain.
- Response to commands.
- Spontaneous eye opening.

2. Intermediate Tests: They were performed in the recovery room thirty minutes after the early tests. They were:
• **Choice reaction time:** A switchboard with four lights of different colours and switches painted with corresponding colours to operate the bulb. The stimulus given was to light the bulb and the response expected was to switch off the light. The time taken for this was noted and the mean of ten observations was taken.

• **Coin sorting test:** Ten coins each of face value of Rs. Two, Rs. One and fifty paise were given to the patient and the patient was asked to separate the different coins. The time taken for the same was noted.

• **Pegboard test:** The subject was presented with a board with sockets of different shapes and correspondingly shaped blocks which fitted exactly into the sockets. The patient was asked to fit the blocks into their sockets and the time taken for the same was noted.

• **Maze test:** The patient was presented with a maze drawn on a paper. The patient was expected to lead a rabbit through the maze to the carrots. The time taken for the same was noted.

• **Triegor dot test:** A paper with dots printed on it was given to the patient. The patient was asked to join the dots and complete the figure. The number of dots missed by the patient was taken as the score.

• **Memory test:** The patient was shown a chart having twenty pictures for thirty seconds. The patient was then asked to recall the objects on the chart after the chart was removed. The number of objects correctly recalled was taken as the score.

**Late Tests:** These were performed in the recovery room every thirty minutes after the intermediate tests. The time from spontaneous eye opening to completion of each of these tests were noted. The tests were:

- Sitting without support.
- Standing without support.
- Walking without support.
- Rhomberg’s Test.

The patients were discharged from the recovery room to their respective wards after their Rhomberg’s test was negative.

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**Observations**

The randomized controlled trial was a comparison between three groups of adult patients each receiving thiopentone sodium, ketamine hydrochloride or propofol as the anaesthetic agent. Analysis of variance (ANNOVA) was applied to all the variables. Barring four parameters the tests of homogeneity were found to be significantly different for the three drugs respectively. Hence it was decided to go for non-parametric tests.

**Table 1:** Early Tests (Mean).

|         | Group 1 | Group 2 | Group 3 |
|---------|---------|---------|---------|
| A (minutes) | 9.7     | 11.5    | 14.1    |
| B (minutes) | 10.3    | 11.9    | 13.2    |
| C (minutes) | 6.85    | 8.2     | 9.45    |

A: Response to pain.
B: Response to commands.
C: Spontaneous eye opening

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**Table 2:** Intermediate Tests (Mean)

| test          | Group 1 | Group 2 | Group 3 |
|---------------|---------|---------|---------|
| CRT (Seconds) | 3.855   | 3.950   | 2.455   |
| CS (Seconds)  | 106.6   | 135.25  | 84.50   |
| PB (Seconds)  | 83.50   | 115.75  | 54.75   |
| MT (Seconds)  | 57.00   | 70.28   | 41.00   |
| TD            | 13.60   | 23.26   | 10.85   |
| Mem T         | 7.10    | 4.90    | 7.70    |

CRT: Choice reaction time. CS: Coin sorting test.
PB: Peg board test.
MT: Maze test.
TD: Triegor dot test.
Mem T: Memory test.
This test states that the null hypothesis as "There is no statistically significant difference for the three drugs respectively."

### Mann-Whitney Test: Group II and Group III: Test Statistics

This test states the null hypothesis, as "There is no statistically significant difference between drug group II and III with respect to each of the considered variables individually at a time."
The recovery from psychomotor and cognitive effects of anaesthetic agents is a great concern, especially after short surgical cases admitted on a day-care basis. The present study is a comparison of recovery pattern after total intravenous anaesthesia using the three commonly used intravenous anaesthetic agents viz. thiopentone sodium, ketamine hydrochloride and propofol for such short surgical cases lasting from 15 minutes to 30 minutes.

A sample of sixty patients was randomly distributed into 3 groups containing twenty patients each. All the patients were comparable on the basis of age, weight, pre-operative investigations and pre-operative haemodynamic parameters. All the patients were posted for open tubal ligation. All the patients premedicated to reduce the incidence of post-operative nausea and vomiting. All patients were premedicated with butorphanol tartarate 0.04 mg/kg and midazolam 1 mg intravenously.

Group I received thiopentone sodium 5mg/kg intravenous as induction agent and was maintained on 25mg intermittent doses as and when required.

Group II received ketamine hydrochloride 2mg/kg intravenous as induction agent and intravenous 10*mg intermittent doses were given as and when required.

Group III received propofol intravenous 2mg/kg as induction agent and maintained with 10 mg intravenous intermittent doses as and when required.

Oxygen was supplemented for all patients intra-operatively.

**Recovery**

Recovery was tested post-operatively in three phases.

**Early phase**

The recovery to consciousness was tested by noting the time taken from the last dose of anaesthetic drug to attain,

A. Response to pain
B. Response to commands
C. Spontaneous eye opening.

The mean time for response to pain after last dose of the anaesthetic drug in Group I patients was 9.7 minutes, Group II patients was 10.3 minutes and Group III patients was 6.85 minutes. The mean time for response to commands after last dose of the anaesthetic drug in Group I patients was 11.5 minutes, in Group II patients was 11.9 minutes and in Group III patients was 8.2 minutes.

The mean time for spontaneous eye opening after last dose of the anaesthetic drug in Group I patients was 14.1 minutes, in Group II patients was 13.2 minutes and in Group III patients was 9.45 minutes.

The observations were compared using Analysis of variance (ANNOVA) as well as non-parametric tests viz. Kruskal-Wallis test and Mann-Whitney test. From these tests there was no statistical difference in the early phase recovery between Groups I & II i.e. thiopentone sodium and ketamine hydrochloride had not much difference in the early phase recovery. But there was a statistically significant difference between Group III and Groups I & II (p<0.01). This means that early phase recovery with propofol as the sole anaesthetic drug was significantly faster than with thiopentone sodium or ketamine hydrochloride.

In a study by Baer and colleagues [1] comparing recovery after thiopentone and ketamine, they observed that patients in the ketamine group woke up early and their laryngeal reflexes seemed to stabilize earlier. In our study we have observed that early phase recovery using with thiopentone or ketamine was equivocal. Also, in a study by Heath &

| Test statistic | Z     | Asymp. Sig. (2-tailed) | P Values |
|---------------|-------|------------------------|----------|
| A             | 4.558 | 0.000                  | 0.01     |
| B             | 4.429 | 0.000                  | 0.01     |
| C             | 4.029 | 0.000                  | 0.01     |
| CRT           | 5.430 | 0.000                  | 0.01     |
| CS            | 5.226 | 0.000                  | 0.01     |
| PB            | 5.253 | 0.000                  | 0.01     |
| MT            | 4.220 | 0.000                  | 0.01     |
| TD            | 5.182 | 0.000                  | 0.01     |
| MemT          | -5.051| 0.000                  | 0.01     |
| Sitting       | 2.978 | 0.003                  | 0.05     |
| Standing      | 4.671 | 0.000                  | 0.01     |
| Walking       | 5.120 | 0.000                  | 0.01     |
| RN            | 5.109 | 0.000                  | 0.01     |

| Test statistic | Z     | Asymp. Sig. (2-tailed) | P Values |
|---------------|-------|------------------------|----------|
| A             | 4.064 | 0.000                  | 0.01     |
| B             | 3.882 | 0.000                  | 0.01     |
| C             | 3.979 | 0.000                  | 0.01     |
| CRT           | 5.387 | 0.000                  | 0.01     |
| CS            | 2.350 | 0.019                  | 0.05     |
| PB            | 4.534 | 0.000                  | 0.01     |
| MT            | 2.522 | 0.012                  | 0.05     |
| TO            | 1.920 | 0.055                  | NS       |
| MemT          | -1.264| 0.206                  | NS       |
| Sitting       | 3.086 | 0.002                  | 0.05     |
| Standing      | 4.671 | 0.000                  | 0.01     |
| Walking       | 5.048 | 0.000                  | 0.01     |
| RN            | 4.253 | 0.000                  | 0.01     |
colleagues comparing recovery for thiopentone, propofol, methohexitone & etomidate, they found that propofol provided the most rapid recovery, as is the observation in our study.

In another study by Boysen and colleagues [2] comparing recovery after thiopentone, propofol and etomidate, they found that time to eye opening on command was longer with propofol than thiopentone or etomidate, which is contrary to our finding that early phase recovery is faster with propofol than thiopentone. In yet another study by Monedaro and colleagues [3] comparing midazolam-alfentanil, propofol-alfentanil and thiopentone-isoflurane-alfentanil, they observed that awakening was earlier in midazolam group after reversal with flumazenil but was followed by resedation later. Awakening was slower in propofol group than in isoflurane group.

Also in a study by Fabregus and colleagues [4] comparing recovery after thiopentone-isoflurane group and propofol grouping neurosurgical patients, early recovery and extubation was quicker in isoflurane group than propofol group.

In yet another study by Sandip & colleagues [5] comparing recovery after propofol-fentanyl with ketamine/midazolam group found that recovery time and total sedation time was much less in the propofol group compared with ketamine group, which has also been found in our study.

This early phase was followed 30 minutes later by an intermediate phase of testing.

Intermediate phase
In this phase mainly fine motor and cognitive tests were performed. The tests performed were:

- Choice reaction time.
- Coin sorting.
- Pegboard.
- Maze test.
- Triegor dot test.
- Memory test.

The mean score of Choice reaction time in Group I were 3.855 seconds, Group II were 3.950 seconds and Group III were 2.455 seconds. The mean time required for Coin sorting in Group I was 106.6 seconds, in Group II was 135.25 seconds and Group III was 84.5 seconds.

The mean time for Pegboard test in Group I was 83.5 seconds, in Group II was 115.75 seconds and in Group III was 54.75 seconds.

The mean time for Maze test in Group I was 57 seconds, in Group II was 70.28 seconds and in Group III was 41 seconds. Also one patient in the Group II couldn't perform the maze test due to tremors and nystagmus.

The mean score for Triegor dot test was 13.6 in Group I, 23.26 in Group II and 10.5 in Group III. One patient in Group II couldn't perform this test due to nystagmus and inability to see the dots properly.

The mean scores for Memory test were 7.1 in Group I, 4.9 in Group II and 7.7 in Group III.

The observations were compared using analysis of variance (ANNOVA) and non-parametric tests viz. Kruskal-Wallis test and Mann-Whitney test. When Group I was compared to Group II, except for choice reaction time all the other tests had a statistically significant difference. The difference for coin sorting test and pegboard test was highly significant (p=0.001) whereas that for maze test was only mildly significant (p=0.05). For all the other tests the difference was moderately significant (p=0.01). This means that except for choice reaction time, the recovery of all other cognitive and fine motor tests was earlier with thiopentone sodium than ketamine hyd rochloride.

When Group II was compared with Group III, there was a statistically significant difference for all the tests, which means that recovery of all cognitive and fine motor functions is earlier with propofol than with ketamine hydrochloride. For all the tests the difference was moderately significant (p=0.01).

When Group I was compared with Group III, there was no significant difference in the scores of the triegor dot test and the memory test. But the difference was statistically significant for all the other tests. For choice reaction time and pegboard test the difference was moderately significant (p=0.01), whereas for coin sorting test and maze test the difference is only mildly significant (p=0.05).

In a study Sandoval and colleagues [6] compared recovery after anaesthesia using diazepam-ketamine and fentanyl-methohexitone, using the trail making test. They observed that recovery was faster in the fentanyl-propofol group. In a study by Boysen and colleagues [2], they observed shorter reaction times and coin counting times after propofol as compared to thiopentone and etomidate. These observations are equivocal with our observations.

In another study by Motsch and colleagues [7], comparing thiopentorice-isoflurane, midazolam-ketamine-alfentanil and propofol, they observed that flicker fusion frequency was significantly higher in the propofol group. Short- term memory also returned earlier in propofol group. The performance for ball bearing test was better in propofol group. Patients in propofol and isoflurane groups required same time for maze test, but in midazolam group the time required was significantly longer. All these observations are consistent with our observations.

In another study by Larsen and colleagues [8], also it was found that perceptive accuracy test results were significantly better during recovery from propofol anaesthesia when compared to isoflurane.

Also in another study by Gupta and colleagues [9], they found that psychomotor recovery tested by using perceptive accuracy test was better with propofol than the thiopentone-isoflurane group.

Contrary to this in another study by Monedaro and colleagues [3], they found that psychomotor recovery tested using the Glg deletion test and memory recall test, was better in the thiopentone-isoflurane group as compared to propofol group and slowest in the midazolam group.

In a study by Blobner and colleagues [10], comparing recovery after methohexitone, propofol and isoflurane, they found that psychomotor recovery was faster in propofol group than methohexitine group using the sedation score, orientation, memory and calculation tests, word generation test and subjective vigilance score. But the difference between propofol and isoflurane groups were minimal and without any clinical significance.

In another study by Jariya and colleagues [11], the psychomotor recovery after propofol was compared with ketamine-midazolam. They used the modified P-deletion test and stroop colour test. They observed that patients in the propofol group showed psychomotor recovery Significantly fast era is consistent with the observations in our study.
Also in another study by Sandip and colleagues, it was observed that sedation time in propofol-fentanyl group was much less than in the ketamine-midazolam group. This was followed by the last phase.

**Last phase**

In this phase the time taken for the patient to perform gross motor activities was noted. The following tests were performed:

- Sitting without support.
- Standing without support.
- Walking without support.
- Rhomberg's test.

The mean time for sitting without support was 1.05 hours in Group I, 1.03 hours in Group II and 0.83 hours in the Group III. The mean time for standing without support was 1.45 hours in Group I, 1.45 hours in Group II and 1.05 hours in Group III.

The mean time for walking without support was 1.6 hours in Group I, 1.7 hours in Group II and 1.1 hours in Group III. The mean time for Rhomberg's test to be negative was 1.7 hours in Group I, 1.921 hours in Group II and 1.225 hours in Group III.

All the observations were compared using the analysis of variance (ANOVA) test and non-parametric tests viz. Kruskal-Wallis test and the Mann-Whitney test.

When comparing Groups I and II, it was found that there was no significant difference between the two groups for sitting, standing and walking without support, whereas there is a mildly significant difference for the Rhomberg's test (p=0.05). This means that gross motor activities recover almost equivalently after anaesthesia with thiopentone sodium and ketamine hydrochloride.

When Groups II and III were compared, it was seen that there is a significant difference between the two groups for all the four tests. For sitting without support the difference is only mildly significant (p=0.05), whereas for standing and walking without support and for the Rhomberg's test to be negative there is moderately significant difference (p=0.01). This means that recovery of gross motor functions is significantly faster with propofol than with ketamine hydrochloride.

When Groups I and III were compared, a significant difference was found to exist between them for all the four tests. For sitting without support the difference was only mildly significant (p=0.05), whereas for all the remaining three tests the difference was moderately significant (p=0.01). This means that recovery of gross motor functions was significantly faster with propofol as compared to thiopentone sodium.

In a study by Jariya and colleagues, it was observed that patients in the propofol group were able to stand, walk and meet the discharge criteria faster than the ketamine-midazolam group. These findings are consistent with our observations.

In the study by Motsch and colleagues, they observed more number of side effects like nausea, vomiting and double vision in midazolam and isoflurane group whereas they were less in the propofol group. Contrary to this in another study Blobner and colleagues observed increased incidence of nausea with propofol and methohexitone anaesthesia as compared to isoflurane.

In our study none of the patients had nausea and vomiting as they received antiemetic prophylaxis. Also, as the patients were well hydrated so there was no incidence of hypotension after induction with propofol or thiopentone sodium. None of the patients have any apnoeic episodes or respiratory depression.

Early phase recovery was earliest with propofol. In the intermediate phase, four out of six test results were better with propofol when compared with thiopentone sodium. When compared to ketamine hydrochloride, all the test results were better with propofol. In the late phase also, recovery was found to be earlier with propofol.

Ketamine hydrochloride causes nystagmus, tremors and delayed recovery of fine motor functions. Also, patients in the ketamine group were drowsier than the patients in the other two groups. One patient in the ketamine group could not perform the maze test while a second patient could not perform the triegor dot test. Also, ketamine hydrochloride produces hallucinations during the recovery so midazolam has to be given to prevent this emergence phenomenon.

None of the patients in our study had hallucinations. Thiopentone sodium has an intermediate recovery profile. Patients in this group were drowsier than the propofol group but more alert than those in the ketamine group. Cognitive and motor functions returned slower than propofol but earlier than ketamine hydrochloride. Thiopentone sodium and propofol do not produce analgesia. Hence, they have to be supplemented with a potent analgesic agent.

**Conclusion**

Thus, after analyzing the results of our study comparing recovery pattern after total intravenous anaesthesia using thiopentone sodium, ketamine hydrochloride and propofol for short surgical cases, we conclude that:

- Recovery of consciousness was earliest with propofol.
- Recovery of cognitive and fine motor functions was earliest with propofol except for short-term memory recall and trieqor dot test results, which were equivocal between propofol and thiopentone sodium.
- Recovery of consciousness, cognitive and fine motor functions with thiopentone sodium was slower than with propofol but earlier than with ketamine hydrochloride.
- Recovery of cognitive and motor functions was slowest with ketamine hydrochloride.
- Recovery of gross motor activities like sitting, standing and walking was earliest with propofol and equivocal between thiopentone sodium and ketamine hydrochloride. Thus, propofol has the best recovery profile when compared with thiopentone sodium and ketamine hydrochloride for short surgical cases.

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**Conflict of interest**

None

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