Original Article

# Effects of oral melatonin premedication on hemodynamic responses to intubation, anesthetic requirements and postoperative sedation: A randomized trial

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## Abstract

**Background and Aims:** Sedative effects of melatonin may have an additive effect on general anesthesia (GA). We compared hemodynamic response to intubation following oral premedication with melatonin versus placebo. Induction dose of propofol, isoflurane and fentanyl consumption were also compared.

**Material and Methods:** This prospective, double-blinded study was conducted in fifty patients randomized into two equal groups. Group M received oral melatonin 6 mg and group P a placebo two hours before surgery. All patients were induced with intravenous propofol of 1.5–2.5mg/kg till loss of response to verbal commands, three minutes after vecuronium, laryngoscopy was done and trachea was intubated. Heart rate (HR) and mean arterial pressures (MAP) were recorded before premedication, before induction, immediately after induction and then at 1,3,5 and 10 minutes after intubation.

**Results:** Mean HR was comparable in both groups throughout the study period. Group M had significantly lower MAP before induction and immediately after induction ($P < 0.05$). At all other time points MAP remained comparable in both groups. Mean isoflurane consumption was significantly lower in group M compared to group P (14.8 ± 4.2 vs 19.7 ± 3.2 mL). Propofol requirement for induction was also significantly lower in group M (102.4 ± 19.6 vs 122.4 ± 26.3mg). Intraoperative fentanyl consumption was comparable.

**Conclusion:** Oral premedication with melatonin 6mg administered two hours before surgery significantly reduced MAP before and after induction of GA with a significant reduction in dose of propofol requirement.Titrating induction dose of propofol till loss of response to verbal commands did not effectively attenuate responses to laryngoscopy and intubation following melatonin oral premedication.

**Keywords:** Anesthesia, intubation, laryngoscopy, melatonin, premedication

## Introduction

Melatonin is a sleep-regulating hormone and its administration has shown to facilitate sleep onset and improve the quality of sleep. It produces a natural sleep pattern with significantly less side effects compared to various other pharmaceutical therapies in current practice for treatment of sleep disorders.[1] Various researchers have used this drug in different doses as premedication in both adults and children.[2,3] Additionally, the protective mechanisms of melatonin on ischemia-reperfusion injury, myocardial chronic intermittent hypoxia injury, pulmonary hypertension, valvular

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heart diseases, vascular diseases, and lipid metabolism are documented.[4] We hypothesized that as melatonin induces natural sleep, its administration as a pre-medicant might augment depth of general anesthesia (GA) with subsequent blunting of hemodynamic responses to intubation and reduced intraoperative anesthetic requirements.

The primary objective was to compare the heart rate response after laryngoscopy and intubation in patients following oral premedication with melatonin versus placebo administered two hours before surgery. The secondary objectives were comparison of blood pressure responses, preoperative and postoperative sedation scores, propofol dose required for induction of general anesthesia, intraoperative requirement of isoflurane and fentanyl in both the groups.

## Material and Methods

The present study was a prospective, randomized, double-blinded study conducted on 50 surgical patients receiving general anesthesia. Inclusion criteria were patients undergoing total thyroidectomy aged 18–60 years, of American Society of Anesthesiologists Physical Status (ASAPS) 1 and 2. All patients were in euthyroid state. Those with anticipated difficult airway, body mass index (BMI) >30 kg/m$^2$, patients on antipsychotic, sedatives, anxiolytics and antiepileptic drugs were excluded. Those who required >1 attempts or >15 seconds for laryngoscopy were also excluded. The study was done after obtaining Institutional ethical committee clearance (IEC-AIMS-2021-ANES-046 dated 12-03-2021) and written informed patient consent. It was registered with Clinical Trial Registry India (CTRI/2021/05/033532). The study period was eight months from May 2021 to December 2021.

Fifty patients were randomized into two equal groups—group M and group P—using computer-generated random sequence of numbers. Allotment of patients to different groups was masked by using sequentially numbered opaque sealed envelopes. Different people who were not involved in the study generated allocation sequence, enrolled patients and assigned participants to interventions. On night prior to surgery, all patients received metoclopramide 10mg and pantoprazole 20mg orally, and standard nil per oral guidelines were followed. Patients in group M received oral melatonin of 6 mg (Tablet Melocet, Aristo Pharmaceuticals Pvt Ltd, India) and patients in group P a multivitamin tablet (Tablet Neurobion Forte, Merck Ltd, India) two hours before surgery with sips of water. Both tablets were removed from foils by a postgraduate student and handed over to a nurse for administration to the patient. Both the patient and the nurse were unaware of the contents of the tablet. The postgraduate student was not involved in the trial. The patients' rooms were kept dark using blackout curtains and the lights were switched off to mimic night conditions. All patients were kept undisturbed, wore black blindfolds and the rooms were kept calm and silent. Patients were shifted to the operation theater ten minutes prior to surgery.

All patients received general anesthesia following a standardized protocol. On arrival, Ringer lactate was started at a rate of 10mL/kg/h in the theater. After attaching preinduction monitors, all patients received midazolam 2 mg, fentanyl 2 μg/kg and glycopyrrolate 0.2 mg intravenously. Patients in both groups were preoxygenated and induced with 1.5–2.5 mg/kg propofol, given slowly over one minute till there was loss of response to verbal commands. After ensuring mask ventilation, all patients were given vecuronium 0.1 mg/kg and ventilated with 1% isoflurane in oxygen. At three minutes, a gentle and short laryngoscopy, not lasting for 15 seconds, was performed and trachea was intubated with 8.0 mm cuffed endotracheal tube (ETT) in males and with 7.0 mm ETT for females. Correct placement of ETT was confirmed with auscultation and by appearance of regular end-tidal carbon dioxide ($EtCO_2$) wave forms. All intubations were performed by a single anesthetist.

Anesthesia was maintained with isoflurane 1%–1.5% in oxygen air mixture (1:1), initially with mechanical ventilation with tidal volume of 6–8 mL/kg, respiratory rate of 12–14 per minute maintaining end-tidal carbon dioxide ($EtCO_2$) between 30 and 35 mmHg. Heart rate (HR) and mean arterial pressures (MAPs) were recorded before premedication, before induction of anesthesia, immediately after induction and then at 1,3,5 and 10 minutes after intubation. An increase in HR >20% from baseline, if associated with hypotension, was treated with 250mL intravenous Ringer's lactate bolus initially. If increase in HR did not respond or was associated with increase in MAP >20% from baseline, isoflurane concentration was increased to 1.5%–2%. If the hemodynamic response was not controlled, incremental boluses of fentanyl 0.5 μg/kg was given to a maximum of 1 μg/kg in one hour. Reduction in MAP <20% from baseline value was taken as hypotension and was treated with 250 mL intravenous fluid bolus; if not responding, incremental doses of phenylephrine 50 μg were given. Isoflurane concentration was reduced to 0.5% at beginning of skin suturing and discontinued at completion of suturing. Neuromuscular blockade was then reversed and extubation was done when patient was opening eyes on command and generating adequate tidal volume with return of protective airway reflexes.

Level of sedation was assessed using Ramsay Sedation Scale (RSS) before induction, at 10 minutes and 30 minutes after extubation. Propofol dose requirement for induction of

general anesthesia as well as intraoperative consumption of isoflurane and fentanyl were noted. Avance CS2 workstation and Tec 7 vaporizer were used for administering anesthesia. At the end of surgery, the volume of isoflurane used was noted from the anesthesia workstation. Number of times interventions were required, like administration of fluid bolus and use of vasopressors, was recorded. Duration of surgery and intraoperative blood loss were also noted.

As there was no similarly published study on melatonin premedication which advocated the same methodology as in our study for induction of general anesthesia and intubation, we conducted a pilot study in 20 patients, divided into two equal groups. Mean HR at 1 minute after intubation was found to be lower in melatonin group compared to placebo group (78.98 ± 9.99 vs 89.90 ± 11.68). Based on this result with 95% confidence interval and 90% power, minimum sample size required to obtain statistically significant result was calculated to be 21 patients per group. However, we recruited 25 patients per group during our study period.

The categorical variables were compared using Pearson's Chi-squared test or Fisher's exact test and the normally distributed continuous variables with independent sample *t*-test. Mann–Whitney *U* test was used to compare RSS. Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 20.0 for Windows (IBM Corporation Armonk, NY, USA).

## Results

Data of 50 patients were analyzed [Figure 1]. Mean age, weight and distribution of gender, ASA PS and Mallampati score were comparable in both groups [Table 1]. The comparison of mean HR did not show statistically significant difference between the groups throughout the study period [Figure 2]. Group M had significantly lower MAP before induction and immediately after induction ($P<0.05$). At all other time points, MAP remained comparable in both groups [Figure 3]. Mean isoflurane consumption was significantly lower in group M compared to group P (14.8 ± 4.2 vs 19.7 ± 3.2mL, $P<0.001$). Propofol requirement for induction was also significantly lower in group M (102.4 ± 19.6 vs 122.4 ± 26.3mg, $P = 0.004$). Intraoperative fentanyl consumption, duration of surgery and intraoperative blood loss were comparable in both groups [Table 2]. Number of times fluid bolus was given, and vasopressors used remained similar in both groups ($P>0.05$). Comparison of RSS before induction and that at 10 minutes and 30 minutes after extubation did not show any significant difference between the groups [Table 3]. No patient required >1 attempt for intubation or >5 sec for laryngoscopy.

## Discussion

In the present study, it was observed that oral premedication with melatonin 6mg administered two hours before surgery did not significantly affect the HR response to intubation compared to placebo. Though group M patients had significantly lower MAP just before and after induction of GA, the hemodynamic responses to intubation were comparable to those who received a placebo. However, melatonin premedication significantly reduced induction dose of propofol and the intraoperative isoflurane requirement without affecting intraoperative fentanyl consumption. There was no excessive sedation preoperatively or postoperatively following melatonin premedication.

Melatonin (N-acetyl-5-methoxytryptamine), secreted principally by the pineal gland, has an endogenous circadian rhythm of secretion induced by the suprachiasmatic nuclei of

**Table 1: Comparison of demographic data and Mallampati scores**

| Variable | Group P | | Group M | | *P* |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Age | 39.4 | 9.3 | 39.6 | 11.4 | 0.935 |
| Weight | 68.0 | 12.4 | 69.1 | 8.7 | 0.729 |
| | *n* | % | *n* | % | |
| Male | 2 | 8.0 | 1 | 4 | 1.000 |
| Female | 23 | 92 | 24 | 96.0 | |
| Mallampati score 1 | 8 | 32 | 6 | 24.0 | 0.529 |
| Mallampati score 2 | 17 | 68.0 | 19 | 6 | |

**Table 2: Comparison of isoflurane, fentanyl and propofol consumption, duration of surgery and blood loss**

| Variables | Group P | | Group M | | *P* |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Isoflurane consumption (mL) | 19.7 | 3.2 | 14.8 | 4.2 | <0.001 |
| Fentanyl consumption (μg) | 161.6 | 26.1 | 155.0 | 24.7 | 0.363 |
| Propofol requirement for induction (mg) | 122.4 | 26.3 | 102.4 | 19.6 | 0.004 |
| Duration of surgery (min) | 164 | 12.4 | 155 | 25.6 | 0.120 |
| Intraoperative blood loss (mL) | 322 | 38.6 | 340 | 28.7 | 0.067 |

**Table 3: Comparison of number of times fluid bolus and vasopressors given and Ramsay Sedation Scale**

| Variables | Group P | | | Group M | | | *P* |
|---|---|---|---|---|---|---|---|
| | Median | IQR | | Median | IQR | | |
| Number of times fluid bolus given | 0.0 | 0.0 | 1.0 | 0.0 | 0.0 | 1.0 | 1.000 |
| No of times vasopressors used | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.727 |
| RSS Before induction | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 1.000 |
| RSS 10 min after extubation | 2.0 | 2.0 | 2.5 | 2.0 | 2.0 | 3.0 | 0.080 |
| RSS 30 min after extubation | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 1.000 |

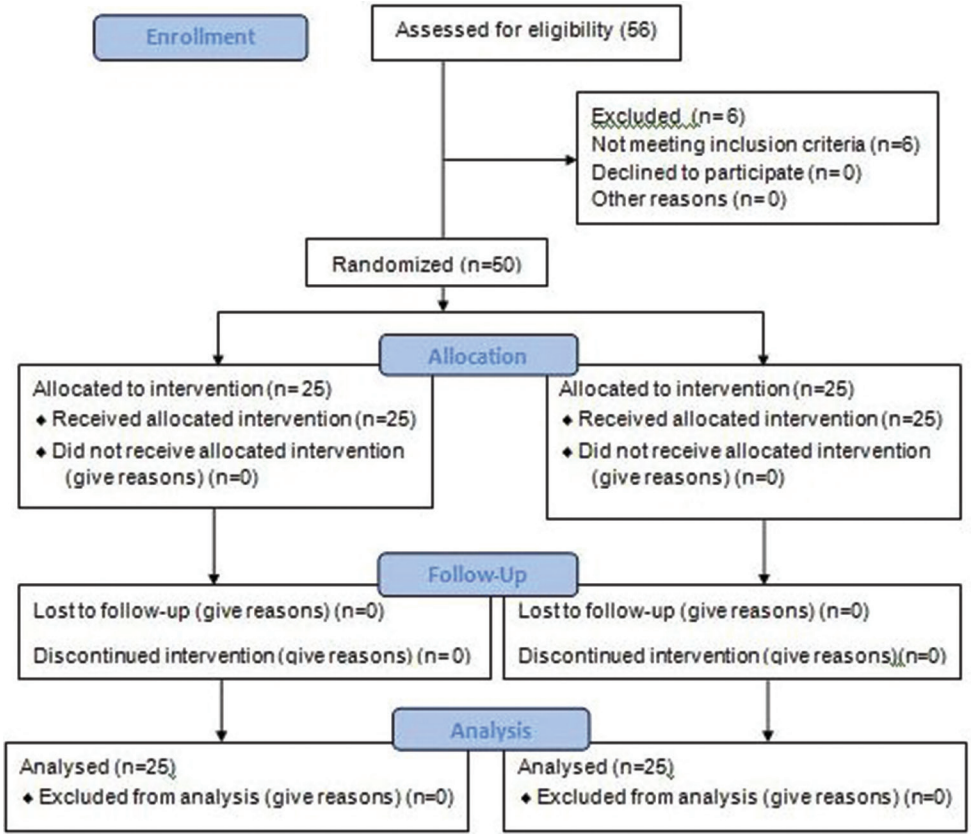


**Figure 1:** CONSORT flow diagram

the hypothalamus that is entrained to the light and dark cycle. It has been used to treat sleep disorders, jet lag, perioperative anxiolysis, sedation, and in cognitive and psychomotor disorders.[2,3,5–7]

After oral melatonin administration, peak plasma concentration occurs within 60 minutes. The reduction in plasma concentrations is biphasic, with a half-life of respectively 2 and 20 minutes. Intake of an usual dose (i.e., 1 to 5 mg), allows within the hour after ingestion, melatonin concentrations 10 to 100 times higher than the physiological nocturnal peak to be obtained, with a return to basal concentrations in 4 to 8 hours.[8] Possible drug interactions include contraceptives, caffeine, fluvoxamine, nifedipine, immunosuppressants, warfarin and methamphetamine.

Many studies have shown melatonin premedication to result in reduction of induction dose of propofol with attenuation of hemodynamic responses to intubation.[9–13]Though we observed reduced requirement of propofol, blunted stress response to intubation was not seen in our study. Sublingually administered melatonin 3 mg, given 50 minutes before surgery to achieve a bi-spectral index of 40 has shown to reduce propofol dose significantly as compared to placebo (49.88 ± 14.48 vs 77.38 ± 23.56mg, $P = 0.002$).[10] Though preoperative hemodynamic variables remained comparable, data on response to intubation was lacking in the study.[10] Melatonin oral premedication, both 3 and 5 mg given 100 minutes before surgery, was also shown to reduce the required dose of propofol to achieve a BIS score of 45(115 ± 19.5 and 114 ± 20.9 mg, respectively).[9] We observed that with a lesser dose of propofol (102.4 ± 19.6mg) induction of anesthesia could be achieved. The difference could be because of the different endpoints of propofol induction used like loss of response to verbal commands in our study and achieving a certain BIS score in other studies.

A study by Gupta P *et al.*[11] had shown that oral melatonin 6 mg given two hours before surgery was effective for attenuating hemodynamic responses to intubation. However, their study was different from our study in that two puffs of 10% lignocaine were sprayed on the larynx before induction, fentanyl 1 μg/kg and a fixed dose of propofol 2 mg/kg were used. Succinylcholine was used to facilitate laryngoscopy and intubation. In our study, larynx was not topicalized, fentanyl 2 μg/kg and titrated doses of propofol till loss of response to verbal commands were used. Vecuronium, a more cardio stable drug, was used as a muscle relaxant. Propofol dose required for induction was <2mg/kg in our study. Topicalized larynx, and the use of fixed dose of propofol might have influenced

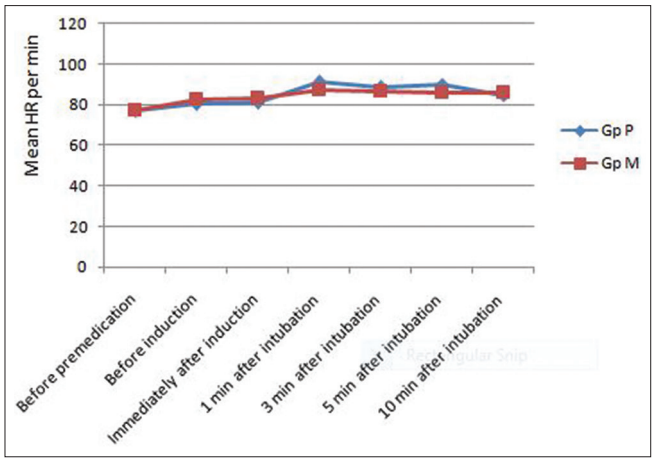


**Figure 2:** Changes in mean hear rate

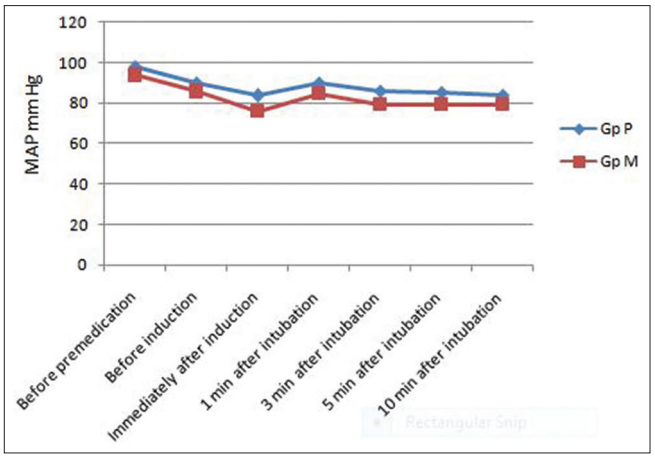


**Figure 3:** Changes in mean arterial pressure

the hemodynamic parameters in their study. We have tried to mimic the night conditions after melatonin administration so as to facilitate its effects. Thus, it could be stated that the results of our study more accurately reflect the effect of oral melatonin premedication on hemodynamic response to intubation.

However, in a study by Kumar *et al.*[12] with a similar methodology, the authors concluded that melatonin premedication resulted in significant attenuation of postintubation rise in HR and MAP with reduced induction dose of propofol and total intraoperative fentanyl consumption. In their study, the mean induction dose of propofol in the melatonin and placebo groups were 74.21 ± 12.483 mg and 118.00 ± 16.361 mg, respectively. The induction dose of propofol required in the melatonin group in our study was 102.4 ± 19.6mg. The use of a lower dose of propofol compared to the study by Kumar *et al.*[12] could be the reason for the conflicting observations made in our study. They observed reduced intraoperative requirement of fentanyl while we did not observe that. Though we observed a lesser opioid consumption following melatonin premedication, statistically, the difference was not significant. The different study populations such as laparoscopic surgery and open thyroidectomy, might have also had some influence.

In the study by Choudhary *et al.*,[13]the authors had shown that oral melatonin 6 mg was superior to oral clonidine 0.2 mg in attenuating the hemodynamic response to laryngoscopy and tracheal intubation, though both drugs effectively blunted the stress response. The study methodology was similar to our study except that they used clonidine instead of placebo in one group. But melatonin 6mg was shown to blunt stress response to intubation. The differences in observations could be because they used a pre-calculated dose of propofol 2 mg/kg for induction while we used titrated dose which was <2 mg/kg. They have hydrated the patients with RL 2ml/kg/h while we used 10mL/kg/h. Better hydration and a use of a lesser dose of propofol in our patients might have helped to reduce the hypotensive effects of propofol. Moreover, patients in their study received alprazolam on the night prior to surgery, while we avoided a sedative premedication on the same night. It is possible that any residual effects of alprazolam might have augmented the effects of melatonin and resulted in attenuation of hemodynamic response to intubation.

Mukherjee D *et al.*[14] had also found that oral melatonin 6mg blunted hemodynamic responses to intubation. The study methodology was different in this study also, as propofol was administered at a fixed dose of 2mg/kg, and fentanyl 1μg/kg and atracurium 0.5mg/kg were used. Use of more propofol, lesser fentanyl and a relaxant known to cause tachycardia could have led to conflicting results compared to our study.

In a Cochrane Database Systematic Review which included randomized, placebo controlled or standard treatment controlled trials, the studies had shown that melatonin premedication in surgical patients might effectively reduce preoperative anxiety, but with unclear effects on postoperative anxiety when compared with placebo. The effects were found to be similar to benzodiazepines in reducing preoperative and postoperative anxiety in adults.[15,16]

Melatonin provides analgesia for inflammation-associated pain in neonates and children, before venepuncture and is a safe adjunct to GA.[17] Oral melatonin 10mg administered on the night prior and 30 minutes before surgery was effective in reducing intraoperative opioid consumption under GA.[18] The same dose given before spinal anesthesia had reduced severity of postoperative pain, prolonged duration of analgesia with less need for analgesics.[19] In our study, though there was a lower intraoperative opioid consumption following melatonin premedication, the difference was not statistically significant,

probably because of a lower dose of melatonin (6mg) used for premedication.

The reduced isoflurane requirement seen in group M could be attributed to the sedative effects of melatonin. The comparable intraoperative hemodynamic parameters in both groups in our study, as reflected by similar use of fluid bolus and vasopressors, were different from many previous studies. Adequate intraoperative hydration with RL of 10mL/kg/h could have helped to negate hypotensive episodes in our study.

Based on analysis of study protocols and results of most of the previous studies, it could be inferred that melatonin 6mg premedication could blunt the hemodynamic responses to intubation most likely when propofol of 2mg/kg or more was used for induction. Titrating induction dose of propofol till loss of response to verbal commands might not be sufficient enough to attenuate the responses to laryngoscopy and intubation.

The strongpoint of the present study was that all intubations were performed by a single anesthesiologist. Therefore, subjective variation due to differing skills on intubation was eliminated. The patient, intubating anesthetist and outcome assessor were blinded to the method of premedication. Our study had many limitations. Depth of anesthesia was monitored intraoperatively only with hemodynamic variables since BIS monitoring was not available always. Use of endtidal and age adjusted isoflurane concentration would have been ideal. Due to the current prevailing COVID conditions, all of the surgical patients were shifted to the theater just before surgery only. If we had shifted the patients to pre-anesthesia area earlier and given premedication there with simulated night conditions, all the beneficial effects of melatonin might have been achieved. Our first RSS recording was done on arrival to theater. This could be the reason for the comparable RSS observed in both groups in our study. If it were done in the patients' room just before shifting to the theater, the assessment would have been more accurate.

As titrating induction dose of propofol till loss of response to verbal commands did not effectively attenuate hemodynamic responses to intubation following melatonin oral premedication, use of higher doses of propofol might be recommended for blunting the intubation responses.

## Conclusion

Oral premedication with melatonin did not have any significant effect on the heart rate response following laryngoscopy and intubation. It significantly reduced MAP before and after induction of general anesthesia but did not attenuate blood pressure response to intubation. Melatonin premedication significantly reduced induction dose of propofol and intraoperative isoflurane requirement without significant reduction in opioid consumption or changes in level of sedation as compared to the placebo.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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