Randomized Controlled Trial

Multimodal Analgesia With Sevoflurane Provides Enhanced Intraoperative Analgesic Effects in Percutaneous Nephrolithotomy: A Randomized, Blinded Clinical Trial

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Background: Percutaneous nephrolithotomy (PCNL) is the first-line and guideline-recommended treatment for large renal calculi. Multimodal analgesia (MMA) comprising a combination of different analgesics is an increasingly popular method for pain control as it has been shown to reduce postoperative pain and reduce opioid use and the risk of opioid misuse, with a shorter recovery time in various procedures and patient populations.

Objective: In this study, we tested the hypothesis that MMA with propofol and sevoflurane (PS) can decrease pain intensity during surgery and used IoC2 as a real-time index of the analgesic effect of sevoflurane.

Study Design: Prospective, single-center, double-blind, randomized controlled clinical trial.

Setting: Xuanwu Hospital of Capital Medical University.

Methods: Patients scheduled for elective percutaneous nephrolithotomy from January 2020 to July 2020 were randomized into 2 groups, standard multimodal analgesia (propofol + sevoflurane group) and control (propofol [P] group). The PS group received propofol 2.5 mg/kg/h along with 1% sevoflurane after induction for 30 minutes during the main anesthetic procedure, and the P group received propofol 5 mg/kg/h by intravenous infusion during the operation. Index of consciousness 2 (IoC2), namely nociception index, intraoperative hemodynamic fluctuation, bispectral index (BIS), electromyography, postanesthesia care unit (PACU) length of stay, visual analog scale (VAS) score, and Aldrete and Steward scores were recorded.

Results: A total of 153 patients undergoing PCNL were enrolled. The demographic and clinical characteristics were similar between the 2 groups. IoC2 was reduced in the PS group compared to the P group at T10, T11, T12, T13, T14, and T15 time points, indicating that analgesia was more effective in the former. The BIS of the PS group did not differ significantly from that of the P group except at T12, T13, T14, and T15. PACU length of stay was shorter in the PS group than in the P group (mean [SD]: 54.35 [16.61] vs 47.39 [13.15], $P = 0.04$). VAS pain scores did not differ significantly between the 2 groups.

Conclusion: MMA with propofol and sevoflurane provided better analgesia than propofol alone and may be an effective method to reduce stress and the intraoperative nociceptive stimulus response in patients undergoing PCNL, thereby promoting rapid postoperative recovery.

Key words: Sevoflurane, propofol, analgesia, nociception index, index of consciousness 2

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Percutaneous nephrolithotomy (PCNL) is the first-line and guideline-recommended treatment for large renal calculi (1). However, the effectiveness of this procedure comes at the cost of greater postoperative pain and discomfort relative to other minimally invasive approaches, with intraoperative torque on the kidney and irritation to retroperitoneal tissues contributing to pain and potentially leading to increased use of opioids (2). Moreover, there are few methods that can effectively reduce visceral nociceptive stress during PCNL surgery. Conventional analgesia with only opioids is often insufficient and is associated with a broad range of adverse effects, including hypotension, urinary retention, ileus, respiratory depression, physical dependence or overdose, and long-term risk of abuse (3). Effective intraoperative pain control is essential for rapid recovery after PCNL.

Multimodal analgesia (MMA) comprising a combination of different analgesics is an increasingly popular method for pain control as it has been shown to reduce postoperative pain and reduce opioid use and the risk of opioid misuse, with a shorter recovery time in various procedures and patient populations. However, the optimal dose, safety, and efficacy of nonopioid MMA are not well-defined. Sevoflurane has a good analgesic effect (4-7), but an effective method to monitor its potency is lacking, and to date there have been no studies on the antinociceptive effect of sevoflurane as general anesthesia in clinical practice.

There are few methods for monitoring the analgesic effect in real time during the operation, although this is essential for optimizing dosage and enhancing the efficacy and safety of anesthesia. The electroencephalography (EEG)-derived index of consciousness 2 (IoC2) namely nociception index (8), is a noninvasive and useful parameter for estimating pain intensity and intraoperative stress response and monitoring the depth of analgesia in real time (9). IoC2 has been used to monitor the analgesic effect under hypothermia in patients undergoing coronary artery bypass graft surgery (10).

In this study, we tested the hypothesis that MMA with propofol and sevoflurane (PS) can decrease pain intensity during surgery and used IoC2 as a real-time index of the analgesic effect of sevoflurane.

Methods

Patient Characteristics, Randomization, and Blinding

One hundred and fifty-three patients scheduled for elective PCNL in Xuanwu hospital from January 2020 to July 2020 were recruited into our research. This study was a prospective, single-center, randomized, blinded, and controlled clinical trial conducted at a tertiary hospital that was approved by the Ethics Committee of Xuanwu Hospital (Institutional Review Board approval no. CINI-ZYLX-202001-50) and registered with ClinicalTrials.gov (NCT03841812). Written, informed consent was obtained from all patients. The patients and the nurse in charge of follow-up observations were blinded to group assignment. The inclusion criteria for patients were as follows: aged 18-80 years, with an American Society of Anesthesiologists (ASA) physical status score of 1-4 and body mass index (BMI) of 20-35 kg/m^2. Exclusion criteria were as follows: patients with Alzheimer's disease, an implanted pacemaker, psychiatric diseases, epilepsy, autonomic nervous system disorders, disorders of consciousness, and severe cardiopulmonary dysfunction. Randomization occurred via random block sizes using a computer-generated randomization schedule. The patients were allocated (1:1) to the MMA (sevoflurane & propofol, [PS]) group or control (propofol [P]) group by random number assignment (Fig. 1).

Outcome Measures

The primary outcome was analgesic effect based on the IoC2 in the PS and P groups. The secondary outcomes were postanesthesia care unit (PACU) length of stay, hemodynamic fluctuations, electromyography (EMG), bispectral index (BIS), and incidence rate of patient-reported postoperative pain based on the visual analog scale (VAS) score at 12 h (VAS.1) and 24 hours (VAS.2) after the operation. Postoperative recovery within 5 minutes of admission to the PACU and after 30 minutes were evaluated with the 40-item quality of recovery questionnaire (Aldrete.1/Aldrete.2 and Steward.1/Steward.2 scores).

Anesthesia Protocol and Study Setting

After admission of the patient to the operating room, an effective and safe venous channel was established. Patients were administered 8 mL/kg/h Ringer's solution with an intraoperative maintenance dose of 4 mL/kg/h. Baseline vital signs were recorded 15 minutes after admission to the operation room. After 3 minutes of 100% oxygen (O_2) supplied via a mask, anesthesia was induced using intravenous etomidate 0.2 mg·kg^{-1} (injection time, 30s), followed by administration of 0.4 μg·kg^{-1} sufentanil (injection time, 30s) and 0.5 mg·kg^{-1} rocuronium (injection time, 30s). Tracheal

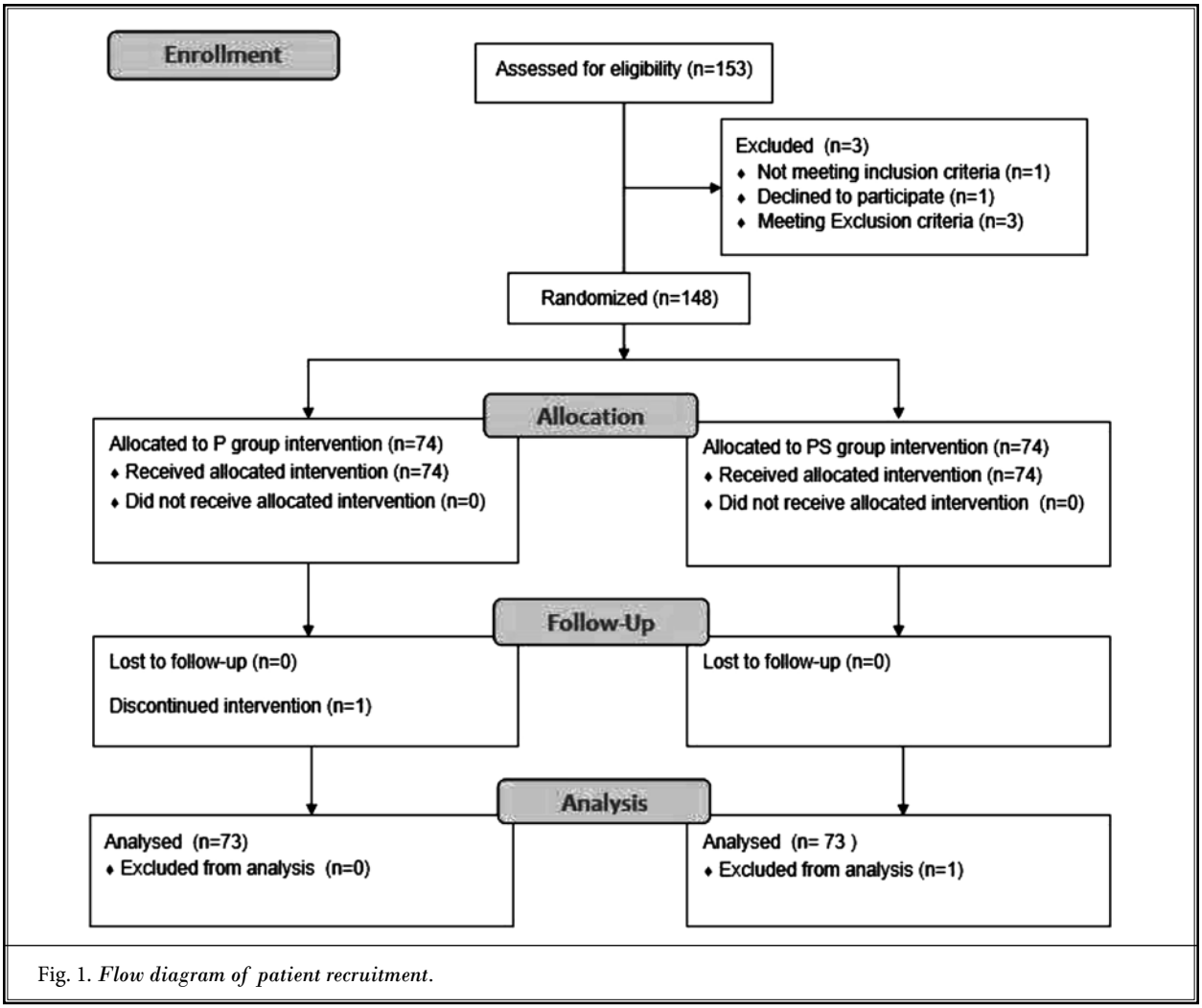

Fig. 1. *Flow diagram of patient recruitment.*

intubation was performed for mechanical ventilation when satisfactory muscle relaxation was achieved (after about 3 minutes). The patient was connected to an anesthesia machine (S5 Advance Datex Ohmeda; Soma Technology, Bloomfield, CT, USA) with a tidal volume of 6 $mL \cdot kg^{-1}$, respiratory rate of 12 breaths/min, inspiration to expiration ratio of 1:2, end-tidal carbon dioxide (CO_2) pressure 35-40 mmHg, and 8 L/min fresh gas flow of 60% O_2. Anesthesia was maintained with a standard general anesthesia protocol, during which 0.3 μg/kg/h remifentanil was administered by continuous infusion. After anesthesia induction, patients were randomly assigned to the 2 groups; the P group received a continuous infusion of 5 mg/kg/h propofol, and the PS group received 2.5 mg/kg/h propofol for 30 minutes after anesthesia induction by inhalation of 1% sevoflurane. In order to prevent fulminant inhibition and the effect of anesthesia induction on anesthesia maintenance, 1% sevoflurane was added after 30 minutes of induction anesthesia. The end-tidal sevoflurane concentration was maintained at 1.0 vol%. Anesthesia was maintained using a semiclosed circuit anesthesia machine (Datex-Ohmeda, Madison, WI, USA) with an end-tidal concentration model and cassette vaporizer (Aladin2; GE Healthcare, Little Chalfont, UK), with a fraction of inspired O_2 maintained at 0.6. At the end of the operation, endotracheal intubation was removed, and the patient was transferred to the PACU.

Intraoperative Monitoring and Recording

For all patients, there was routine monitoring of invasive blood pressure and pulse pressure variation after connecting the artery catheter to a precalibrated fluid-filled pressure transducer (DELTRAN II Disposable

Pressure Transducer System, 3 CC/HR flow rate; Utah Medical Products, West Midvale, UT, USA). Electrocardiography, heart rate (HR), and peripheral O_2 saturation (SpO_2) were monitored with a blood pressure monitoring system (M8007A; Philips Medizin Systeme Boeblingen GmbH, Boeblingen, Germany). The partial pressure of end-tidal (PET)CO_2 and end-tidal sevoflurane were also monitored during the operation. We recorded variations during the operation at 15 time points (T1-T15): 15 minutes after admission to the operating room (T1); after anesthesia induction (T2); immediately after tracheal intubation (T3); 5-30 minutes after anesthesia induction (at 5-minute intervals, T4-T8); immediately after sevoflurane administration (T9); and 5-30 minutes after sevoflurane administration (at 5-minute intervals; T10-T15). For all patients, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), HR, SpO_2, and $PETCO_2$ were continuously recorded at these 15 time points. The data were stored on a hard drive for further analysis. BIS was continuously recorded with a BIS monitoring system (Medtronic, Minneapolis, MN, USA) (17) that combines different spectral features of EEG-derived activity to monitor the depth of sedation. Muscular activity as measured by EMG recording reflects muscular relaxation; the signal quality index (which reflects the presence of artifacts) and burst suppression rate (which reflects over-inhibition of brain function) were also recorded.

Evaluation of Intra-Operative IoC2

IoC2 is a dimensionless analgesia-related parameter with values ranging from 0 to 99 that is correlated with EEG spectral features and reflects the depth of analgesia, with values > 90 and < 20 indicating insufficient and excessive analgesia, respectively. The recommended range of IoC2 values during an operation is 30-80. Patients were connected to an IoC2 sensor with 2 forehead and 1 temporal probe. All monitoring data were simultaneously collected using a multiparameter anesthesia monitoring system (Angel-6000D; Shenzhen Weihaokang Medical Technology Co, Shenzhen, China).

Statistical Analysis

Data are presented as mean ± SD or as numbers and percentages. Categorical data were compared with the chi-squared test or Fisher's exact test where appropriate. The normality of distributions of numeric variables was tested with the Shapiro-Wilk test. Continuous data were compared with a 2-sided t-test and Wilcoxon rank-sum test. Parameters across different time points were compared by 1-way analysis of variance (ANOVA) with post hoc Tukey's honestly significant difference correction for multiple comparisons. The Wilcoxon signed-rank test was also used to evaluate differences between paired data. Statistical analyses were performed using R v3.0.1 (http:/www.Rproject.org), and the level of statistical significance was set to $P < 0.05$.

Results

Patient Characteristics and Baseline Hemodynamic Values

A total of 153 consecutive patients who underwent PCNL at our center were enrolled and 148 completed the study. Five patients were excluded (one refused participation, and one had BMI > 35; one had a history of epilepsy, and 2 had severe cardiopulmonary dysfunction). All patients recovered normally after the operation. There were no significant differences in age, gender, body weight, height, ASA physical status, and baseline clinical data between the 2 groups (Table 1). There were also no differences in operative time and anesthesia time between groups.

Power Analysis

The trial was conducted and reported according to the Consolidated Standards of Reporting Trials 2010 statement. We used G*Power software for power analysis. We assumed a small effect size with partial η^2 set to 0.02. Based on the sample size used in this study, our power analysis indicated that we had at least 95% power to perform the repeated-measures ANOVA. In the functional analysis, the expected effect value H was the most difficult parameter to determine. According to the Cohen effect benchmark proposed in 1988, we divided the statistical test into an effect value range of 0.2-0.9. The pwr.2p2b.test function in R package PWR was used to test the efficiency (Fig. 2). When the sample size was N1 (P group)= 73 and N2 (PS group)= 73, significance level was 0.05, and the test was 2-tailed, the effect value was H = 0.5, and test efficiency power was 0.841; when h was 0.8, the power was 0.997.

Fluctuations in IoC2

IoC2 did not differ between the PS and P groups from T1 to T9 (Fig. 3). IoC2 was significantly lower in the PS group than in the P group at T10-T15 after 1% sevoflurane administration (T10: 3.94 ± 13.20 vs 49.01 ± 8.33, $P < 0.001$; T11: 76.51 ± 12.01 vs 45.16 ± 7.90, $P < 0.001$; T12: 76.25 ± 11.58 vs 44.51 ± 9.14, $P < 0.001$;

T13: 76.58 ± 11.46 vs 44.33 ± 8.63, $P < 0.001$; T14: 77.35 ± 10.36 vs 43.48 ± 8.80, $P < 0.001$; T15: 77.70 ± 11.75 vs 43.29 ± 8.17, $P < 0.001$) (Fig. 3), indicating that the PS group experienced a lower intensity of pain at these time points.

Variations in BIS and EMG Values and Intraoperative Hemodynamic Fluctuations

BIS was significantly lower in the PS group at T12, T13, T14, and T15 compared to the P group (T12: 58.42 ± 14.19 vs 50.07 ± 9.11; T13: 56.10 ± 8.71 vs 50.69 ± 8.77; T14: 57.28 ± 9.08 vs 49.55 ± 8.12, $P < 0.001$; T15: 58.72 ± 10.87 vs 50.55 ± 6.79, $P < 0.001$) (Fig. 4). EMG values were similar between groups at all time points (Figs. 5,7). Intraoperative MAP, SBP, DBP, and HR did not differ between the PS and P groups (Figs. 6,7).

No serious adverse events were observed in either the PS or P group, with no differences in PACU time, postoperative nausea and vomiting incidence, and VAS scores between groups. PACU length of stay was significantly shorter in the PS group than in the P group ($P = 0.04$). VAS scores were similar between groups at postoperative 12 h (VAS.1; $P = 0.65$) and 24 h (VAS.2; $P = 0.6$). There were also no differences in Aldrete.1 score (P not available) and Aldrete.2 ($P = 0.76$) between groups. The PS group had lower Steward.1 and Steward.2 scores before discharge from the PACU than the P group (P not available and $P = 0.37$, respectively) (Figs. 8, 9).

Subgroup Analysis of Anesthesia-Related Indices

In both groups, BIS, DBP, EMG, and HR did not differ among across subgroups of age, ASA physical status score, BMI, and gender. However, IoC2 was significantly decreased after sevoflurane administration in all subgroups (Supplemental Fig 1).

Discussion

In our study, MMA with propofol and sevoflurane significantly reduced IoC2 during PCNL, indicating decreased nociceptive activation and deep analgesic effect. Thus, the adjunctive use of sevoflurane is a good option for reducing nociception activation during surgery. This is the first study to evaluate the effect of sevoflurane as an intraoperative analgesic in a clinical setting. Adjunctive sevoflurane anesthesia was also associated with a lower risk of side effects than propofol used alone and effectively maintained anesthesia after induction (11). Sevoflurane has been increasingly recommended for MMA in various studies (12). Administration of end-tidal sevoflurane led to a significant decrease in IoC2 to the recommended range. An increasing number of studies have shown that opioids alone cannot completely inhibit the intraoperative stress response and do not exert the most potent analgesic effect. A higher IoC2 value represents a higher probability of pain and stress responses (13). We found that IoC2 gradually increased after anesthesia induction and remained at > 60 before sevoflurane addition, indicating that total intravenous anesthesia with even a high dose of opioid did not completely block nocicep-

Table 1. *Demographic and clinical data for the study population.*

	P group	PS group	t/χ^2	*P*
Age, years	57.18 ± 13.36	55.16 ± 13.69	0.89	0.38
Gender				
Male	43 (58.90%)	34 (46.58%)	2.55	0.11
Female	30 (41.10%)	39 (53.42%)		
Height, cm	166.42 ± 7.29	165.46 ± 8.77	0.70	0.49
Weight, kg	70.56 ± 12.24	70.88 ± 11.66	−0.16	0.87
Operation time, min	116.6 ± 34.5	118.09 ± 40.1	−0.24	0.81
Anesthesia time, min	164.88 ± 45.83)	164.42 ± 45.81	0.059	0.95
ASA				
I/II	52 (71.23%)	54 (73.97%)	0.40	0.53
III/IV	21 (28.76%)	19 (26.03%)		

Data are presented as mean ± SD or n (%).
$P < 0.05$ was considered statistically significant.
ASA, American Society of Anesthesiologists; P, propofol; PS, propofol + sevoflurane.

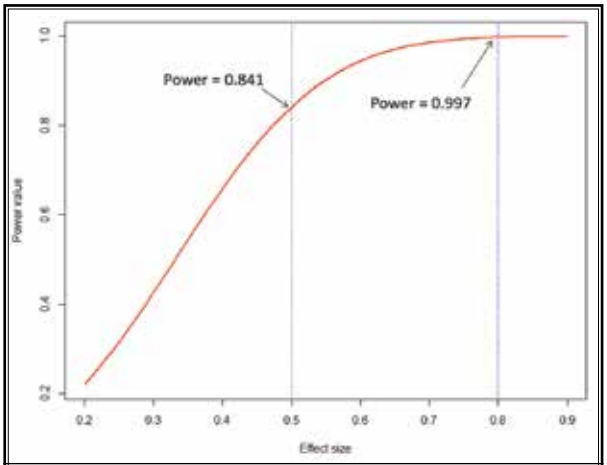

Fig. 2. *Power analysis.*

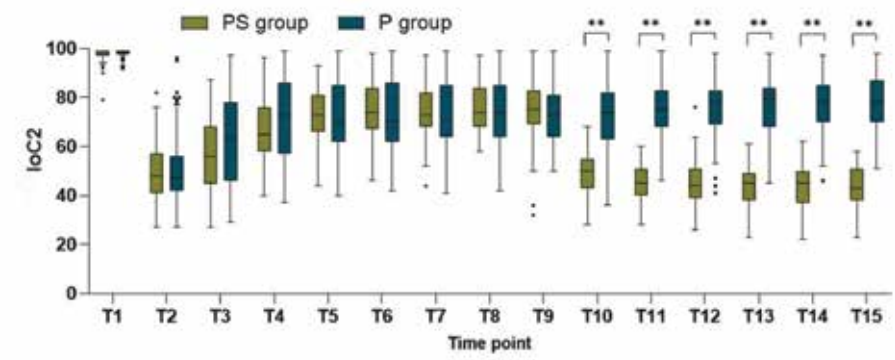

Fig. 3. *Variation in IoC2 before and after administration of 1% sevoflurane during the anesthesia procedure. *P < 0.05; **P < 0.01.*

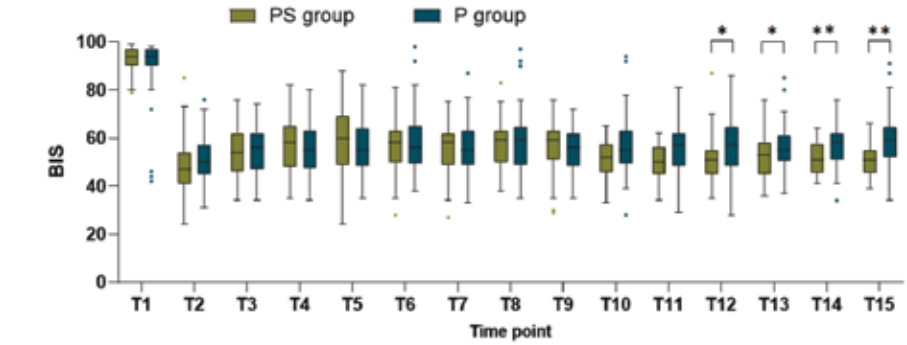

Fig. 4. *Variation in BIS before and after administration of 1% sevoflurane during the anesthesia procedure. *P < 0.05; **P < 0.01.*

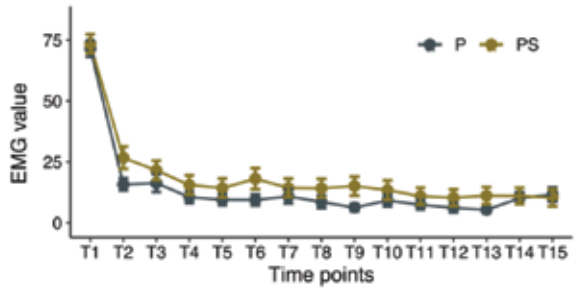

Fig. 5. *Variations in EMG recordings. *P < 0.05; **P < 0.01.*

tion. This is supported by the finding that significantly higher opioid doses than those typically employed in clinical practice inhibited neuronal responses by just 41% (14). Thus, sevoflurane was a major factor contributing to a low IoC2 in our study.

The analgesic effect of sevoflurane has been observed under a variety of surgical conditions. Subanesthetic levels of sevoflurane in intrauterine perinatal asphyxia or administration of sevoflurane during labor may alleviate pain (4-7). There are 3 key mechanisms that could potentially explain the reduction in IoC2 after sevoflurane administration. Firstly, sevoflurane exerts an analgesic effect by acting on key receptors involved in analgesia that are different from opioid receptors, which could enhance the blockade of other nociception pathways. For example, sevoflurane targets glycine receptor (2,3), which is involved in neurotransmission in the spinal cord and brainstem; nicotinic acetylcholine receptors (15,1); and spinal γ-aminobutyric acid receptors associated with pain processing (16-18). Sevoflurane was shown to depress sensory neuronal responses mediated by glutamate receptors following noxious stimuli by modulating potassium channel conductance (19). Secondly, sevoflurane can exert an antinociceptive effect by suppressing inflammation (20-26). Thirdly, sevoflurane acts synergistically with other anesthetic agents (27,28). Opioid peptide receptors are involved in sevoflurane-induced suppression of spinal nociception (29). Moreover, sevoflurane but not propofol significantly reduced the H reflex amplitude (30). Thus, MMA with sevoflurane can effectively reduce pain.

Sevoflurane is known to induce hypnotic and analgesic effects (31,32). We observed no significant changes in BIS during most of the operation but major

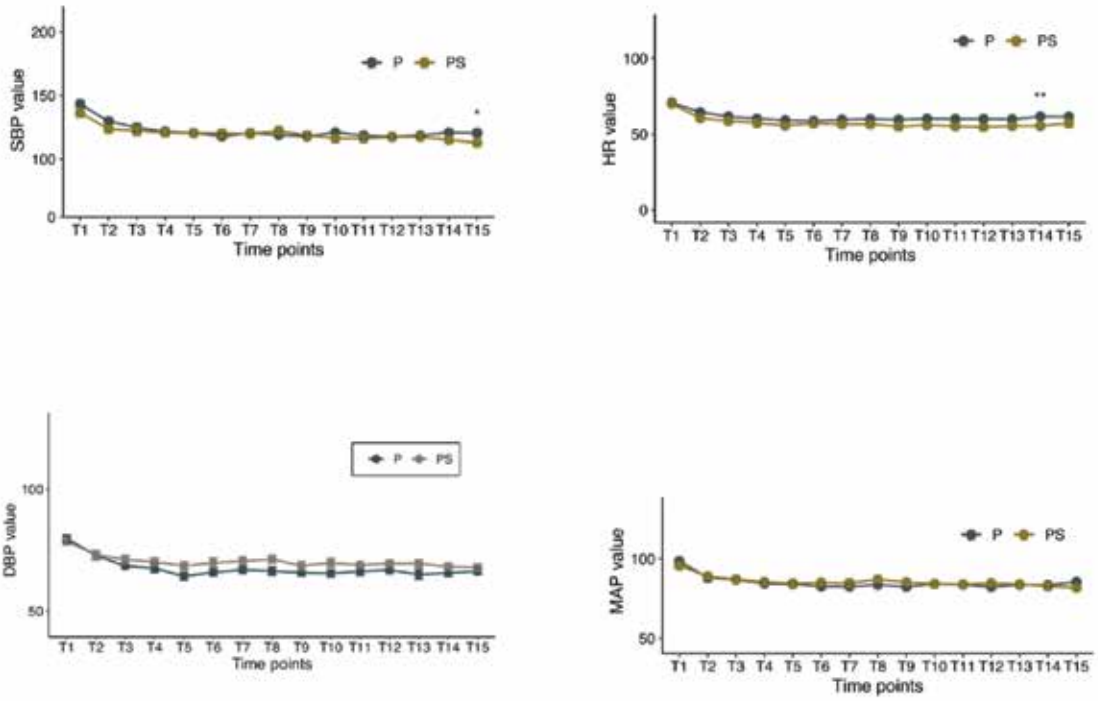

Fig. 6. *Variations in hemodynamic parameters (SBP, HR, DBP, and MAP). *P < 0.05; **P < 0.01.*

changes at the last 4 time points examined; although at both time points, the value remained within the recommended range for depth of sedation. Sedation and analgesia are 2 closely related effects of sevoflurane that are reflected by a decrease in relative IoC2. BIS as a measure of the sedative effect of sevoflurane showed a moderate decrease and did not vary greatly, unlike IoC2. The fluctuation of IoC2 values suggests that the analgesic effect of sevoflurane is more potent than its hypnotic effect.

SBP did not show notable fluctuations during the surgical procedure after anesthesia induction because of the application of vasoactive drugs. However, end-tidal sevoflurane administration did not significantly reduce SBP. The same trend was observed for MAP, which did not increase after 1% sevoflurane administration, as well as HR, which did not fluctuate in response to sevoflurane or a noxious stimulus. Although hemodynamic parameters are important in anesthesia monitoring, they often lack predictive power or sensitivity to detect the antinociceptive effect of a drug. Neural pathways associated with nociception may be activated during deep levels of anesthesia even when clinical responses and fluctuations in hemodynamic parameters are abolished (33). This can explain why

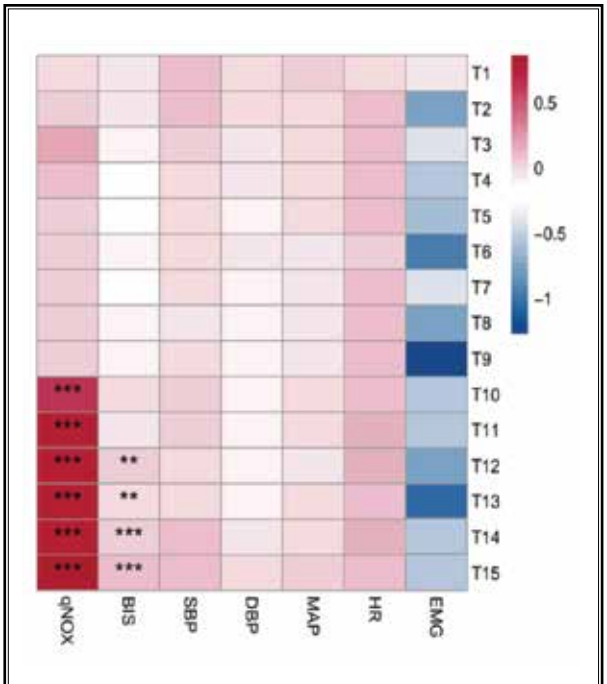

Fig. 7. *Heat map of all variations.*

**$P < 0.05$; * **$P < 0.01$.

Variable	Mean (sd) P group	Mean (sd) PS group	P value
PACU	54.35 (16.61)	47.39 (13.15)	0.04
Aldrete.1	9 (0)	9 (0)	NA
Aldrete.2	9.82 (0.39)	9.84 (0.37)	0.76
Steward.1	6 (0)	6 (0)	NA
Steward.2	6 (0)	6 (0)	NA
VAS.1	2.75 (0.78)	2.83 (0.74)	0.65
VAS.2	2.66 (0.61)	2.73 (0.52)	0.6

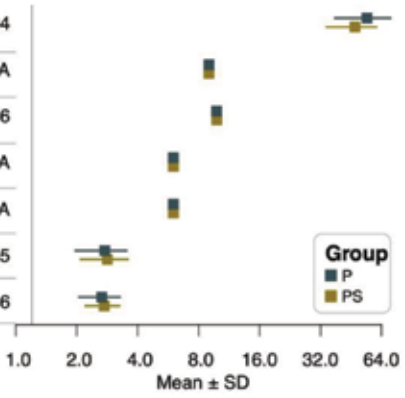

Fig. 8. *Forest plot of postoperative PACU length of stay, Aldrete score 1, Aldrete score 2, Steward score 1, Steward score 2, VAS.1 score, and VAS.2 score.*

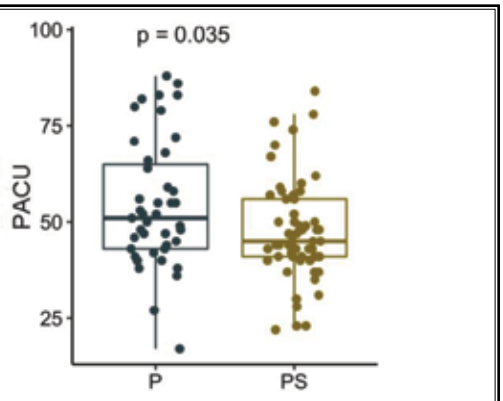

Fig. 9. *Spot plot of PACU stay length (min).*

sevoflurane induces an antinociceptive effect with a larger impact on IoC2 but a smaller one on hemodynamic fluctuations. We were unable to observe changes in respiration when the mechanical ventilation settings during general anesthesia were fixed. Thus, the cardiorespiratory response was an indirect reflection of the stress response, with IoC2 correlated with stress parameters. Additionally, in our study BIS, DBP, EMG, and HR did not differ across subgroups, although IoC2 was significantly decreased by sevoflurane administration in all subgroups. This indicates that sevoflurane only affected IoC2 and the level of pain. This strong correlation between sevoflurane and IoC2 underscores the high analgesic efficacy of intravenous/inhalation MMA with no effects on hemodynamics. Our results highlight the beneficial and synergistic effects of the inclusion of sevoflurane in intravenous anesthesia protocols with propofol. Taken together, the results of our study support our hypothesis that MMA with sevoflurane has a superior analgesic effect—as measured by IoC2—to propofol alone in patients undergoing PCNL, resulting in a better outcome with no complications and stable hemodynamics.

Limitations

There were some limitations to this study. There were no long-term data on patient outcomes. In a future study, we plan to follow up patients for 3 months after the operation to evaluate the long-term benefits of MMA with sevoflurane. Additionally, comparing the risk/benefit profile of sevoflurane to that of other general anesthetics will guide its rational and optimal use.

Conclusions

MMA with sevoflurane diminished pain intensity by providing deeper analgesia and accelerated postoperative recovery without adverse effects and is thus a safe and effective option for intraoperative analgesia of patients undergoing PCNL.

Availability of data and materials: The raw data for this study are available upon reasonable request to the corresponding author.

Supplemental material available at painphysicianjournal.com

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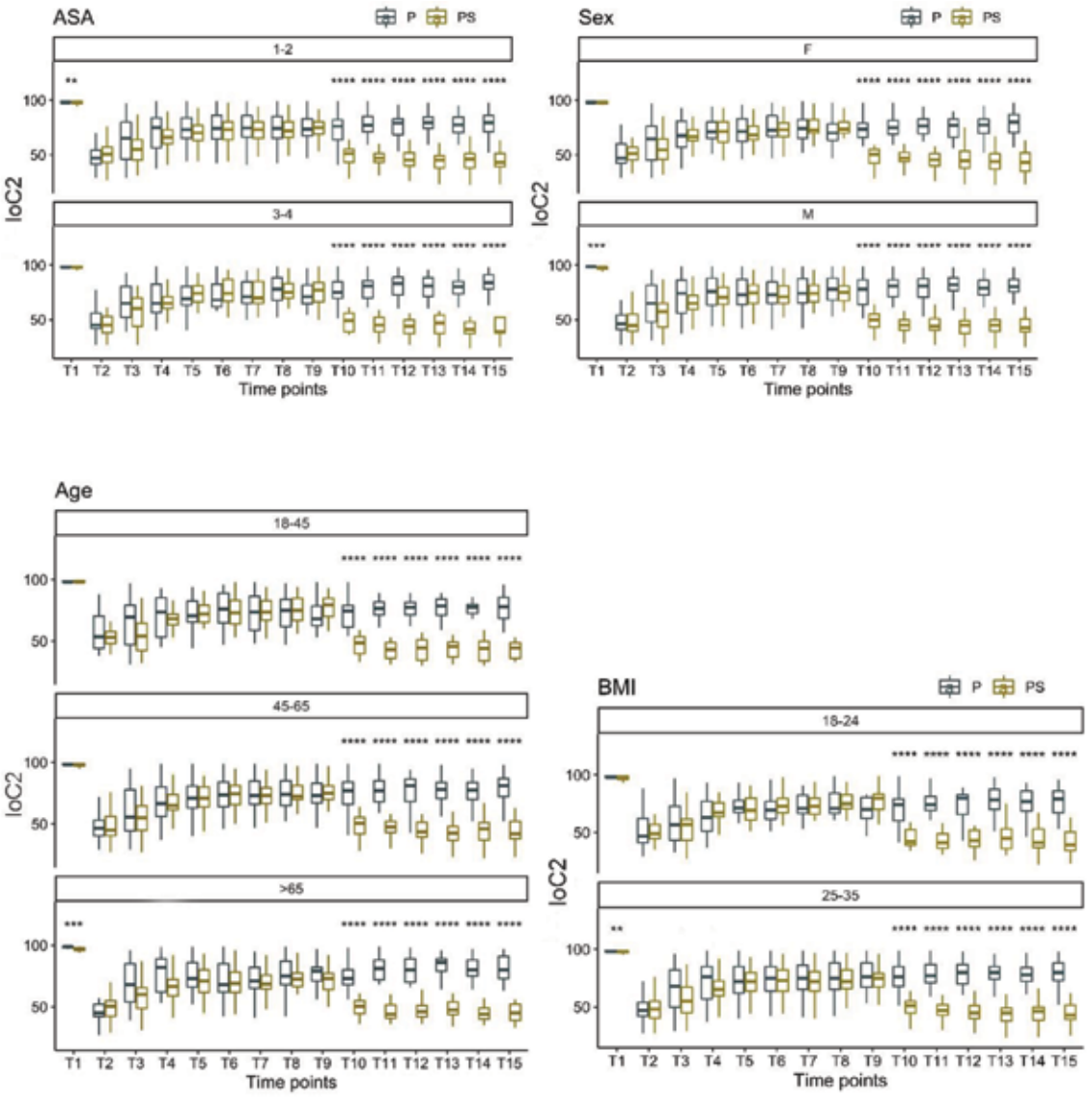

Supplemental Figure. *Subgroup analysis of IoC2 index. The IoC2 index only effected by sevoflurane, not effected by ASA score, gender, age, and BMI.*