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Sedative and analgesic validity and administration routes of dexmedetomidine and fentanyl combined with ketamine in awake fiberoptic intubation: An exploratory randomized controlled trial

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Abstract

Background: Awake fiberoptic bronchoscope intubation (AFOBI) is the gold standard technique for the management of patients with difficult airways. Adequate sedation and analgesia are essential for successful AFOBI. The aim of this study was to evaluate the sedative and analgesic validity and administration routes of dexmedetomidine and fentanyl combined with ketamine in awake fiberoptic intubation.

Methods: Patients undergoing head and neck surgery under general anesthesia with predicted difficult airways were included. Participants were randomly assigned to 6 different groups (n = 6): groups 1-3 were intravenous (IV), while groups 4-6 were intranasal (IN) (group 1: dexmedetomidine (DEX) 1 μg/kg + fentanyl (FEN) 1 μg/kg; groups 2-3: DEX 1 μg/kg + FEN 0.7 μg/kg + ketamine (KTM) 0.1/0.2 mg/kg; group 4: DEX 1.5 μg/kg + FEN 1.4 μg/kg; and groups 5-6: DEX 1 μg/kg + FEN 1 μg/kg + KTM 0.4/0.6 mg/kg). The visual analog scale (VAS) score during intubation, time required for the modified observer's assessment of alertness/sedation scale (OAA/S) score to reach above 2 and for the bispectral index (BIS) to decrease to 60-80, motor activity assessment scale (MAAS) score, changes in vital signs and adverse effects were recorded.

Results: Among the IV groups, the VAS score of group 1 (5.65 ± 2.11) was higher than those of group 2 (1.89 ± 2.16, $P = 0.012$) and group 3 (1.15 ± 0.98, $P = 0.001$). Among the IN groups, the VAS score was lower in group 6 (0.86 ± 1.27) than in group 4 (7.20 ± 2.70, $P < 0.001$) and group 5 (3.93 ± 2.73, $P = 0.031$). Participants in group 5 and group 6 were less likely to cough when intubated than those in group 4 ($P = 0.002$), while the differences among IV groups were not significant. There were no significant differences in the other endpoints.

Conclusions: Our study indicates that the addition of subanesthetic doses of ketamine, either intravenous or intranasal, could reduce the fentanyl and dexmedetomidine consumption used in AFOBI and provide better sedative and analgesic effects.

Trial registration: Chinese Clinical Trial Registry (www.chictr.org.cn; ChiCTR1900021185), prospectively registered on February 1st, 2019.

Background

The estimated incidence of difficult airways during clinical anesthesia is 1–18% [1, 2]. Severe events may occur, such as respiratory depression, hypoventilation, hypoxemia, brain damage and even death if the patient's airway is not secured [3]. Although local anesthesia and many types of medicines are used to mitigate anxiety and pain, awake intubation can be an extremely unpleasant experience. Inadequate sedative and analgesic effects of a low-dose single-agent often result in inability to cooperate with the tracheal intubation procedure for patients. However, excessive sedation and analgesia can lead to severe adverse effects, such as hypoventilation and inhibition of the circulatory systems, which may threaten the lives and safety of patients [4,5].

Dexmedetomidine (DEX) is a selective α-2-adrenoceptor agonist that has the ability to sedate, functions as an anxiolysis, is analgesic sparing, and reduces salivary secretion [6]. It can induce a 'awakable' state that mimics the physiological sleep state. There have been many studies on the use of dexmedetomidine in awake fiberoptic bronchoscopy intubation (AFOBI) [7]. A recent review reported that dexmedetomidine can cause fewer desaturation episodes than propofol and opioids when used in AFOBI [8]. As a classic opioid analgesic, fentanyl (FEN) can pass through the blood-brain barrier and takes effect quickly due to its high lipid solubility. When used in excessive doses, fentanyl can cause respiratory depression, asphyxia, muscle stiffness and bradycardia. However, it cannot provide adequate analgesia at low doses. Fentanyl is thus often used in combination with other anesthetics in clinical scenarios to achieve sufficient analgesia and to avoid potential adverse events.

Ketamine (KTM) is a N-methyl-D-aspartate (NMDA) receptor antagonist and is used for sedation and analgesia in children as well as adults. It can provide an adequate analgesic effect at subanesthetic doses (<1 mg/kg) while having a rather fast onset [9]. Despite its mild respiratory depressive effects, ketamine has potent sympathetic effects that can increase heart rate, blood pressure and bronchiectasis. It is suitable for patients with circulatory instability or asthma [10, 11]. However, the adverse reactions caused by excessive doses of ketamine, including increased sputum production, brain metabolism and cerebral blood flow, can be alleviated by combining it with other complementary intravenous anesthetics [12]. Low-dose ketamine can reduce the target concentration of dexmedetomidine required for the loss of consciousness, enhance the sedative effect of the dexmedetomidine, and ensure more stable hemodynamics [13]. Furthermore, low-dose ketamine can significantly reduce the dosage of fentanyl required for reaching a satisfactory sedative effect when used in combination with dexmedetomidine [14].

In addition to intravenous application, intranasal application is another common route of drug administration. The bioavailability of intranasal dexmedetomidine can reach 82% of that of intravenous administration. Regarding fentanyl, the efficacy of intranasal fentanyl spray has been reported in several studies; these studies showed a rapid time to analgesic effect and indicated that the bioavailability of intranasal fentanyl was 89% of the intravenous bioavailability [15, 16]. A more recent study indicated that pain could be significantly alleviated in 5 min in cancer patients with the intranasal administration of fentanyl; it is as effective as intravenous morphine in adults, and its bioavailability is 70% [17]. The intranasal bioavailability of ketamine can reach 50% and 45% of the intravenous bioavailability in children and adults, respectively [18]. To date, there have been few reports about the combined usage of ketamine, dexmedetomidine and fentanyl in AFOBI, either intravenously or intranasally.

The aim of this study was to evaluate the sedative and analgesic validity and the different administration routes of dexmedetomidine and fentanyl combined with ketamine in awake fiberoptic intubation.

Methods

Ethical considerations

The trial protocol was approved by the Clinical Research Ethics Committee of Shanghai Ninth People's Hospital affiliated with Shanghai Jiaotong University, School of Medicine (approval number, SH9H-2018-T38-3). It was registered with the Chinese Clinical Trial Registry (www.chictr.org.cn; ChiCTR1900021185). Written informed consent was obtained from all participants or their legal representatives the day before surgery. This study adhered to CONSORT guidelines.

Participants and groups

We screened the patients the day before surgery and recruited those who met all the following criteria: (1) undergoing elective head and neck surgery with a predictive difficult airway and with BMI > 26 kg/m^2, toothless, obstructive sleep apnea hypopnea syndrome (OSAHS)/snoring, Mallampati grade III/IV, limited mandibular protrusion, short hyperthyroidism (< 6 cm) and mass that may influence intubation; (2) age ≥ 16 and < 60 years old; and (3) ASA physical status I or II. Patients who met any of the following criteria were excluded: (1) had chronic systemic diseases, such as high blood pressure, coronary disease, asthma, or thyroid disease (hyperthyroidism); (2) had cardiac electrophysiological disease, such as sinus bradycardia and atrioventricular heart blockage; (3) had intracranial hypertension or mental illness; and (4) special situations that needed to be determined by the chief surgeon.

A total of 36 patients in Shanghai Ninth People's Hospital were randomly assigned to 6 different groups (n = 6): groups 1-3 received intravenous medication, while groups 4-6 received intranasal medication (group 1 DEX 1 μg/kg + FEN 1 μg/kg; groups 2-3: DEX 1 μg/kg + FEN 0.7 μg/kg + KTM 0.1/0.2 mg/kg; group 4: DEX 1.5 μg/kg + FEN 1.4 μg/kg; groups 5-6: DEX 1 μg/kg + FEN 1 μg/kg + KTM 0.4/0.6 mg/kg). Random numbers were generated by professionals in the department of statistics and placed in random envelopes that were opened on the day of operation. Anesthesiologists administered drugs according to the patient's assigned subgroup. Patients and the personnel who collected and analyzed the data were blinded to the specific grouping.

Anesthesia procedure and data collection

Standard fasting guidelines were followed. No preoperative medication was administered. Patients lay in the supine position, and a peripheral vein in the dorsal venous hand or a cephalic vein was established. At the same time, the patient inhaled oxygen (2 L/min), and the electrocardiogram (ECG), noninvasive blood pressure (NIBP), pulse oxygen saturation (SpO_2), respiration rate (RR), and bispectral index (BIS) were recorded.

For the intravenous (IV) route (Fig. 1A), each group was given DEX (Guorui Medical, Inc., Sichuan, China; 0.1 mg/ml) at a total dose of 1 μg/kg of body weight, which was diluted with sterile saline solution (Chimin Pharmaceutical Co., Ltd., Zhejiang, China) to a final concentration of 4 μg/ml and intravenously pumped for 10 min. FEN (Humanwell Pharmaceutical Co., Ltd., Yichang, China; 0.05 mg/ml) was given intravenously 6 min after dexmedetomidine administration. The dose given to group 1 was 1 μg/kg, and that given to groups 2 and 3 was 0.7 μg/kg. Nine minutes later, groups 2 and 3 were intravenously injected with KTM (Gutian Medical, Inc., Fujian, China; 50 mg/ml) at doses of 0.1 mg/kg or 0.2 mg/kg of

body weight, respectively. After 10 min, the patients underwent thyrocricocentesis with 2% lidocaine hydrochloride (Hualu Pharmaceutical Co., Ltd., Shandong, China; 0.02 g/ml) for local anesthesia. Lidocaine aerosol (Xiangxue Pharmaceutical Co., Ltd., Guangzhou, China; 50 g:1.2 g) was sprayed into nose in preparation for intubation, and then the nasal cavity was contracted with ephedrine hydrochloride and nitrofurazone nasal drops (Winguide Huangpu, Shanghai, China; 10 ml:2 mg). Then, the patients were intubated intranasally with a fiberoptic bronchoscope. At the same time, the motor activity assessment scale (MAAS) score was determined (Table 1) [19]. All patients breathed spontaneously during the procedure.

For the intranasal (IN) groups (Fig. 1B), monitoring was the same as for the intravenous groups, and anesthetics were administered intranasally using a mucosal atomizer device (MAD, Wolfe Troy Medical Inc., Utah, USA). An independent investigator prepared and administered the anesthetics or placebo (0.9% saline) with a 2.5-ml syringe that was attached to an MAD via a lure lock connector. All the anesthetics used were diluted with 0.9% saline to a final volume of 1.5 ml. The unilateral nasal cavity administration volume was no more than 0.3 ml each time, and administration intervals of 1 min were observed to ensure that the drug was completely absorbed through the nasal mucosa. Dexmedetomidine was given to group 4 or groups 5-6 at a dose of 1.5 μg/kg or 1 μg/kg of body weight, respectively. Ten minutes later, ketamine at 0.4 mg/kg or 0.6 mg/kg was given to group 5 or group 6, respectively. Then, 20 min later, fentanyl at 1.4 μg/kg or 1 μg/kg was given to group 4 or groups 5-6, respectively. Thirty minutes later, local anesthesia was administered as described above, and nasal tracheal intubation was performed using fiberoptic bronchoscopy.

Vital signs such as RR, HR, NIBP, and SpO_2 were recorded before drug administration as the baseline and were collected every 5 min during the procedure. The modified observer's assessment of alertness/sedation Scale (OAA/S) score was assessed every 3 min three times and each minute after 9 min (1 Completely awake, responding normally to normal call responses; 2 Slow response to normal call; 3 No response to normal call, response to repeated loud calls; 4 No response to repeated loud calls, only response to tapping the body; 5 No response to slap the body, but response to noxious stimuli. No response to noxious stimuli is anesthesia). The MAAS score and the time required for the BIS to reach 60-80 were recorded. Atropine (0.5 mg) was given when HR was lower than 45 beats per minute, and 6 mg ephedrine was given when systolic blood pressure (SBP) was lower than 90 mmHg or diastolic blood pressure (DBP) was lower than 60 mmHg or either dropped below 70% of the baseline value. The visual analog scale (VAS) score during intubation was noted. The VAS is a 10-cm line with 0 at the left end indicating painless and 10 at the right indicating severe and unbearable pain. Patients could mark on the scale to match their pain level subjectively. In consideration of the lack of cooperation when sedated, patients were required to recall the level of pain during intubation and to mark on VAS on the first postoperative day. Anesthetics which might induce anterograde amnesia, such as midazolam, were not used in this study. All intubations were performed by the same senior anesthesiologist.

The primary endpoint was the VAS score. Secondary endpoints included the time required for the modified OAA/S score to reach above 2 and for the BIS value to decrease to 60-80; the MAAS score;

changes in HR, RR, NIBP, and SpO_2; and the incidence of adverse reactions such as nausea, vomiting, coughing, sinus bradycardia and low blood pressure (a decrease in SBP/DBP of more than 30% compared to the baseline value).

Statistical analysis

Continuous variables were analyzed with one-way ANOVA or paired *t*-test. Categorical variables were analyzed with Chi-square test or Fisher's exact test. A *P*-value < 0.05 was considered statistically significant. SPSS 24.0 for Windows (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

Participant characteristics

A total of 36 patients were consecutively enrolled and randomized to 6 groups from February 1, 2019 to March 25, 2019. All participants were able to complete the study (Fig. 2), while being woken up during the intubation procedures. There was no significant difference in age, sex, or BMI among all patients (Table 2).

Outcome analysis

Primary outcome

All patients accomplished the VAS score after the operation. For IV groups, the VAS score of group 1 (5.65 ± 2.11) was higher than those of group 2 (1.89 ± 2.16, t = 3.043, df = 10, *P* = 0.012, 95% CI 1.01 to 6.50) and group 3 (1.15 ± 0.98, t = 4.733, df = 10, *P* = 0.001, 95% CI 2.38 to 6.61). The difference between group 2 and group 3 was not significant (Fig. 3A). For IN groups, the VAS score was lower in group 6 (0.86 ± 1.27) than in group 4 (7.20 ± 2.70, t = 5.198, df = 10, *P* < 0.001, 95% CI 3.62 to 9.05) and group 5 (3.93 ± 2.73, t = 2.499, df = 10, *P* = 0.031, 95% CI 0.33 to 5.81) (Fig. 3B). Group 6 had the lowest score of all groups, which was significantly different from those of groups 1, 4 and 5.

Secondary outcomes

The time required for the OAA/S score to reach above 2 was not significantly different among IV groups or IN groups (Fig. 3C, D). There was no obvious difference in the time needed for the BIS to decrease to 60-80 (Fig. 3E, F) or in the MAAS score (Fig. 3G, H). The same results were obtained for HR, NIBP, and SpO_2 (Fig. 4). In addition, we found that the respiration rates of group 1 and group 2 differed at the 10-, 15-, and 20-min time points, with a *P* value <0.05. However, it was difficult to determine the difference among two drug administration due to initial differences among two groups at 0 min.

We found that the participants in group 5 and group 6 were less likely to cough when intubated than those in group 4 (16.67%, 16.67%, 100.00%, respectively, *P* = 0.002), while no difference was found

among IV groups. No significant differences in the incidences of other adverse effects (nausea, vomiting, sinus bradycardia and hypotension) were recorded among all groups.

Discussion

Our study found that the VAS score was inversely proportional to the dose of ketamine. Low doses of ketamine can result in satisfactory analgesic and sedation effects, which is essential for AFOBI procedures. Furthermore, the MAAS score of all groups were below 4 which confirmed the adequate analgesia and sedation effects by ketamine for AFOBI procedures.

The main purpose of medication during AFOBI is to keep patients responsive and cooperative while preventing potential respiratory and cardiovascular function depression [6, 21]. To achieve this, the anesthetic agents used during the procedure must have a fast onset of action, be easily titratable while providing adequate sedation [22]. The three anesthetics used in our study all acted quickly when administered intravenously with strong sedation and analgesia effects. Dexmedetomidine is often used at 1 μg/kg over 10 min as a loading dose with or without a maintenance dose of 0.3 μg/kg/h to 0.7 μg/kg/h [9,23-28] in clinical scenarios. For the purpose of the present study, a loading dose of 1 μg/kg of DEX was infused intravenously over 10 min with no continuous infusion, considering that dexmedetomidine was given in combination with other anesthetics. Fentanyl takes 1 min to take effect when injected intravenously and 4 min to reach its peak, and the analgesia effect is maintained for 30 to 60 min. The induction dosage of fentanyl for general anesthesia differs among various surgical procedures, ranging from 1 μg/kg to 4 μg/kg. The final intravenous injection dosage of fentanyl was set at 1 μg/kg which was based on current literature [2]. A previous study reported that low doses of ketamine could provide analgesia and modulate opioid tolerance, which is consistent with our study [9]. Ketamine is typically administered intravenously and has a relatively short half-life (2-3 h). However, it is inconvenient for use in emergency settings [29]. There have been few studies on the use of ketamine in awake intubation. Considering that dexmedetomidine and fentanyl were administrated in junction, a final dosage gradient of 0.1 mg/kg and 0.2 mg/kg was set for IV, which is lower than the dosage used to treat cancer pain intravenously [30].

In our study, the incidences of coughing were lower in group 5 and group 6 than in group 4 (P=0.002), indicating that ketamine could suppress coughing. A previous study reported that a mixture of ketamine and dexmedetomidine could suppress coughing induced by fentanyl which was consistent with our study [31]. However, no difference was found among the IV groups. The results of our study suggest that the addition of ketamine could reduce coughing, especially when administered intranasally. This outcome may result from the local anesthetic effect of ketamine [32].

In this study, we calculated the dosages of intranasally administered drugs according to their bioavailability. Considering that the dosage of ketamine was 0.75 mg/kg in the study of Andolfatto G. et al. [33], we chose lower doses of 0.4 and 0.6 mg/kg. To achieve the maximum analgesic effect of drugs at the same time, we set the dosing interval by referring to the pharmacokinetic data reported in other

studies. Intubation was performed when the blood concentrations of the three anesthetics were at their highest - that is, when sedation and analgesia were at their best - to minimize patients' pain and anxiety. However, it is worth noting that the long induction time of IN sedation may limit its application for emergency intubation procedures.

There were also a few limitations in our study. The sample size was not large enough due to the nature of the present study being an exploratory study. More samples should be recruited in the future. In addition, small doses of dexmedetomidine was given repeatedly due to inadequate pharmaceutical concentration of it.

We also noted a few tips that might ensure the effectiveness of intranasal administration. First, we examined the patients' nasal structure and mucosa, cleaned the nasal cavities and minimized the barriers to drug absorption. Second, we tried to increase the concentration of the drugs by not diluting them. Third, we used a special nasal spray device to distribute the drug evenly onto the nasal mucosa to reduce drug loss. Fourth, we performed nasal administration in both nasal cavities to increase the nasal mucosal surface area that could absorb the drugs. Fifth, an administration method that repeatedly provided a small amount of the drug was used, and the amount delivered to a single nasal cavity was controlled to be no more than 0.3 ml at a time. Finally, the participants were asked to lean their heads back during spraying and to breathe with their mouths temporarily.

Conclusions

Our study indicated that the addition of subanesthetic doses of ketamine could reduce the dosages of fentanyl and dexmedetomidine required for AFOBI procedures while providing better sedative and analgesic effects both intravenously and intranasally. Furthermore, the addition of intranasal ketamine could suppress coughing during AFOBI procedure, while no difference was found for the groups that received intravenous ketamine.

Declarations

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Authors' contributions

JH, YJ, LC, and PJ designed the project. LC wrote the manuscript with PJ and YJ providing revisions of the manuscript. LC and PJ recruited the subjects and clinical assessments and acquired the data. SY, HR and WH helped to design the overall study and analyze the data. All authors reviewed the final manuscript. All authors have given their final approval for the manuscript.

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Availability of data and materials

The datasets supporting the conclusions of this article are included within the article.

Ethics approval and consent to participate

The trial protocol was approved by the Clinical Research Ethics Committee of Shanghai Ninth People's Hospital affiliated with Shanghai Jiaotong University, School of Medicine (approval number, SH9H-2018-T38-3). Written informed consent was obtained from all participants or their legal representatives the day before surgery.

Consent for publication

Participants have expressed their consent for anonymized data publication in written or verbal form.

Competing interests

The authors declare that they have no competing interests.

Abbreviations

AFOBI: awake fiberoptic bronchoscope intubation; DEX: dexmedetomidine; FEN: fentanyl; KTM: ketamine; IV: intravenous; IN: intranasal; VAS: visual analog scale; OAA/S: observer's assessment of alertness/sedation scale; BIS: bispectral index; MAAS: motor activity assessment scale; ECG: electrocardiogram; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIBP, noninvasive blood pressure; SpO_2, pulse oxygen saturation; RR, respiration rate.

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Tables

Table 1 Motor Activity Assessment Scale (MAAS)[20].

Score	Description	Definition
0	Unresponsive	Does not move with noxious stimuli
1	Responsive only to	Open eyes, raises eyebrows or turns head toward stimulus; moves limbs with noxious stimulus
2	noxious stimuli	Open eyes, raises eyebrows or turns head toward stimulus when touched or name is loudly spoken
3	Responsive to touch or	No external stimulus in required to elicit movement; adjusts sheets or clothes purposefully, follows commands
4	name	No external stimulus in required to elicit movement; picks at sheets or tubes, uncovers self, follows commands
5	Calm and cooperative	No external stimulus in required to elicit movement, attempts to sit up or moves limbs out of bed, does not consistently follow commands (for example, will lie down when asked to but soon reverts back to attempts to sit up or move limbs out of bed)
	Restless and cooperative	No external stimulus in required to elicit movement; pulls at tubes or catheters, thrashes side to side, strikes at staff, tries to climb out of bed, does not calm down when asked
6	Agitated	
	Dangerously agitated, uncooperative	

Table 2 Baseline characteristics.

target	1	2	3	4	5	6
Age(yr)	44.83 ±	41.33 ±	35.17 ±	37.50 ±	25.33 ±	39.67 ±
Sex (Male)	15.88	13.98	14.76	16.23	5.47	12.03
Sex	50%	83.33%	50%	33.33%	66.67%	33.33%
(Female)	50%	16.67%	50%	66.67%	33.33%	66.67%
BMI	22.03 ± 2.55	21.60 ± 1.79	22.23 ± 3.16	20.00 ± 1.46	21.17 ± 3.78	21.05 ± 2.61

Data are presented as the mean (SD) ± median (interquartile range) or percentage (%) of patients.

Figures

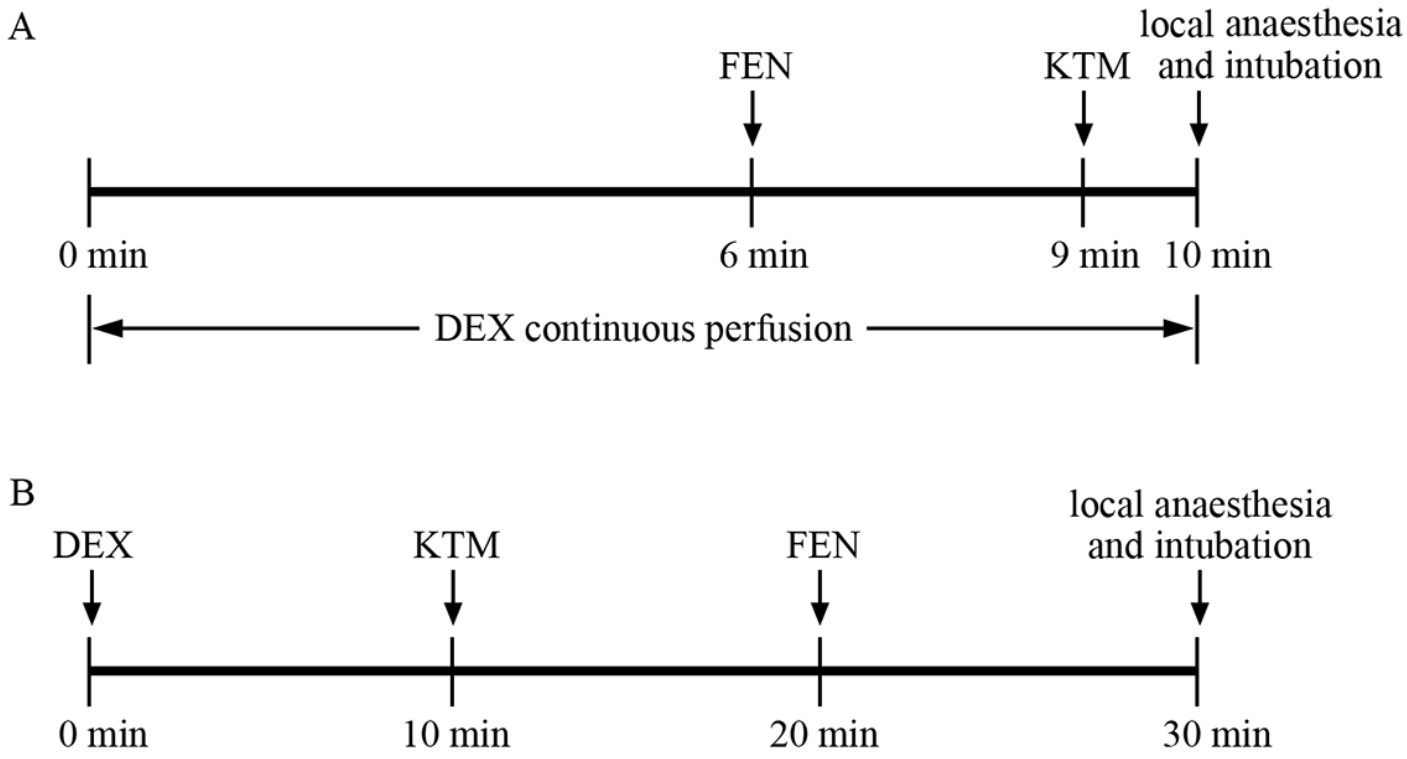

Figure 1

Drug administration flow. A. Intravenous (IV) administration. B. Intranasal (IN) administration. KTM, ketamine; DEX, dexmedetomidine; FEN, fentanyl. IV groups: group 1: DEX 1 μg/kg + FEN 1 μg/kg; groups 2-3: DEX 1 μg/kg + FEN 0.7 μg/kg + KTM 0.1/0.2 mg/kg; IN groups: group 4: DEX 1.5 μg/kg + FEN 1.4 μg/kg; and groups 5-6: DEX 1 μg/kg + FEN 1 μg/kg + KTM 0.4/0.6 mg/kg.

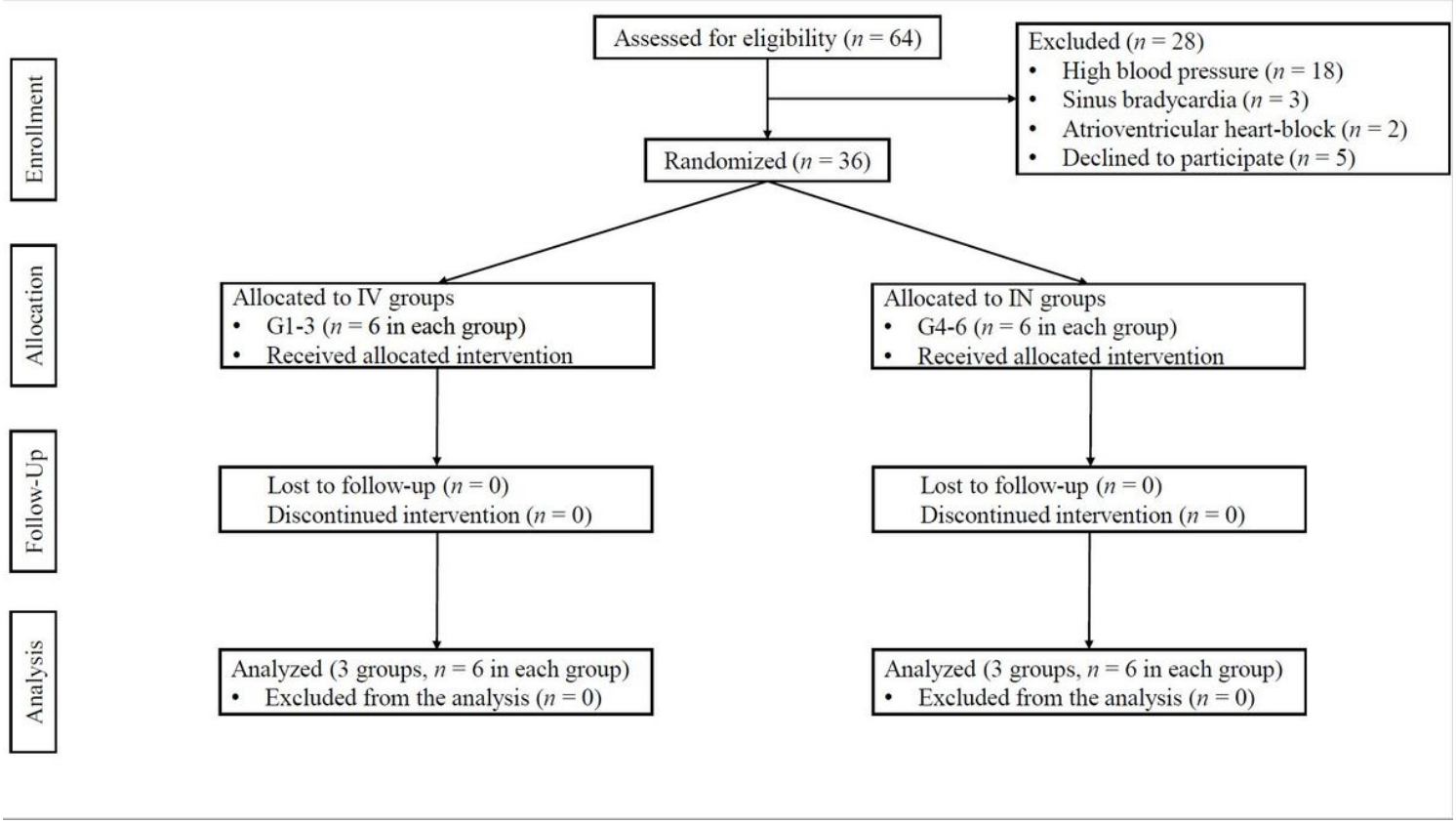

Figure 2

CONSORT diagram.

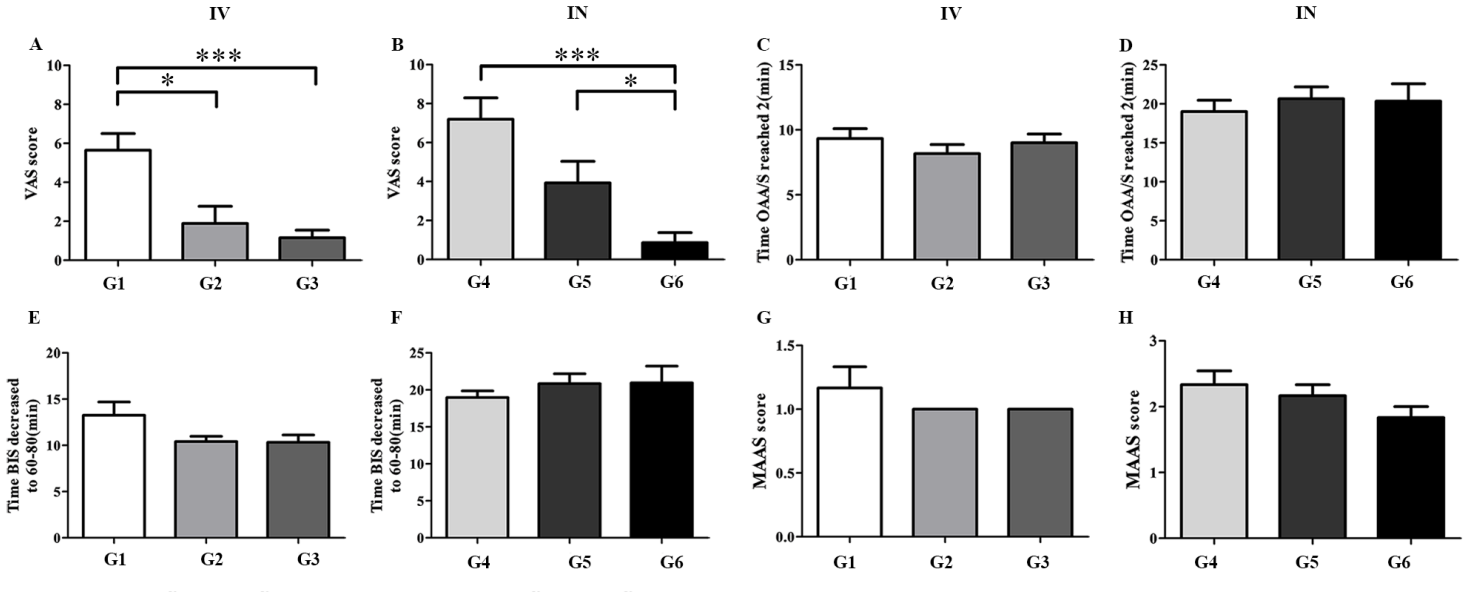

Figure 3

Degree of analgesia and sedation. A-B. VAS score. For intravenous administration, the ketamine-conjugated group received reduced doses of dexmedetomidine and fentanyl, and the VAS score was lower in group 2 and group 3 than in group 1 (P values are 0.012 and 0.001). For intranasal

administration, the VAS score of group 6 was significantly lower than that of group 4 (P < 0.001) and group 5 (P = 0.031) (G, group; *, P < 0.05; **, P < 0.01; ***, P < 0.001). C-D. The times required for OAA/S to reach above 2. E-F. The times required for BIS to decrease to 60-80. G-H. MAAS scores. For C-H, there were no significant differences among the IV groups or the IN groups.

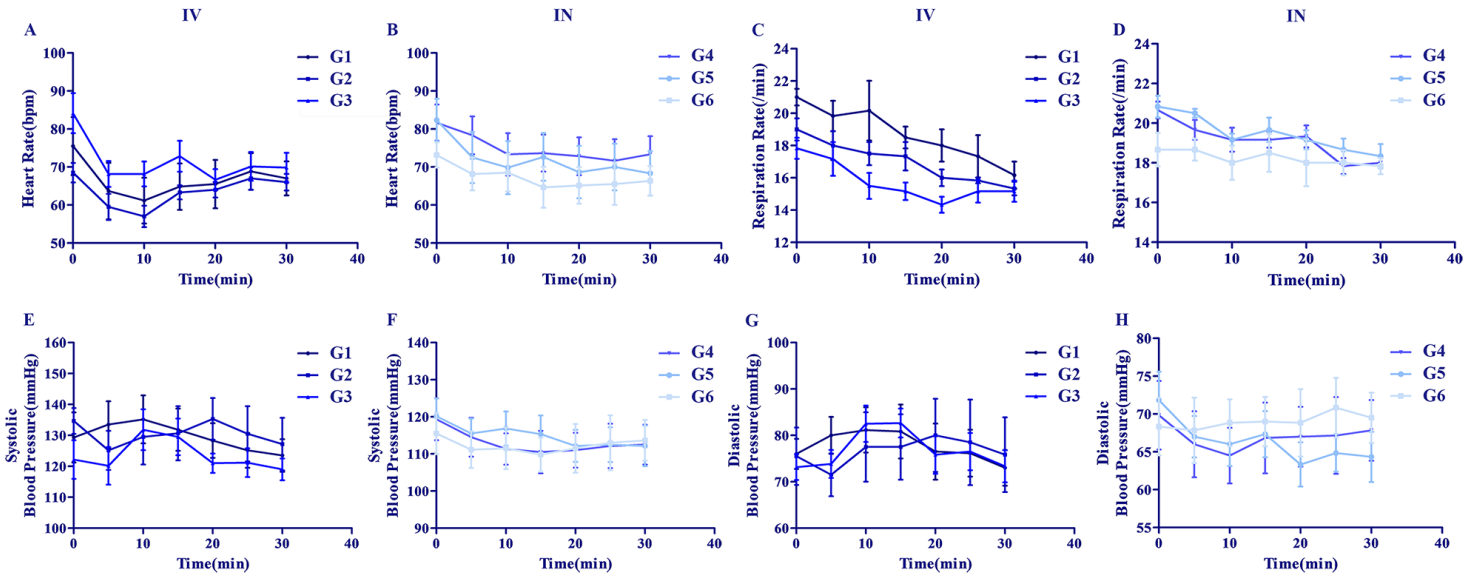

Figure 4

Changes in vital signs. There were no significant differences in vital signs among the IV groups or the IN groups. A-B. Heart rate; C-D. Respiration rate; E-F. Systolic blood pressure; G-H. Diastolic blood pressure.

Supplementary Files

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- CONSORTChecklist.doc