Comparison of a small dose of oxycodone and sufentanil for the prevention of sufentanil-induced cough during general anesthesia induction: a prospective randomized controlled trial

Lingli Shi
Children' s Hospital of Nanjing Medical University
Yong He
The Second Affiliated Hospital of Nanjing Medical University
Huanhuan Ni (154478090@qq.com)
Children' s Hospital of Nanjing Medical University

Research Article

Keywords: Oxycodone, Sufentanil, General anesthesia, Cough

Posted Date: April 1st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-355169/v1

Abstract

Background: Sufentanil is widely used during anesthesia induction. However, sufentanil injections can cause cough through different mechanisms. This study aimed to evaluate the effectiveness of a small dose of oxycodone and sufentanil in suppressing sufentanil-induced cough (SIC) during general anesthesia induction.

Methods: This prospective, randomized, controlled trial was conducted form February 12, 2019 to December 30, 2019. A total of 174 patients were scheduled for elective surgery, and 144 screened patients were randomly divided into 3 groups (n=48). Five minutes before sufentanil bolus (0.4 μg/kg), patients in group O received 0.02 mg/kg oxycodone intravenously within 5 s, those in group S received 0.02 μg/kg sufentanil within 5 s and those in group N received an equal volume of 0.9% normal saline within 5 s. Sufentanil was diluted to 5 μg/ml and administered within 5s after pretreatment. The incidence and severity of cough in the three groups were evaluated within 1 minute after sufentanil injection during anesthesia induction. Mean arterial pressure (MAP) and heart rate (HR) were recorded at T0 (after entering the operation), T1 (3 minutes after pretreatment), T2 (before intubation), and T3 (1 minute after intubation).

Results: The incidences of cough in group N, group O, and group S were 20 (41.6%), 7 (14.5%), and 6 (12.5%), respectively. Compared with group N, group O and group S exhibited significantly reduced incidence and severity of cough, and the severity of cough in group O and group S was dramatically reduced compared with that in group N ($P<0.05$). No significant differences in the rangeability of MAP and HR were noted at the four time points in the three groups ($P> 0.05$).

Conclusion: Intravenous oxycodone (0.02 mg/kg) and sufentanil (0.02 μg/kg) represent effective approaches to reducing SIC in anesthesia induction and ensuring a relatively stable hemodynamic state during general anesthesia induction.

Trial registration: Chinese Clinical Trial Registry (ChiCTR1900021087, registered date: January 28, 2019), http://www.chictr.org.cn

Background

Sufentanil has some advantages, such as a fast onset time, strength of analgesic function and cardiovascular stability, and is considered an ideal option that is widely used by anesthesiologists for general anesthesia[1]. However, sufentanil brings on cough during the induction of general anesthesia. The incidence of sufentanil-induced cough (SIC) during the induction of anesthesia has been reported by different studies to range from 16 to 47%[2-4].

Although SIC appears to be transient in most cases, this pathological condition may result in disastrous consequences in patients with compromised central nervous system (CNS) injury, open eye injury, or cardiovascular diseases. Certain patients should maintain an absolutely stable hemodynamic status and

intracranial or intraocular pressure during anesthesia induction. Explosive cough may increase intraabdominal pressure and increase the risk of regurgitation and aspiration[5]. Clinical interventions have been reported to reduce SIC[1-3, 6-13], including pretreatment with drugs (butorphanol, dezocine, remifentanil and dexmedetomidine), changing the administration route or diluting the concentration of sufentanil. However, the interventions were restricted in clinical use due to several side effects, such as long onset time, bradycardia, and respiratory depression. Thus, the key to inhibiting SIC is to identify a certain drug and apply the appropriate dosage.

Oxycodone is a derivative of thebaine and is mainly used to alleviate perioperative pain. Oxycodone inhibits μ and κ agonists and exerts obvious antitussive effects by directly acting on the cough center of the medulla oblongata[14]. A previous study found that pre-emptive use of a small dose of opioids may suppress opioid-induced cough without applying additional drugs[10, 15, 16].

In this study, we explored the effect of pretreating patients with a small dose of oxycodone and sufentanil on the incidence and severity of SIC when larger doses of sufentanil (0.4 μg/kg) were subsequently administered during the induction of general anesthesia.

Methods

This study was approved by the institutional ethics committee (The Second Affiliated Hospital of Nanjing Medical University, the committee's reference number is KY2018-117.) and registered at the Chinese Clinical Trial Registry with registration number ChiCTR1900021087. All participants provided written informed consent. In addition, this study is adhered to CONSORT guidelines.

Participants

In our study, 174 patients with ASA physical status I-II, aged 18–65 years, BMI 18.5–30 kg/m^2 and scheduled for elective surgery under general anesthesia between February 2019 and December 2019 were enrolled in this study. The exclusion criteria included a history of asthma or chronic obstructive pulmonary disease (COPD); upper respiratory tract infection in the last two weeks; smoking, bronchodilator or steroid therapy; chronic administration of opioids; impaired kidney and liver function; and allergy to oxycodone, anti-cough medication or angiotensin-converting enzyme (ACE) inhibitors. Patients were excluded if they were diagnosed with increasing intracranial or intraocular pressure.

Study protocol

The scheduled patients were randomly divided into three groups (n=58) using computer-generated random numbers. No pretreatment drug was administered before surgery. Upon arrival in the operating room, monitoring was accomplished by heart rate, invasive arterial blood pressure, respiratory rate and oxygen saturation. Venous access was established on the wrist cephalic vein of the nondominant hand with a 20-G intravenous cannula after patients came into the operation room, and the IV cannula was connected to T-connectors for drug infusion and injection in the operating room. Intravenous perfusion

was Ringers' solution of 8 ml/kg/h after venous catheterization was completed. The vertical distance from the drip bottle to the venous access was 70 cm in all the patients in this study. Patients inspired 100% oxygen by a face mask.

Group O patients were administered 0.02 mg/kg oxycodone (diluted to 2 ml) intravenously within 5 s, group S patients were administered 0.02 mg/kg sufentanil (diluted to 2 ml) intravenously within 5 s, and group N patients were administered 2 ml of normal saline. The preparation and administration of the pretreated drugs were performed by nurse anesthetists and anesthesiologists, respectively. Five minutes after pretreatment with the drugs, 0.4 μg/kg sufentanil with an injection time of 5 s was administered to all patients. A stopwatch was used to monitor the time. After sufentanil injection, the symptoms of the explosive cough, including the number and severity, were recorded within 1 min by a nurse anesthetist who was blind to the study. Depending on the number of coughs within 1 min, the patient was classified into four grades: 0 (no cough), 1 (mild, 1-2 times), 2 (moderate, 3–5 times) and 3 (severe, > 5 times). Anesthesia induction was subsequently completed with 2 mg/kg propofol and 0.6 mg/kg rocuronium, and orotracheal intubation was performed 5 minutes later.

MAP and HR were recorded at baseline after entering the operation (T0), 3 min after injecting the pretreatment (T1), before orotracheal intubation (T2) and 1 min after orotracheal intubation (T3). We excluded patients who had unacceptable hypertension (≥ 160/90 mmHg) for the three measurements after calming down for 5 min.

Sample size determination

Sample size estimates were performed by PASS 11 software (PASS, Kaysville, UT, USA). According to our pilot study, the incidence of cough induced by 0.4 μg/kg sufentanil was 40% (8/20). The incidence was reduced to 15% (3/20) after pretreatment with 0.02 mg/kg oxycodone, and pretreatment with a dose of 0.02 μg/kg sufentanil reduced the incidence of SIC to 18% (4/22). To achieve 80% statistical power with α = 0.05, each group would require no less than 46 patients. Considering the 20% drop-out rate, we recruited 58 patients in each group.

Statistical analysis

SPSS 22.0 software (IBM Corp, Armonk, NY, USA) was used for statistical analysis. Data are expressed as the mean ± standard deviation for continuous variables or n patients (%). Repeated measures ANOVA was applied to analyze the quantitative variables in three groups for MAP and HR at different time points. The incidence of cough (categorical data) was compared by the chi-squared test, and Bonferroni correction was used for pairwise comparisons. The grade data for the severity of cough were analyzed using the rank sum test. $P < 0.05$ was considered statistically significant.

Results

Demographic characteristics

In total, 174 patients were screened. Among these patients, 18 patients did not meet the inclusion criteria, 6 patients refused to participate, and 7 patients were excluded because of unacceptable hypertension. Finally, 144 patients participated in the study (Figure 1).

The demographic data (age, sex, BMI, weight) and ASA physical status were not significantly different among the three groups ($P > 0.05$, Table 1).

Incidence and severity of cough for SIC

The incidences of cough in group N, group O, and group S were 20 (43.5%), 7 (14.5%), and 6 (12.2%), respectively. Compared with group N, group O and group S exhibited significantly reduced incidences of cough (*P<0.05*, Table 2). No significant differences were observed in groups O and S (*P>0.05*). The severity of cough in group O and group S was dramatically reduced compared with that in group N (*P<0.05*), especially the severity grade of moderate and severe cough. No significant differences were noted between group S and group N (*P > 0.05*, Table 2).

Hemodynamic changes

No significant differences in the rangeability of MAP and HR were noted at the four time points in the three groups (*P > 0.05*, Table 3).

Discussion

The study demonstrated that 0.02 mg/kg oxycodone and 0.02 μg/kg sufentanil reduce the incidence and severity of SIC without aggravating hemodynamic changes.

Opioid analgesics are widely used in anesthesia induction and commonly possess the characteristics of strong analgesic effects and slight impact on hemodynamics. Cough is one of the side effects of administering sufentanil intravenously, and the discrepancies in the incidence and severity of cough may depend on the injection dose, speed and venous catheter type. According to previous studies, the incidence of SIC varies between 16% and 47%[2-4]. Special patients who require stable anesthesia induction, such as those with hypertension and intracranial or intraocular pressure increases, may experience adverse effects due to SIC.

The mechanism of cough induced by opioids remains unclear; however, various studies have presented possibly reasonable explanations. Opioids inhibit central sympathetic nerves and activate the vagus nerve, inducing cough and reflexing bronchoconstriction[17]. Pulmonary chemoreflex mediated by either irritant receptors or vagal C-fiber receptors adjacent to pulmonary vessels may represent a mechanism[17-19]. Opioid receptors exist in the tracheobronchial wall. These receptors are irritated by opioids; thus, tracheal smooth muscle is stimulated to be constricted[20]. Sufentanil-induced histamine release from lung mast cells [19]or supraglottic obstruction by soft tissue[21, 22] represent other likely mechanisms of cough. A study demonstrated that the closure of the vocal cord after injecting sufentanil may be the major mechanism of cough[23].

Various pretreatment drugs that are used to suppress opioid-induced cough, such as dexmedetomidine, ketorolac tromethamine, and lidocaine, have been proven to be effective. However, potential risks and additional side effects may impose restrictions on the clinical application of these drugs. Zhou et al.[24] demonstrated that pretreatment with 0.6 μg/kg dexmedetomidine infused intravenously over 10 mins could significantly decrease the incidence and severity of fentanyl-induced cough. However, anesthesia induction may require a prolonged infusion, and dexmedetomidine may cause bradycardia (<50 beats/min), respiratory depression, and hypotension. Tian et al.[2] found that applying ketorolac tromethamine 0.5 mg/kg intravenously ahead of injecting 0.5 μg/kg sufentanil can effectively reduce SIC. Ketorolac tromethamine is a type of nonsteroidal anti-inflammatory drug (NSAID) and may afford a risk of bleeding by inhibiting platelet function in the perioperative period. Relevant studies on ketorolac tromethamine suppressing SIC are lacking, and the prophylactic administration of ketorolac tromethamine (0.5 mg/kg) may not be the most appropriate dose for inhibiting SIC. In addition, 0.5 mg/kg lidocaine effectively suppresses remifentanil-induced cough when intravenously administered 1 min prior to remifentanil; however, lidocaine has a potential defect in systemic toxicity[25].

The onset time of intravenous oxycodone was 2~3 min, and the peak time was 5 min. Oxycodone is the only opioid double-receptor agonist available clinically, and the pharmacological effects include analgesia, anti-anxiety and antitussive effects. According to previous studies, two possible mechanisms potentially explain how oxycodone suppresses FIC. First, oxycodone may directly restrain the cough center in the medulla oblongata and then produce antitussive effects in the clinic. Additionally, it may act on the μ and κ receptors of tracheal and bronchial trees, which inhibit the reflex contraction of trachea. There are a few studies associated with oxycodone inhibiting opioid-induced cough, and the proper antitussive dosage remains controversial. Dai et al.[14] concluded that 0.075 mg/kg oxycodone can prevent FIC effectively in general anesthesia induction and that the effect of suppression was dose dependent. However, another study found that oxycodone dosages of 0.025, 0.050, and 0.075 mg/kg reduce the incidence and severity of FIC[26]. However, there was no difference among the groups, suggesting that oxycodone intravenous injection could inhibit FIC in a dose-dependent manner. The conclusions remain different between the two studies. Side effects may occur as the dosage increases; in particular, the risk of respiratory depression was higher when the dosage of oxycodone was increased to 0.1 mg/kg.

In our study, we established group S (0.02 μg/kg sufentanil) based on several studies that hold that pretreatment with a small dose of opioids could reduce opioid-induced cough. We selected a dosage of 0.02 μg/kg, which depended on the equivalent dose conversion (sufentanil:oxycodone= 1000:1). Opioids may suppress the reflex of cough by directly affecting the cough center in the medulla, in which the pre-emptive dose used was less than required for analgesia. Hung et al.[16] hold that pretreatment with 25 μg fentanyl could reduce the cough that was caused by the induction dose of 125 μg or 150 μg fentanyl. Pretreatment with 0.3 μg/kg remifentanil intravenously one minute before the analgesia of sufentanil could effectively inhibit coughing caused by sufentanil[5]. One mechanism by which pretreatment inhibits opioid-induced cough may involve decreasing plasma concentration fluctuations. In addition, the pre-emptive use of opioids may deplete neurotransmitters in nerve fibers.

This study demonstrated that a small dose of 0.02 mg/kg oxycodone and 0.02 μg/kg sufentanil could effectively reduce the incidence and severity of SIC. The mechanism of the two pretreatments that suppress cough may be hypothesized. No adverse reactions, such as vomiting, hypotension, respiratory depression and bradycardia, occurred when the small dosage we administered. The rangeability of MAP and HR remained synchronous at four time points, which might be due to the very low dose.

There were two limitations in our study. Few studies have shown the explicit doses of pretreated sufentanil that are used to suppress cough induced by sufentanil. The low dosage of sufentanil, which is used to suppress cough, was obtained by referring to the equivalent doses of oxycodone. Additionally, in terms of applying a small equivalent analgesic dosage between oxycodone and sufentanil, there were no differences in inhibiting SIC. We do not know whether oxycodone could have a more effective antitussive function than sufentanil when increasing the dose of oxycodone to 0.03, 0.04, and 0.05 mg/kg.

Conclusion

Intravenous administration of a small dose of 0.02 mg/kg oxycodone and 0.02 μg/kg sufentanil effectively reduced the incidence and severity of cough induced by sufentanil without adverse reactions during anesthesia induction.

List Of Abbreviations

Full name	Abbreviation
sufentanil-induced cough	SIC
Mean arterial pressure	MAP
heart rate	HR
central nervous system	CNS
chronic obstructive pulmonary disease	COPD
angiotensin-converting enzyme	ACE

Declarations

Ethics approval and consent to participate

The pilot trial was approved by the medical ethics committee of the second affiliated hospital of Nanjing Medical University. Informed consent was received from the patient. The committee's reference number is KY2018-117.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests

Funding

This trial was funded by institutional departmental funds.

Authors' contributions

Huanhuan Ni proposed ideas and defined precise methods for this study. Lingli Shi participated in major data analysis, interpretation of results and drafted the manuscript. Yong He for completion data collection. All authors read and approved the manuscript.

Acknowledgements

Corresponding author Huanhuan Ni was transferred work from the Second Affiliated Hospital of Nanjing Medical University to Children's Hospital of Nanjing Medical University. Thanks to Yong He for completing the data collection. Thank you for Lingli Shi for completing the writing of the article.

References

[1] Yin F, Zhang T. A Small Dose of Butorphanol Prevents Sufentanil-induced Cough During General Anesthesia Induction. The Journal of craniofacial surgery. 2019;30(8):2499-2501.

[2] Tian Z, Hu B, Miao M, Zhang L, Wang L, Chen B. Ketorolac tromethamine pretreatment suppresses sufentanil-induced cough during general anesthesia induction: a prospective randomized controlled trial. BMC anesthesiology. 2020;20(1):205.

[3] An LJ, Gui B, Su Z, Zhang Y, Liu HL. Magnesium sulfate inhibits sufentanil-induced cough during anesthetic induction. International journal of clinical and experimental medicine. 2015;8(8):13864-13868.

[4] Agarwal A, Gautam S, Nath SS, Gupta D, Singh U. Comparison of the incidence and severity of cough induced by sufentanil and fentanyl: a prospective, randomised, double-blind study. Anaesthesia. 2007;62(12):1230-1232.

[5] Lim KJ, Lee SK, Lee HM, Park EY, Kim MH, Kim YS, Kang MH. Aspiration pneumonia caused by fentanyl-induced cough -a case report. Korean journal of anesthesiology. 2013;65(3):251-253.

[6] Xiong Z, Yi P, Song J, Tan M. Dezocine prevents sufentanil-induced cough during general anesthesia induction: a meta-analysis of randomised controlled trials. BMC anesthesiology. 2020;20(1):154.

[7] Wang J, Duan J, Wang Q, Lu Y. Pretreatment with Nalbuphine Prevents Sufentanil-Induced Cough During the Anesthesia Induction: A Randomized Controlled Trial. Therapeutics and clinical risk management. 2020;16:281-286.

[8] Zou Y, Ling Y, Kong G, Tang Y, Huang Q, Zhang L, Wei L. Effect of Tramadol Pretreatment on Sufentanil-Induced Cough. Journal of perianesthesia nursing : official journal of the American Society of PeriAnesthesia Nurses. 2019;34(6):1181-1186.

[9] Liu M, Li Z, Wang S, Liu Y, Zhong X, He R, Li F. Application via mechanical dropper alleviates sufentanil-induced cough: a prospective, randomized, single-blinded trial. Trials. 2019;20(1):170.

[10] Lin W, Sun J, Fu S. A small dose of remifentanil pretreatment suppresses sufentanil-induced cough during general anesthesia induction: a randomized, double-blind, placebo-controlled trial. BMC anesthesiology. 2019;19(1):164.

[11] He J, Zhu L, Zhu H, Gu X, Li P, Yang Y, Yang L. Dose selection of central or peripheral administration of sufentanil affect opioid induced cough?: a prospective, randomized, controlled trial. BMC anesthesiology. 2018;18(1):38.

[12] Liu XS, Xu GH, Shen QY, Zhao Q, Cheng XQ, Zhang J, Gu EW. Dezocine prevents sufentanil-induced cough during general anesthesia induction: A randomized controlled trial. Pharmacological reports : PR. 2015;67(1):52-55.

[13] Sun S, Huang SQ. Effects of pretreatment with a small dose of dexmedetomidine on sufentanil-induced cough during anesthetic induction. Journal of anesthesia. 2013;27(1):25-28.

[14] Dai B, Cao X. Comparing the different oxycodone doses of prevent oxycodone for prevention of preventing fentanyl-induced cough during induction of general anaesthesia. International journal of clinical practice. 2020;74(12):e13642.

[15] Du BX, Cao L, Zhao WL, Xu ZH, Song J, Shi XY. Pre-emptive small dose of fentanyl suppresses fentanyl-induced cough: a meta-analysis of randomized controlled trials. International journal of clinical and experimental medicine. 2014;7(4):826-836.

[16] Hung KC, Chen CW, Lin VC, Weng HC, Hsieh SW. The effect of pre-emptive use of minimal dose fentanyl on fentanyl-induced coughing. Anaesthesia. 2010;65(1):4-7.

[17] Reitan JA, Stengert KB, Wymore ML, Martucci RW. Central vagal control of fentanyl-induced bradycardia during halothane anesthesia. Anesthesia and analgesia. 1978;57(1):31-36.

[18] El Baissari MC, Taha SK, Siddik-Sayyid SM. Fentanyl-induced cough--pathophysiology and prevention. Middle East journal of anaesthesiology. 2014;22(5):449-456.

[19] Karlsson JA, Sant'Ambrogio G, Widdicombe J. Afferent neural pathways in cough and reflex bronchoconstriction. Journal of applied physiology. 1988;65(3):1007-1023.

[20] Agarwal A, Azim A, Ambesh S, Bose N, Dhiraj S, Sahu D, Singh U. Salbutamol, beclomethasone or sodium chromoglycate suppress coughing induced by iv fentanyl. Canadian journal of anaesthesia = Journal canadien d'anesthesie. 2003;50(3):297-300.

[21] Naldan ME, Arslan Z, Ay A, Yayik AM. Comparison of Lidocaine and Atropine on Fentanyl-Induced Cough: A Randomized Controlled Study. Journal of investigative surgery : the official journal of the Academy of Surgical Research. 2019;32(5):428-432.

[22] Lin CS, Sun WZ, Chan WH, Lin CJ, Yeh HM, Mok MS. Intravenous lidocaine and ephedrine, but not propofol, suppress fentanyl-induced cough. Canadian journal of anaesthesia = Journal canadien d'anesthesie. 2004;51(7):654-659.

[23] Bennett JA, Abrams JT, Van Riper DF, Horrow JC. Difficult or impossible ventilation after sufentanil-induced anesthesia is caused primarily by vocal cord closure. Anesthesiology. 1997;87(5):1070-1074.

[24] Zhou W, Zhang D, Tian S, Yang Y, Xing Z, Ma R, Zhou T, Bao T, Sun J, Zhang Z. Optimal dose of pretreated-dexmedetomidine in fentanyl-induced cough suppression: a prospective randomized controlled trial. BMC anesthesiology. 2019;19(1):89.

[25] Kim JY, Lee SY, Kim DH, Park SK, Min SK. Effect-site concentration of propofol for reduction of remifentanil-induced cough. Anaesthesia. 2010;65(7):697-703.

[26] Bian Q, Xu Q, Xu Z, Zhang M, Gu L. Efficacy of different doses of oxycodone for prevention of fentanyl-induced cough during induction of general anesthesia((in chinese with English abstract). Chin J Anesthesiol. 2018;38(7):800-802.

Tables

Table 1 Demographic characteristics of patients in the three groups

characteristics	Group N	Group O	Group S
Age (years)	47.3±11.8	45.6±12.9	43.4±11.9
Gender (males/females)	15/33	17/31	15/33
Weight (kg)	62.4±9.4	64.9±10.1	64.3±12.3
BMI (kg/cm^2)	23.6±3.6	24.0±3.1	23.9±3.2
ASA (I/II)	23/26	20/28	21/27

Values are expressed as the mean ± standard deviation or as the number of cases.

Table 2 Incidence and severity of sufentanil-induced cough

Cough	Group N	Group O*	Group S*
Incidence	20 (41.6)	7 (14.6) *	6 (12.5) *
Severity			
0 (no cough)	28 (58.3)	41 (85.4)	42 (87.5)
1 (mild)	8 (16.6)	4 (8.3)	5 (10.4)
2 (moderate)	7 (14.6)	3 (6.2)	1 (2.0)
3 (severe)	5 (10.4)	0 (0)	0 (0)

Note: Values are numbers (percentage).

*$P < .05$ vs Group N

Table 3 Changes in MAP and HR in the three groups

Variables	T0	T1	T2	T3	*P*
MAP (mmHg)					0.313
Group N	92.6±13.8	91.0±12.2	67.3±13.8	86.9±18.7	
Group O	90.3±12.9	89.3±13.7	64.6±10.9	80.7±13.9	
Group S	92.5±11.5	92.2±15.0	67.8±8.4	82.4±14.3	
HR (bpm)					0.335
Group N	76.7±12.2	76.2±10.7	66.8±10.0	84.2±14.5	
Group O	75.5±9.0	74.5±9.3	67.3±11.3	85.2±11.1	
Group S	80.0±14.9	78.3±12.9	70.6±12.7	85.5±11.4	

Values are expressed as the mean ± standard deviation.

MAP, Mean arterial pressure; HR, heart rate.

T0 (after entering the operation), T1 (1 minute after the pretreatment), T2 (before intubation), T3 (1 minute after intubation).

Figures

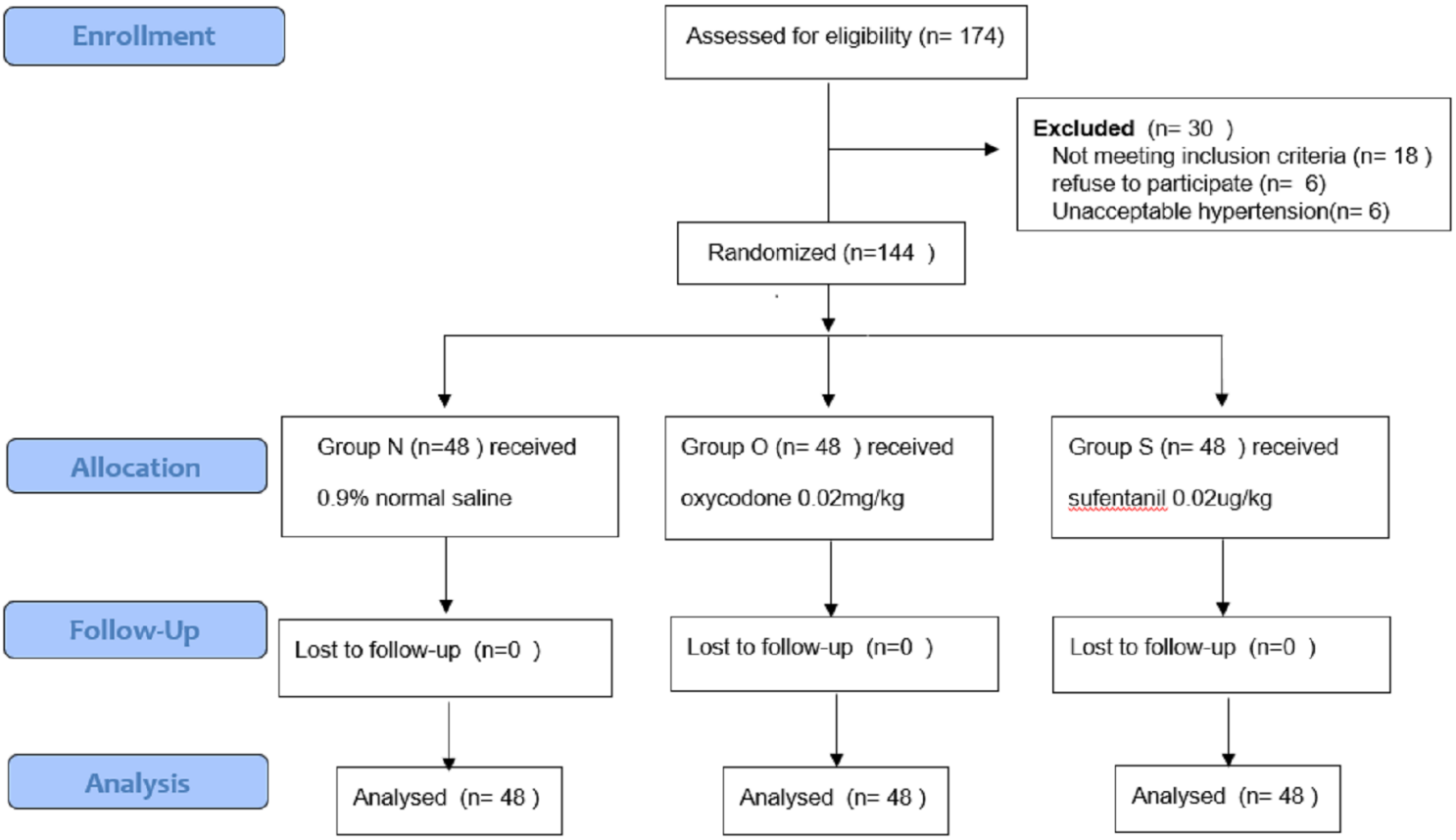

Figure 1

Flow diagram of the study