Dexdemetomidine for Prevention of Cough Response and Agitation in Patients with Intubation after Flap Reconstructive Surgery for Oral Cancer

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Abstract

Background: To investigate whether intraoperative infusion of dexmedetomidine could safely prevent the incidence of cough response and agitation in patients with intubation after flap reconstructive surgery for oral cancer.

Methods: Sixty-four patients undergoing flap reconstructive surgeries were randomly divided into dexmedetomidine (D) group and control (C) group. Within 15 min before anesthesia induction, dexmedetomidine was infused with a 0.5μg/kg loading dose followed by a maintenance dose of o.4μg/kg/h in group D, while the same volume saline was administered in group C. All patients kept the tracheal tube and maintained spontaneous respiratory in intensive care unit (ICU). Postoperative cough response, the Richmond Agitation-Sedation Scale (RASS) score, the behavioral pain scale (BPS) score, blood oxygen saturation (SpO_2), respiratory rate (RR) and end-tidal carbon dioxide ($EtCO_2$) were recorded at 10min (T_1), 20 min(T_2), 30 min (T_3), 1h(T_4), 6h(T_5), 12h(T_6) and 24h (T_7) after surgery. Meanwhile, the length of ICU stay and adverse effects were also calculated.

Results: The data of 32 patients in each group were included in this study. The incidence of cough response were significantly lower in group D than that in group C at $T_{1\text{-}6}$ (P<0.05); The RASS scores in group D were significantly lower than that in group C at $T_{1\text{-}5}$ (P<0.05); The BPS score in group C was much higher than that in group D at all time-points (P<0.05). And there was no significant difference in the SpO_2, RR, $EtCO_2$, the length of ICU stay and other complications.

Conclusion: Dexmedetomidine as an anesthetic adjuvant could safely prevent the incidence of cough response and agitation in patients with intubation after flap reconstructive surgery for oral cancer.

Trial registration: Chinese Clinical Trial Registry, ChiCTR-1800018367.

Background

Oral cancer is a common malignant tumor with a 5-year survival rate of 50% [1]. With the improvement of maxillofacial surgery and people's quality of life, radical resection and flap reconstruction have become the mainstays of treatment for oral cancer. Swollen wounds, reconstructed flaps, and changes in oral anatomy decrease pharyngeal airway-protective reflexes and increase the risk of upper airway obstruction [2]. Moreover, at present, more and more patients kept tracheal catheter after flap surgery instead of tracheotomy with the rapid development of oral and maxillofacial ICU. However, the tracheal tube is a strong irritation and could increase postoperative cough response and agitation, which not only cause acute hemodynamic changes and failure of the transferred flap, but also significantly delay the patient's rehabilitation [3, 4]. Allak et al. indicated that agitation occurs in nearly 65% of patients after flap reconstruction [5]. In author's hospital, coughing and agitation are common in patient intubated after flap surgery. Several medications have been attempted to alleviate these adverse events, however, the

interventions may lead to other problems, such as respiratory depression, vomiting and hallucinations [6–9].

Dexmedetomidine as a highly selective α_2-adrenoceptor agonists has the effects of sedative, anxiolytic, analgesic, and sympatholytic properties [10–12]. Its applications in clinic widened over the past few years. However, data on its effects on oral surgeries are limited. The primary objective of our study was to investigate the effect of dexmedetomidine on cough response and agitation in patients with intubation after flap reconstructive surgery for oral cancer. The secondary objective was to assess its safety and adverse events.

Methods

The present study was approved by the Ethics Committee of School and Hospital of Stomatology, Wuhan University (IRB-2018B23) and registered in the Chinese Clinical Trial Registry (ChiCTR-1800018367).This study adhered to Consolidated Standards of Reporting Trials (CONSORT) guidelines.

All patients provided written informed consent and were scheduled for radical operation and immediate reconstruction with forearm free flap. All surgeries were operated on by the same surgeon. Patients classified as American Society of Anesthesiologist (ASA) physical status to and aged 30 to 70 were enrolled. Exclusive criteria included bradycardia (preoperative heart rate < 60 beats/min), mental illness, or major systemic illness. None had received the chemotherapy, radiotherapy or immunotherapy before operation. Patients who need a requirement for perioperative blood transfusion were also excluded from study. We used a computer-generated randomisation sequence (in a 1:1 ratio) to randomly assign patients to two groups.

Within 15 min before anesthesia induction, dexmedetomidine (Lot number: 180604BP, Jiangsu Hengrui Medicine Co. Ltd, Nanjing, China) was infused with a 0.5μg/kg loading dose followed by a maintenance dose of o.4μg/kg/h in the dexmedetomidine group. The same volume of normal saline was given to patients in the control group. Patients received the same anesthetics and postoperative pain therapy. They were all transferred to ICU and administrated the same treatment with continuous perfusion of propofol (0.5-1mg/kg/h) and hydromorphone (4–8μg/kg/h). All patients kept the tracheal tube and maintained spontaneous respiratory in ICU.

An anesthesiologist who didn't participate in the grouping of patients recorded the results. Postoperative cough response, RASS score, BPS score, SpO_2, RR and $EtCO_2$ were recorded at 10min (T_1), 20 min(T_2), 30 min (T_3), 1h(T_4), 6h(T_5), 12h(T_6) and 24h (T_7) after surgery. Meanwhile, the length of ICU stay, the incidence of hypotension, bradycardia, shivering, nausea-vomiting and delirium after surgery were also calculated. Cough response was assessed on four-point scale: 0 no cough; 1 single cough; 2 more than one episode of non-sustained cough; 3 sustained and repetitive cough with head lift [6]. The level of agitation was assessed using the Richmond Agitation-Sedation Scale (RASS) [13]: +4 combative; +3 very agitated; +2 agitated; +1 restless; 0 alert and calm; -1 drowsy; -2 light sedation; -3 moderate sedation; -4

deep sedation; -5 unarousable. Agitation was defined as any score on the RASS ≥ + 2. The BPS is a behavioral pain assessment tool for sedated patients and is based on the sum score concerning the 3 behavioral items: facial expression, movements of the upper limbs and ventilation. Each item is scored from 1 (no responses) to 4 (full response). The total BPS score ranges from 3 (no pain) to 12 (maximal pain) [14].

According to the published article, the incidence of agitation is nearly 65% of patients after flap reconstruction [5], using Chinese High Intellectualized Statistical Software, with a type-Ⅰerror of 5% and a power of 80%, we needed 28 patients in each group. Anticipating a 10% dropout rate, we recruited a sample size of 35 per group (70 in total). All statistical analysis were performed by GraphPad Prism 7. Continuous variables are reported as mean and standard deviation (SD). Categorical variables are expressed as number and percentage (%). Student-*t* test was performed to compare the differences in the age, BMI, duration of surgery, blood loss, liquid infusion volume, BPS score, SpO_2, RR, $EtCO_2$ and the length of ICU stay. The gender, ASA, cough response, agitation and other side effects were compared using chi-square tests and Fisher's exact test. $P < 0.05$ indicated statistically significant difference.

Results

This study was carried out at School and Hospital of Stomatology of Wuhan University and conducted according to the declaration of Helsinki between September 2018 and March 2019.

Among 70 patients who were assessed for eligibility, 2 patients refused to consent, and 4 patients received intraoperative blood transfusion. Therefore, we were left with 32 patients in each group (Fig. 1). There were no significant differences between the two groups in terms of age, gender, BMI, ASA, duration of surgery, blood loss, and liquid infusion volume ($P > 0.05$, Table 1).

Table 1
Demographics and Surgical Profiles of the patients

	group D	group C	*P* value
Age(y)	49 ± 10	51 ± 11	0.454
Gender(male/female)	25/7	24/8	0.768
BMI(kg/m^2)	22.9 ± 3.5	21.81 ± 2.7	0.159
ASA status(Ⅰ/Ⅱ)	22/10	23/9	0.784
Duration of surgery(h)	6.6 ± 0.5	6.4 ± 0.6	0.108
Blood loss(ml)	302 ± 53	280 ± 54	0.080
Liquid infusion volume(ml)	3006 ± 320	3072 ± 295	0.336
Note: Data are expressed as mean ± standard deviation or number.			

The incidence of cough response was significantly lower in group D than that in group C at T_{1-6} (40.6% vs. 71.9% at T_1; 43.7% vs. 78.1% at T_2; 40.6% vs. 75.0% at T_3; 34.4 vs. 65.6% at T_4; 25.0% vs. 56.2% at T_5, 15.6% vs. 43.7% at T_6, all $P < 0.05$, Fig. 2). The incidence of agitation was significantly lower in group D than that in group C at T_{1-5} (31.2% vs. 59.4% at T_1; 37.5% vs. 75.0% at T_2; 25.0% vs. 62.5% at T_3; 15.6% vs. 43.7% at T_4; 3.1% vs. 25.0% at T_5, all $P < 0.05$, Fig. 3).

The BPS score was significantly lower in group D than that in group C at T_{1-7} ($P < 0.05$, Fig. 4). There were no statistically significant differences in SpO_2, RR and $EtCO_2$ between two groups (Table 2) and no differences were observed in the length of ICU stay and the incidence of hypotension, shivering, nausea-vomiting and delirium after surgery ($P > 0.05$, Table 3). In addition, none of the patients had respiratory infections and flap crisis in the two groups. However, the incidence of bradycardia in group D was higher than that in group C ($P = 0.016$).

Table 2
Respiratory parameters after flap reconstruction for oral cancer

	Group	T_1	T_2	T_3	T_4	T_5	T_6	T_7
SpO_2 (%)	D	99.2 ± 1.0	99.0 ± 0.8	98.4 ± 1.1	98.3 ± 1.0	98.5 ± 1.1	98.2 ± 1.0	98.2 ± 0.9
	C	99.2 ± 0.7	98.4 ± 1.1	98.3 ± 1.1	98.2 ± 1.1	98.4 ± 1.1	98.6 ± 1.0	98.3 ± 1.0
RR(bpm)	D	11.0 ± 1.0	11.4 ± 0.8	11.9 ± 0.7	11.8 ± 0.8	12.1 ± 0.9	12.2 ± 1.0	12.3 ± 1.0
	C	11.8 ± 0.9	11.7 ± 0.9	12.0 ± 0.8	12.1 ± 0.8	12.0 ± 0.8	11.9 ± 0.9	12.0 ± 0.8
$EtCO_2$ (mmHg)	D	41.5 ± 3.6	39.8 ± 3.6	39.6 ± 3.1	39.0 ± 2.8	39.5 ± 2.6	41.3 ± 2.0	39.7 ± 2.4
	C	40.2 ± 2.7	39.3 ± 1.7	39.9 ± 2.2	39.8 ± 2.6	38.9 ± 1.8	39.0 ± 2.1	39.3 ± 1.9

Note: Data are expressed as mean ± standard deviation. Differences not significant.

Table 3
Incidence of adverse events after surgery between two groups

	group D (n = 32)	group C (n = 32)	*P* value
The length of ICU stay(h)	40.0 ± 1.2	39.5 ± 2.0	0.225
Shivering	9 (28.1%)	7 (21.9%)	0.774
Hypotension	14(43.7%)	7(21.9%)	0.109
Bradycardia in OR	12 (37.5%)*	3 (9.4%)	0.016
Nausea- vomiting	5 (15.6%)	6 (18.8%)	1
Delirium	1 (3.1%)	3 (9.4%)	0.613
Note: Values are the number of patients (%); Compared with group C, $^{*}P < 0.05$.			

Discussion

This prospective, randomized, controlled trial revealed dexmedetomidine could prevent the cough response and agitation in patients with intubation after flap reconstruction for oral cancer. Meanwhile, dexmedetomidine was a safe anesthetic adjuvant, it didn't affect the patient's spontaneous respiration after surgery or extend ICU stay time.

Perioperative airway management is essential for oral flap reconstructive surgery. Postoperative swelling wound, changes in oral physiological anatomy and free flaps easily lead to airway obstruction or suffocation [2]. With the development of oral and maxillofacial ICU, more and more patients maintain tracheal tube after surgery instead of preventive tracheotomy which is associated with the neck injuries and higher postoperative pulmonary infection [15]. However, the tracheal catheter is a strong irritation that is difficult for patients to tolerate, and is prone to coughing and agitation. According to previous researches, the incidence of cough response from general anesthesia was about 67% and Allak et al. indicated that the incidence of agitation was nearly 65% after flap reconstruction [4, 5]. These adverse events are related to activation of the sympathetic nervous system that manifests with serious cardiovascular responses, and severe agitation can lead to self-harm, failure of the transferred flap and greatly affect the patient's rehabilitation [3, 4, 16]. It's essential to take effective anesthetic to make the patient awake smoothly from general anesthesia and keep a well sedated state after flap surgery.

Various medications have been applied to improve these problems, however, none of them were completely successful. Studies have shown that though low-dose opioids were effective in preventing cough and agitation, they may result in postoperative respiratory depression and vomiting [6, 7]. Cho et al. found midazolam may prolong the patient's stay in operating room and ICU [8]. Although Ketamine has a sedative and analgestic effects with little respiratory depression, Abu-shahwan reported the adverse effects of patients were also very obvious including hallucinations and lowering the threshold of seizures

[9]. Dexmedetomidine is a highly selective α_2-adrenoceptor agonists with sedative, anxiolytic, analgesic, and sympatholytic properties [10–12]. It was first approved by the United States Food and Drug Administration for mechanical ventilation in adult ICU in 1999 and its applications have been widened over the past few years including adjuvant medication in general anesthesia, outpatient sedation and organ protective properties [11].

The present study showed that when dexmedetomidine was infused with a 0.5μg/kg loading dose followed by a maintenance dose of 0.4μg/kg/h, the incidence of cough response and agitation were significantly reduced in patients intubation after flap reconstruction surgery ($P < 0.05$, Fig. 2, 3). In addition, the BPS score was much lower in the dexmedetomidine group than that in the control group ($P < 0.05$, Fig. 4).These results indicated that dexmedetomidine provided a smooth recovery from general anesthesia and patients are more likely to tolerate tracheal catheter stimulation and other discomforts. The reason may be related to its sedative and analgesic effects [11]. Sedative effect of dexmedetomidine is thought be mediated through activation of central presynaptic and postsynaptic α_2-receptors in the locus coeruleus [10–12]. Analgesic effect is thought be mediated by α_2-receptors binding in central and spinal cord α_2-receptors [10, 11]. This result was consistent with that of previous studies. A recent systematic review and network meta-analysis investigated which medications' relative efficacies on decreasing emergence cough after general anesthesia, the result found dexmedetomidine ranked more effective than lidocaine, remifentanil and fentanyl in reducing moderate to severe cough reponse [17]. Kim et al. found a calm state at emergence in the group receiving dexmedetomidine compared with that receiving placebo for nasal bone fracture surgery [18]. A meta-analysis including 19 randomized controlled trials concluded that dexmedetomine significantly reduced the incidence of agitation and severe pain during recovery period [19].

The present study also found dexmedetomidine didn't affect postoperative SpO_2, RR, $EtCO_2$, the length of ICU stay, the incidence of hypotension, shivering, nausea-vomiting and delirium after surgery. The result suggested the application of dexmedetomidine was very safe, it didn't affect the patient's postoperative spontaneous respiration, and didn't extend ICU stay time, which can reduce hospitalization costs and the adverse complications of long-term ICU admission. Our result showed that the incidence of bradycardia in the dexmedetomidine group was higher than that in the control group, which may be associated with inhibiting the sympathetic nervous system and increasing vagal activity. Ebert et al. indicated that dexmedetomidine dose-dependently reduced plasma catecholamines by 45%-76% [20]. Although bradycardia is the most commonly reported adverse reactions of dexmedetomidine, it can be easily managed with atropine and vasoactive agents [21]. Moreover, lower heart rate decreases myocardial oxygen consumption and increase diastolic filling time, which may be a certain protective effect on patients [22].

Some limitations were encountered in the present study. The hospitalization periods and long-term prognosis were not tracked. Additionally, the result found the incidence of postoperative delirium in the dexmedetomidine group was lower than that in the control group (3.1% vs 9.4%), but the difference was

not statistically significant (P = 0.613). Su et al. showed that prophylactic low-dose dexmedetomidine significantly decreased the occurrence of delirium during the first 7 days after surgery in patients aged over 65 years after non-cardiac surgery [23]. Therefore, more prospective randomized controlled trials are also needed.

In conclusion, dexmedetomidine as an anesthetic adjuvant could prevent the incidence of cough response and agitation in patients with intubation after flap reconstructive surgery for oral cancer. As shown by the study, the application of dexmedetomidine is very safe, no patients have postoperative respiratory depression, and the length of ICU stay has not been prolonged.

Abbreviations

ICU: intensive care unit; RASS: Richmond Agitation-Sedation Scale; BPS: behavioral pain scale; SpO_2: blood oxygen saturation; RR: respiratory rate; $EtCO_2$: end-tidal carbon dioxide; ASA: American Society of Anesthesiologists; BMI: Body Mass Index; D: dexmedetomidine; C: control; T_1: 10min after surgery; T_2: 20 min after surgery; T_3: 30 min after surgery; T_4: 1h after surgery; T_5: 6h after surgery; T_6: 12h after surgery; T_7: 24h after surgery.

Declarations

Ethics approval and consent to participate

After obtaining approval from the Ethics Committee of School and Hospital of Stomatology (IRB-2018B23), the study was performed in School and Hospital of Stomatology, Wuhan University. Written informed consent was obtained from all subjects participating in the trial.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available as permission from participants to publicity share the dataset has not been obtained. However, these datasets are available from the corresponding author on reasonable request.

Competing interests

The authors declare that there is no conflict of interests.

Funding

Not applicable

Authors' Contributions

HLL: designed the study and analyzed the data. QCQ: designed the study, analyzed the data, and wrote the manuscript. WL: recorded and analyzed the data. All authors read and approved the final manuscript.

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Figures

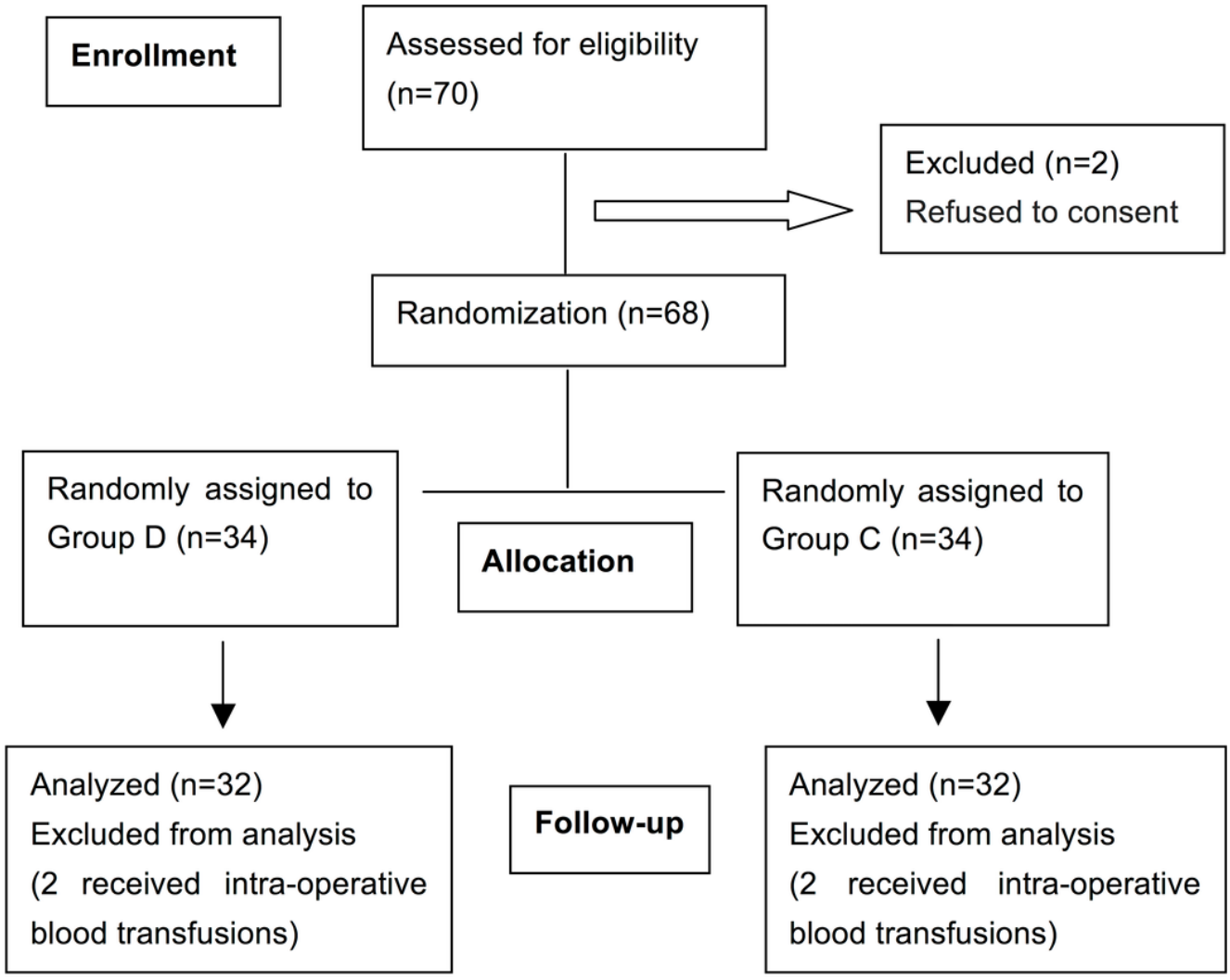

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the patients included in the study.

Figure 1

Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the patients included in the study.

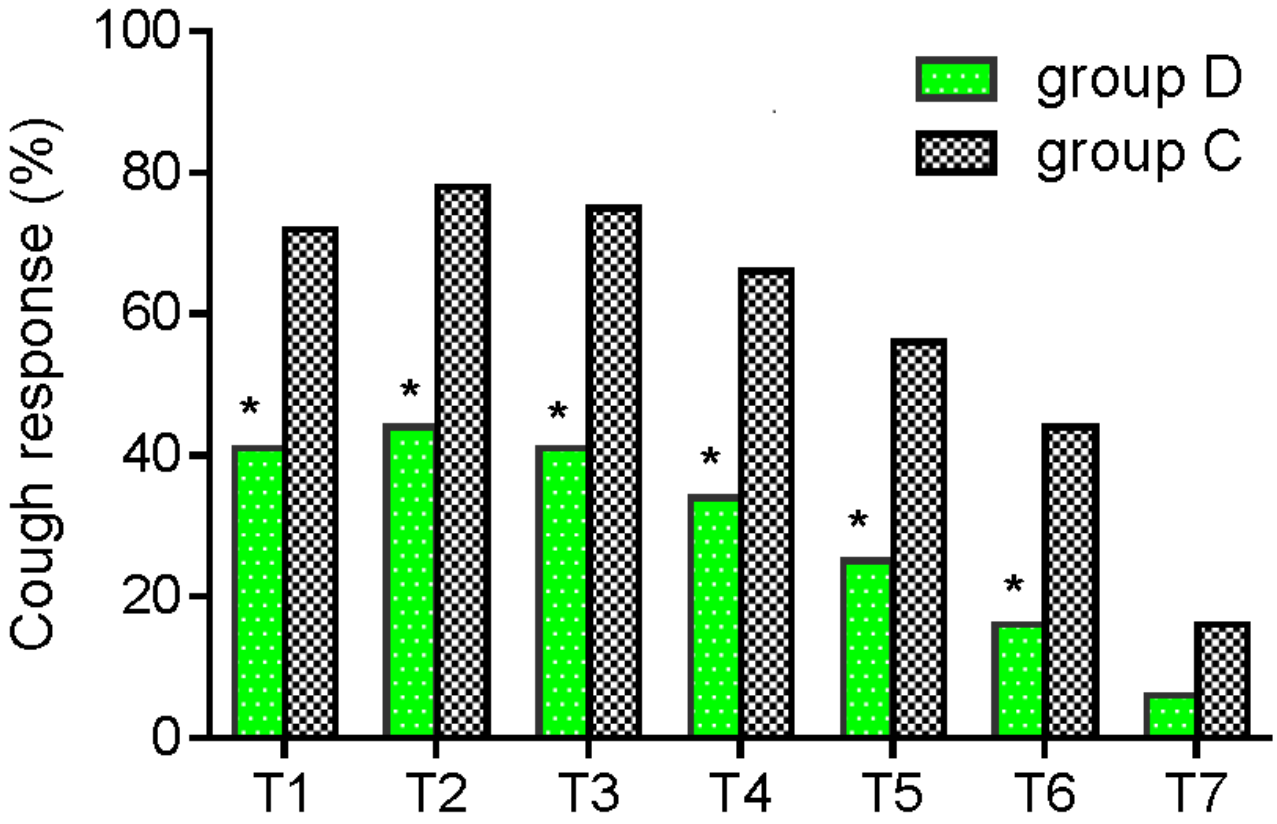

Figure 2

Comparion of incidence of cough response after flap reconstruction for oral cancer. Data are presented as percentage (%). *P<0.05 compared with group C.

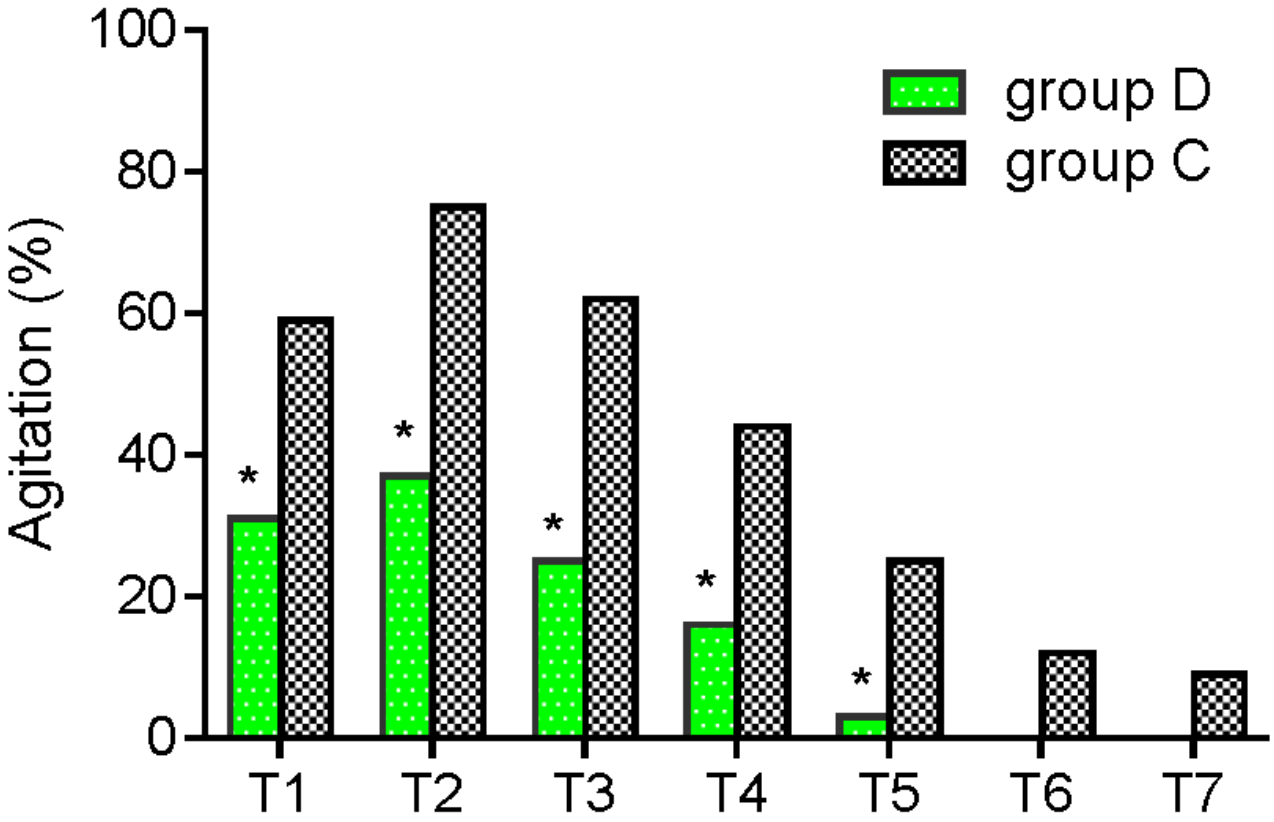

Figure 3

Comparion of incidence of agitation after flap reconstruction for oral cancer. Data are presented as percentage (%). *P<0.05 compared with group C.

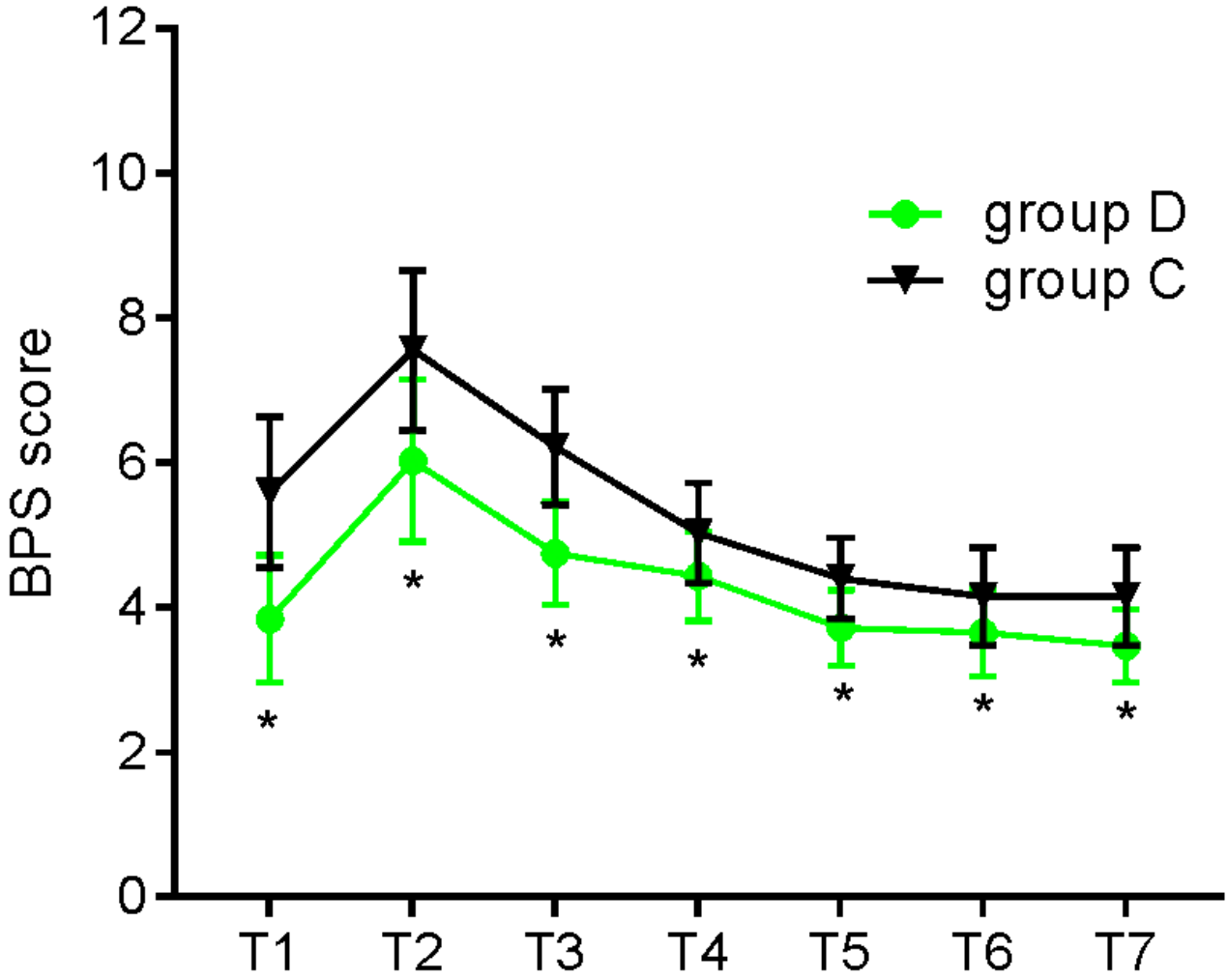

Figure 4

The BPS score after flap reconstruction for oral cancer. *P<0.05 compared with group C.

Supplementary Files

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- CONSORT2010Checklist.docx