

## Research Article

# Clinical Observation of Low-Temperature Plasma Knife Tonsil Adenoidectomy for Pediatric Snoring and Analysis of Influencing Factors

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**Objective.** To investigate the clinical efficacy of low-temperature plasma knife tonsil adenoidectomy for pediatric snoring and to analyze the factors influencing the efficacy. **Methods.** 90 children with snoring who were scheduled for surgical treatment in our hospital from June 2020 to December 2021 were selected as the research objects. According to the random number table method, they were divided into control group (group C) and observation group (group O), with 45 cases in each group. The children in group C were treated with power cutting system to remove adenoids combined with conventional peeling of bilateral tonsils, while the children in group O were treated with low-temperature plasma adenoidectomy combined with bilateral tonsillectomy, and both the groups received psychological care, preoperative preparation, health guidance, postoperative posture care and close monitoring of vital signs during the perioperative period. The clinical efficacy, perioperative related indexes (including operation time, intraoperative bleeding, postoperative pain time, and hospital stay) were compared between the two groups. The apnea-hypopnea index (AHI), oxygen decrement index (ODI), longest apnea time (LAT), and lowest oxygen saturation (LSaO<sub>2</sub>) were measured before operation and 1 week after operation to evaluate the ventilatory function of the two groups. According to the curative effect, 90 children with snoring were divided into cure + significant effective group and valid + invalid group. The general data and preoperative biochemical indexes of the two groups were collected, and logistic regression model was used to analyze the related influencing factors of the curative effect. **Results.** The total effective rate of group O (100.00%, 45 cases) was significantly higher than that of group C (91.11%, 41 cases) ( $P < 0.05$ ); the operative time, intraoperative bleeding, postoperative pain time, and hospitalization time of group O were shorter/less than those of group C; the AHI, ODI, and LAT of group O at 1 week after surgery were shorter/less than those of the control group; and LSaO<sub>2</sub> was higher than that of group C. The differences were statistically significant ( $P < 0.05$ ). Univariate analysis showed that there were significant differences in age, BMI, course of disease, preoperative AHI, preoperative LsaO<sub>2</sub>, and surgical method between cure + significant effective group and valid + invalid group ( $P < 0.05$ ). Multivariate analysis showed that high BMI, high preoperative AHI, and power cutting system for adenoids combined with routine peeling of the bilateral tonsils were independent risk factors for postoperative outcome in children with obstructive sleep apnea syndrome (OSAS) ( $P < 0.05$ ).

## 1. Preface

Pediatric snoring, also known as pediatric obstructive sleep apnea hypopnea syndrome (OSAS), is a disease characterized by more than one partial airway obstruction and/or intermittent complete obstruction in childhood. It can affect

the sleep and respiratory rhythm of the children and make them in a state of chronic hypoxia, leading to excessive dreaming, daytime lethargy, lethargy, and memory loss, which affects the intellectual and physical development of children and easily affects the personality change of children [1, 2]. In childhood, OSAS if not treated in a timely manner,

TABLE 1: Comparison of general information between group C and group O at the time of admission.

Indicators		Group C ( $n=45$ )	Group O ( $n=45$ )	$t/\chi^2$ values	$P$ values
Gender ( $n, \%$ )	Male	30 (66.67)	32 (71.11)	0.207	0.649
	Female	15 (33.33)	13 (28.89)		
Age (years, mean $\pm$ SD)		7.24 $\pm$ 2.23	7.49 $\pm$ 2.32	0.521	0.604
BMI ( $\text{kg}/\text{m}^2$ , mean $\pm$ SD)		16.53 $\pm$ 4.12	16.13 $\pm$ 3.85	0.476	0.635
Duration of disease (months, mean $\pm$ SD)		13.25 $\pm$ 2.28	13.72 $\pm$ 2.37	0.959	0.340
Degree of tonsillar hypertrophy ( $n, \%$ )	II degree	25 (55.56)	19 (42.22)	1.601	0.206
	III degree	20 (44.44)	26 (57.78)		

can have a serious impact on the growth and development of the affected children; infants can develop sudden sleep death, and children can develop short stature, low intelligence, poor learning ability, or even dementia, which has serious implications for both families and society [3, 4].

In recent years, the problems arising from OSAS in children have received increasing attention from pediatricians, but it is believed that most cases are due to incomplete obstruction of the upper airway causing poor ventilation, snoring, and abnormal respiratory movements, and that adenoid and/or tonsillar hypertrophy is the most common cause of OSAS in children [5, 6]. For most children with simple adenoid and/or tonsillar hypertrophy, adenoidectomy and tonsillectomy are the most effective treatment modalities, with an effective rate of up to 90%. Low-temperature plasma knife tonsil adenoidectomy performer is to ablate the adenoid tissue at a lower temperature in the ion field by the energy generated by low-temperature plasma radiofrequency [7], and the study [8] showed that low-temperature plasma surgery has the characteristics of light pain, small trauma, and quick postoperative recovery, and its tip has multiple functions such as flushing, hemostasis, and ablation. It does not need to change the instrument during operation, and it can be easily operated even if the oropharyngeal space is narrow.

Low-temperature plasma knife tonsil adenoidectomy has been applied in clinical practice and its efficacy has been recognized, but few studies have reported on the factors affecting the efficacy in children. Therefore, this study selected 90 children as the research objects in order to observe the clinical efficacy and influencing factors of low-temperature plasma tonsillectomy in the treatment of children with OSAS.

## 2. Data and Methods

### 2.1. General Information

**2.1.1. Study Subjects.** 90 children with snoring who were scheduled for surgical treatment in our hospital from June 2020 to December 2021 were selected as the research objects. According to the random number table method, they were divided into the control group (group C) and observation group (group O), with 45 cases in each group. The children in Group C were treated with the power cutting system for adenoidectomy combined with conventional peeling of bilateral tonsils, and the children in Group O were treated with low-temperature plasma adenoidectomy combined with bilateral tonsillectomy, and both the groups received

psychological care, preoperative preparation, health guidance, postoperative posture care, and close monitoring of vital signs during the perioperative period. The differences between the general information of the two groups were not statistically significant ( $P > 0.05$ ) and were comparable, as shown in Table 1.

**2.1.2. Diagnostic Criteria.** The diagnostics criteria include the following: (1) the symptoms include increased night urine, daytime sleepiness, and snoring; (2) blood oxygen saturation ( $\text{SpO}_2$ ) decreased  $\geq 0.04$ ; (3) the apnea-hypopnea index was higher than 5 times/h; (4) the lowest  $\text{SpO}_2$  was lower than 0.92 [9].

**2.1.3. Inclusion Criteria.** The inclusion criteria include the following: (1) those who met the abovementioned diagnostic criteria and combined with clinical examination to make a clear diagnosis; (2) patients aged 3~14 years; (3) patients who had no contraindication to anesthesia or tonsil surgery; those who met the indications for surgical treatment; (4) consent was given by the family of the child and approved by the ethical committee of the hospital.

**2.1.4. Exclusion Criteria.** The exclusion criteria include the following: (1) those with liver, kidney, lung, brain, heart, and other important organ damage; (2) those who have neurological disease, hematologic disease, and impaired consciousness; (3) those with a previous history of airway surgery; (4) those accompanied by acute tonsil inflammation and allergic rhinitis; (5) those with combined respiratory tract infection at admission; (6) those with a history of respiratory drug use within 4 weeks prior to admission.

## 3. Methods

### 3.1. Surgical Methods

**3.1.1. Group C Method.** The adenoids were removed by the child's mobility cutting system in combination with routine stripping of the bilateral tonsils. An opener was placed to expose the oropharynx, and if the tonsils were enlarged and met the indications for removal, the tonsils were removed by the stripping method, and sutures and hemostasis were applied at the end of stripping. Then, the soft palate was pulled by a fine silicone tube to expose the adenoids, and a 70° nasal endoscope was placed. Under the guidance of 70°

nasal endoscope, hypertrophic adenoid tissue was excised by the nasal dynamic system.

**3.1.2. Methodology of Group O.** All children were placed in supine position, intubated under general anesthesia, shoulder pads, and exposed oropharynx with upper mouth opener after routine disinfection. For children with combined tonsillar hypertrophy, a double tonsillar radio-frequency ablation was performed first, and then a thin catheter was introduced from each side of the nasal cavity to the oropharynx, and the soft palate was lifted and fixed with a knot to expose the nasopharynx. A 70° or 30° nasal endoscope was introduced through the mouth to observe the degree of adenoid proliferation, whether it entered the posterior end of bilateral nasal cavity and whether it squeezed the bilateral eustachian tube pillow. Afterwards, a low-temperature plasma radiofrequency ablation tip was introduced and the hypertrophied adenoids were completely removed under direct vision.

Both the groups were treated with anti-inflammatory and other symptomatic treatments after surgery and were given adjuvant treatments such as mometasone furoate nasal spray and Sinupret drops.

### 3.2. Nursing Care Methods

**3.2.1. Preoperative Care.** Nursing staff needed to take the initiative to communicate and exchange with the children and their families, patiently explained the characteristics of the disease, the general process of surgical treatment, the expected effect, and matters needing attention, so as to enhance their confidence and alleviate their bad emotions and make good preoperative preparations.

**3.2.2. Intraoperative Care.** After entering the operating room, the child was positioned and anesthetized. After the nursing staff should apply gentamicin eye ointment on the child's eyes, and use cortisol patch to glue the eyelid to prevent corneal damage during surgery. The child was placed in a supine position with a soft pillow under the shoulders and the head was secured with a headband according to the needs of the operation. Intraoperative monitoring of the child's vital signs and bleeding should be performed, and the fluid volume and drip rate should be controlled.

**3.2.3. Postoperative Care.** After surgery, the child should be placed in a lying head position so that the secretions in the child's mouth could be cleared in a timely manner and the respiratory tract could be ensured. Routine ECG, blood pressure, and oxygen monitoring were performed for 6 h after the operation, and the respiratory status and lip color of the child were closely monitored. Dietary guidance should be given for children who underwent adenoidectomy and tonsillectomy at the same time and gradually transition from liquid diet to semiliquid diet to soft food according to the recovery of the operated area, and gradually return to a

normal diet about 2 weeks after surgery. The child's operating area should be closely observed, and the child's family should be informed not to cough or swallow frequently after the child was awake to prevent bleeding in the operating area, and to report to the doctor for treatment if the child has active bleeding or infection in the operating area.

**3.2.4. Discharge Instructions.** Most of the children were not completely healed when they were discharged from the hospital, so good discharge instructions were needed. In addition to continuing the application of antibiotics, it was very necessary to continue reasonable diet and supplement high-protein, high-calorie, and high-fiber diet due to the gradual shedding of wound pseudomembrane. The child was also instructed to rinse his mouth to keep it clean and prevent upper respiratory tract infection. The child was allowed to be reviewed in the outpatient clinic 2 weeks after discharge; if the child developed high fever, severe sore throat, or coughing up blood during discharge, promptly seek medical attention.

### 3.3. Observation Indexes

**3.3.1. Clinical Efficacy.** Evaluation of the cure rate and total efficiency of the two groups: the efficacy of patients was evaluated at 6 months of postoperative follow-up: cure: snoring, open-mouth breathing, and sleep apnea disappeared, and the lateral X-ray showed no residual adenoids. Significant effect: snoring, open-mouth breathing, and sleep apnea improved significantly compared with the preoperative performance, but did not disappear completely. Valid: snoring, open-mouth breathing, and sleep apnea did not improve significantly compared with the preoperative performance. Invalid: no significant improvement in snoring, open-mouth breathing, sleep apnea, and other manifestations compared with the preoperative period. Total effective rate = (number of cured cases + number of significant effect cases + number of valid cases)/total number of cases × 100%.

**3.3.2. Perioperative Indicators.** Perioperative indicators include operative time, intraoperative bleeding, pain duration, and hospital stay.

**3.3.3. Ventilation Function.** The instrument was Shanghai Trex HD polysomnography, and the indexes were apnea-hypopnea index (AHI), oxygen decrement index (ODI), longest apnea time (LAT), and lowest oxygen saturation (LSaO<sub>2</sub>).

**3.3.4. Analysis of Risk Factors Affecting the Efficacy.** (1) Basic clinical information including gender, age, and height and clinical information such as main symptoms, concomitant symptoms, past history, growth and development history, and family history were collected. (2) Metabolism-related indexes: all admitted subjects collected 3 ml of venous blood specimens in a fasting state between 7:30 and 8:00 am after completion of PSG, centrifuged at 3500 r·min<sup>-1</sup> for 10 min

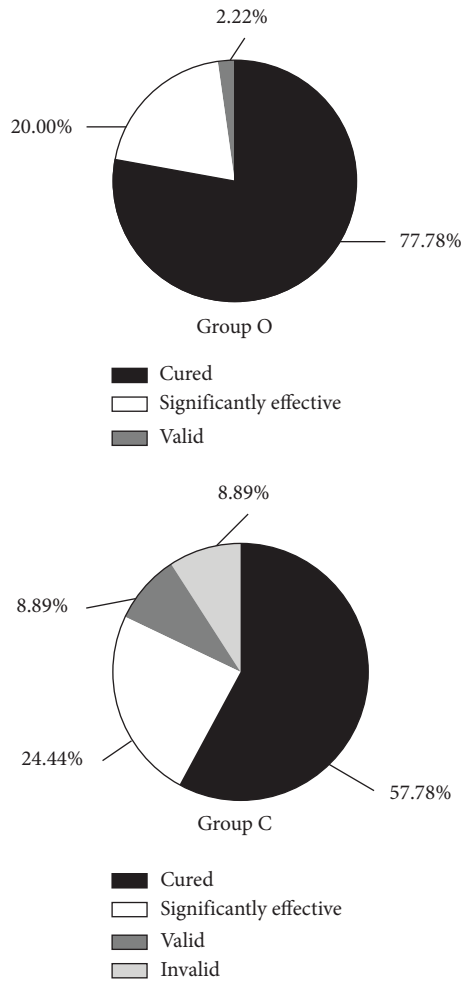


FIGURE 1: Comparison of clinical efficacy between group C and group O.

and then measured glucose (Glu), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), and total cholesterol (TC) levels by the homogeneous enzyme colorimetric method.

**3.4. Statistical Methods.** SPSS 22.0 statistical software was applied to process the data. The *t*-test and repeated measures ANOVA were used for the measurement data, and the  $\chi^2$  test and rank sum test were used for the count data; the influence factors were analyzed by logistic regression model.  $P < 0.05$  was considered statistically significant difference.

## 4. Results

**4.1. Comparison of General Information between Group C and Group O at Admission.** The general data of OSAS children at admission were compared between the two groups. The results showed that there were no statistically significant differences between the two groups in terms of gender, age, BMI, disease duration, and degree of tonsillar hypertrophy ( $P > 0.05$ ) (Table 1).

## 5. Comparison of Clinical Efficacy between Group C and Group O

In group O, the percentages of cured, significant effect, and valid were 77.78% (35 cases), 20.00% (9 cases), and 2.22% (1 case), respectively, and no invalid cases were found. In group C, the percentages of cured, significant effect, valid, and invalid were 57.78% (26 cases), 24.44% (11 cases), 8.89% (4 cases), and 8.89% (4 cases), respectively. Comparison of the total effective rate between the two groups showed that the total effective rate in group O (100.00%, 45 cases) was significantly higher than that in group C (91.11%, 41 cases), and the difference was statistically significant ( $\chi^2 = 4.186$ ,  $P = 0.041$ ) (Figure 1).

## 6. Comparison of Perioperative Indicators between Group C and Group O

The operating time, intraoperative bleeding, postoperative pain time, and hospital stay were shorter in group O than in group C, and the differences were statistically significant ( $P < 0.05$ ) (Figure 2).

**6.1. Comparison of Preoperative and 1-Week Postoperative Ventilatory Function between Group C and Group O.** There were no significant differences in AHI, ODI, LAT, and L $SaO_2$  levels between the two groups before operation ( $P > 0.05$ ). At 1 week after surgery, the AHI, ODI, and LAT levels in both the groups decreased significantly, and L $SaO_2$  levels increased significantly, which were significantly different from those before surgery ( $P < 0.05$ ); meanwhile, the AHI, ODI, and LAT levels in group O at 1 week after surgery were lower than those in group C, and L $SaO_2$  levels were higher than those in group C, and the differences were statistically significant ( $P < 0.05$ ) (Figure 3).

**6.2. Univariate Analysis of Children's Efficacy.** We evaluated the efficacy of the children and divided them into a cure+significant effect group and a valid+invalid group according to their efficacy. The indicators with statistically significant differences between the two groups included age, BMI, disease duration, preoperative AHI, preoperative L $SaO_2$ , and surgical approach ( $P < 0.05$ ). Indicators with no statistically significant differences between the two groups included gender, preoperative Glu, LDL, HDL, TC, TG, preoperative ODI, and preoperative LAT ( $P > 0.05$ ) (Table 2).

**6.3. Multifactor Analysis of Child's Outcome.** The 'child's outcome was used as the dependent variable, and the statistically significant indicators of univariate analysis were used as the dependent variables and substituted into the logistic regression model for analysis. The results of the analysis showed that high BMI, high preoperative AHI, and power cutting system for adenoids combined with routine removal of bilateral tonsils were independent risk factors for

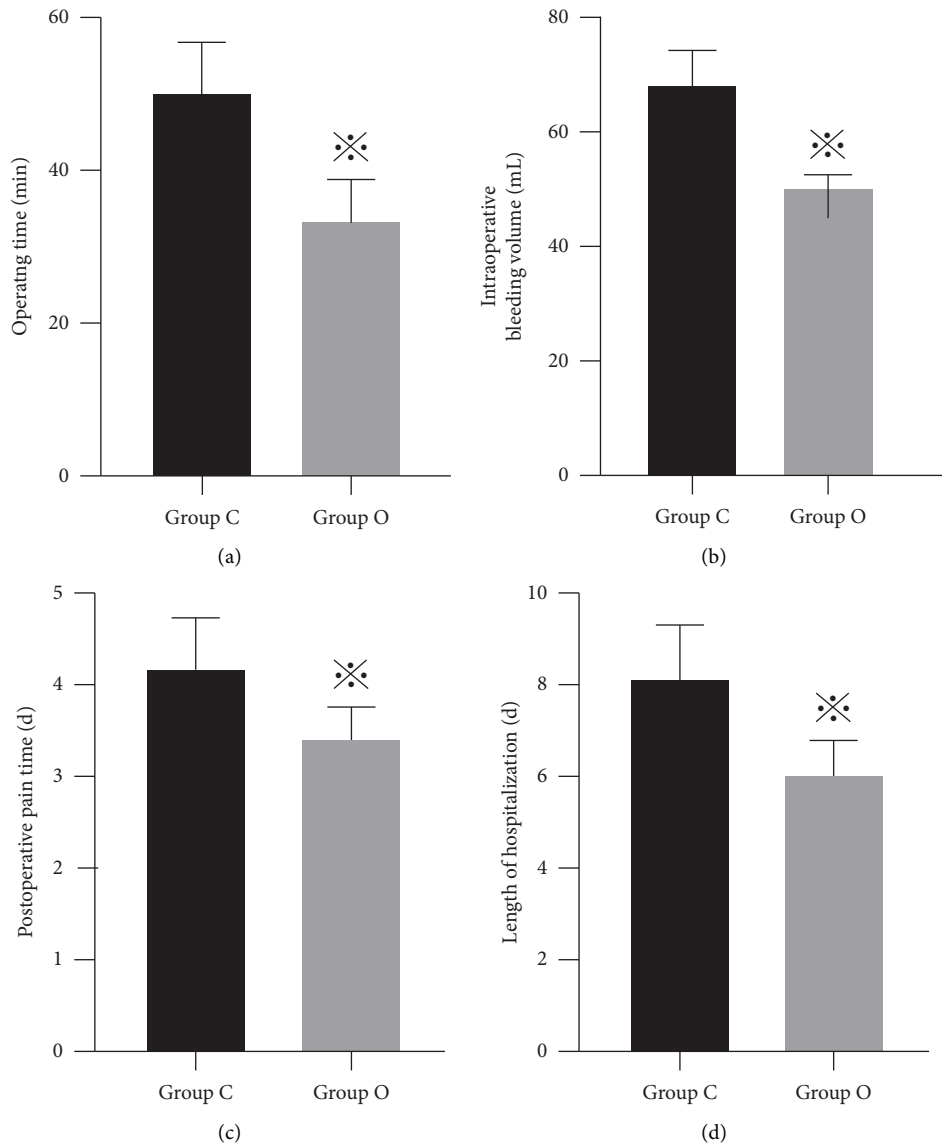


FIGURE 2: Comparison of perioperative indicators between group C and group O. Note: Figures 2(a)~(d) indicate the operative time, intraoperative bleeding, postoperative pain time, and hospital stay, respectively. ※ indicates  $P < 0.05$  compared with group C.

postoperative outcome in children with OSAS ( $P < 0.05$ ) (Tables 3 and 4).

## 7. Discussion

Childhood snoring is a common clinical disease, which is mainly caused by airway obstruction caused by adenoid hypertrophy or tonsillar hypertrophy, resulting in poor breathing and even apnea syndrome in children during sleep, with clinical manifestations of nasal congestion, snoring, apnea, and open-mouth breathing [10, 11]. When the abovementioned symptoms occur, children often show mental atrophy, daytime sleepiness, memory loss, and other phenomena [12], and even lead to cerebral hypoxia, which seriously affects the normal development and healthy growth of children in the future. The causes and mechanisms of the disease have not yet been fully elucidated, but are

thought to be related to anatomical lesions of the upper airway, such as hypertrophy of the adenoids and tonsils, which cause a series of symptoms such as paroxysmal hypoventilation by obstructing the upper airway [13, 14]. Based on its pathogenesis and adenoids and tonsillar hypertrophy, the clinical treatment is usually surgical. However, although traditional surgery such as adenoids scraping is convenient, it has the disadvantages of longer operation time and more difficult to stop bleeding as well as easy postoperative bleeding, which can lead to postoperative infection and fever and increase secondary injuries. In recent years, with the further development of clinical techniques, nasal power excision [15] and low-temperature plasma radiofrequency ablative resection [16] have been widely used and promoted.

Low-temperature plasma knife uses the energy generated by bipolar radiofrequency to form a thin layer of plasma only

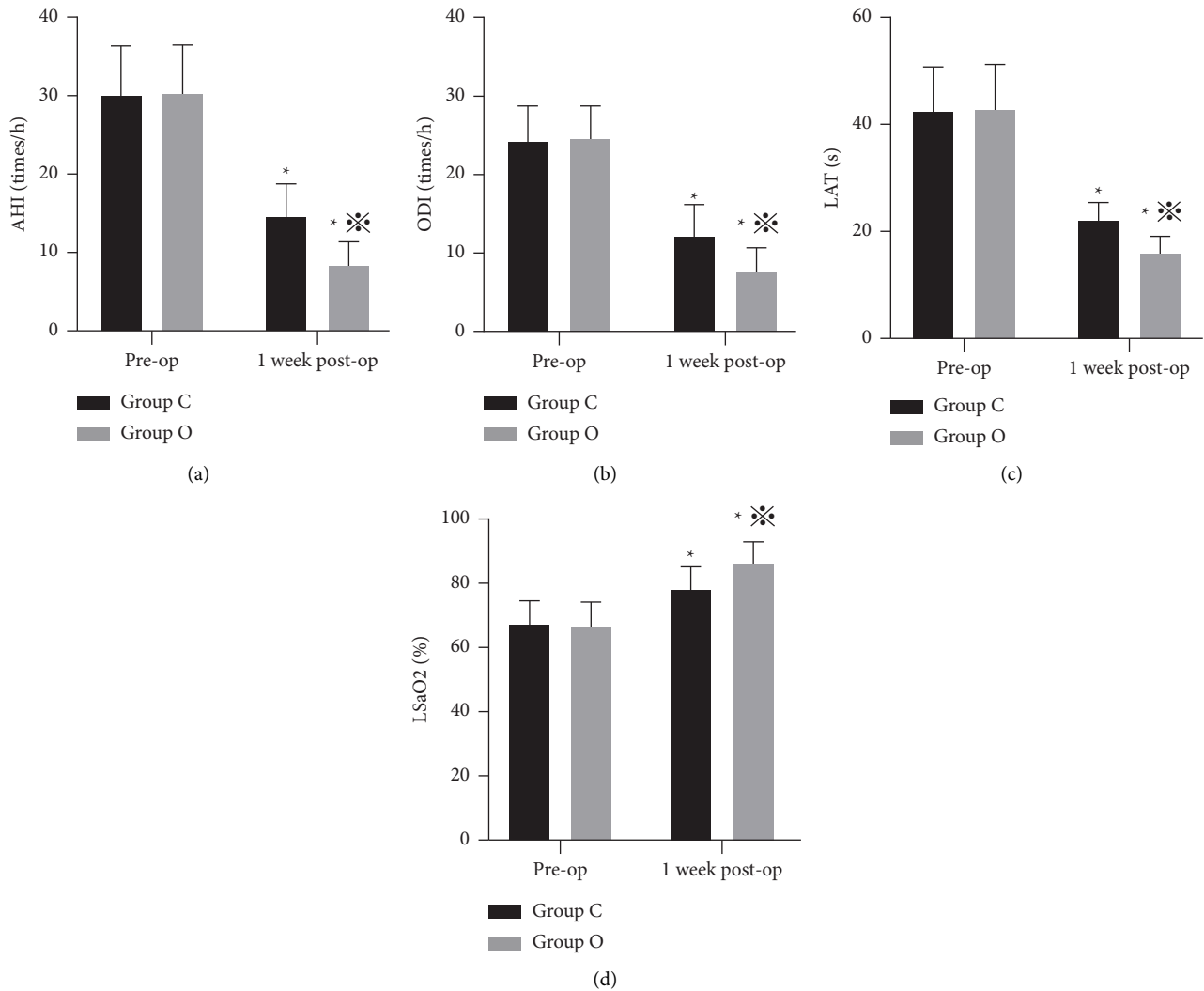


FIGURE 3: Comparison of preoperative and 1-week postoperative ventilatory function between group C and group O. Note: Figures 3(a)~(d) indicate AHI, ODI, LAT, and LSaO<sub>2</sub>, respectively. \* indicates comparison with the same group before surgery,  $P < 0.05$ . ✕ indicates comparison with group C at one week after surgery,  $P < 0.05$ .

between the electrode and the tissue, and the ions in the layer are accelerated by the electric field and transfer energy to the tissue. Under the condition of 40–70°C, the intercellular molecular binding bonds are opened, and the cells are lysed into simple carbohydrates to achieve the purpose of tissue ablation [17]. The low-temperature plasma tip combines surgical cutting and suction in one, allowing clear separation of the tonsillar peritonsium and simultaneous aspiration of blood, thus shortening surgical time and reducing intraoperative bleeding. The results of this study showed that the operative time, intraoperative bleeding, postoperative pain time, and hospital stay were significantly shorter in group O than in group C. The total clinical efficiency was significantly higher in the 45 children with OSAS treated with cryoplasma studied in this group. In addition, this study found that ventilation function improved in both the groups of children after treatment, with the low-temperature plasma protocol showing a better improvement than the power cutting system. The reason may be that the operation field of low-

temperature plasma knife is clear and the operation area is well exposed, which can cauterize the lymphatic follicular tissue at the base of the tongue, reduce the proliferation of lymphatic tissue, help reduce the tonsil residue, and achieve the purpose of improving airway stenosis [18, 19]. In addition, this study found that the power cutting system protocol was an independent risk factor for the efficacy of OSAS in children, which laterally corroborates that cryoplasma adenoidectomy combined with bilateral tonsillectomy is more effective.

Adenoidal hypertrophy or tonsillar hypertrophy is the main cause of OSAS in children. Surgical removal of the adenoids and/or tonsils is the preferred treatment for OSAS in children when there are no contraindications to surgery, but there is still a significant proportion of children who do not achieve complete improvement in sleep apnea after surgery. Therefore, in this study, we further analyzed the factors influencing the outcome of children, and the logistic regression model revealed that high BMI and high

TABLE 2: Univariate analysis of factors affecting postoperative outcomes in children with OSAS.

Influencing factors		Cure + significant effect (n = 81)	Valid + invalid (n = 9)	t/ $\chi^2$ value	P value
Gender (n, %)	Male	56 (69.15)	6 (66.67)	0.023	0.879
	Female	25 (30.86)	3 (33.33)		
Age (years, mean $\pm$ SD)		7.01 $\pm$ 2.02	10.55 $\pm$ 1.94	5.005	0.001
BMI (kg/m <sup>2</sup> , mean $\pm$ SD)		15.55 $\pm$ 3.20	23.33 $\pm$ 3.38	6.883	0.001
Duration of disease (months, mean $\pm$ SD)		13.12 $\pm$ 2.11	16.56 $\pm$ 1.94	4.673	0.001
Degree of tonsillar hypertrophy (n, %)	II degree	37 (45.68)	7 (77.78)	3.340	0.068
	III degree	44 (54.32)	2 (22.22)		
Preop glu (nmol/L, mean $\pm$ SD)		5.67 $\pm$ 1.13	6.12 $\pm$ 1.09	1.137	0.259
Preop LDL (mmol/L, mean $\pm$ SD)		3.36 $\pm$ 0.87	3.74 $\pm$ 0.91	1.238	0.219
Preop HDL (mmol/L, mean $\pm$ SD)		1.03 $\pm$ 0.12	0.97 $\pm$ 0.09	1.452	0.150
Preop TC (mmol/L, mean $\pm$ SD)		1.14 $\pm$ 0.41	1.23 $\pm$ 0.39	0.627	0.532
Preop TG (mmol/L, mean $\pm$ SD)		3.12 $\pm$ 0.56	3.43 $\pm$ 0.62	1.560	0.123
Preop AHI (times/h, mean $\pm$ SD)		29.43 $\pm$ 5.42	39.56 $\pm$ 4.85	5.368	0.001
Preop ODI (times/h, mean $\pm$ SD)		24.33 $\pm$ 4.23	27.22 $\pm$ 5.36	1.893	0.062
Preop LAT (s, mean $\pm$ SD)		42.56 $\pm$ 7.63	46.89 $\pm$ 10.98	1.542	0.127
Preop L <sub>Sa</sub> O <sub>2</sub> (% , mean $\pm$ SD)		67.27 $\pm$ 6.64	75.89 $\pm$ 8.07	3.617	0.001
Surgical method (n, %)	Class A	44 (54.32)	1 (11.11)	6.049	0.014
	Class B	37 (45.68)	8 (88.89)		

Note: Class A indicates low-temperature plasma adenoidectomy combined with bilateral tonsillectomy, and Class B indicates power cutting system for adenoidectomy combined with conventional peeling of bilateral tonsils.

TABLE 3: Multifactor assignment.

Variables	Serial numbers	Assignment
BMI	X1	Continuous variables
Preoperative AHI	X2	Continuous variables
Surgical approach	X3	Class A = 0, Class B = 1

Note: Class A indicates low-temperature plasma adenoidectomy combined with bilateral tonsillectomy, and Class B indicates power cutting system for adenoidectomy combined with conventional peeling of bilateral tonsils.

TABLE 4: Multifactorial analysis affecting the postoperative outcome of children with OSAS.

Indicators	B	SE	Walds	OR	95%CI	P values
BMI	0.523	0.201	15.248	1.687	1.138~2.502	<0.001
Preoperative AHI	0.673	0.259	18.120	1.960	1.180~3.256	0.001
Surgical approach	1.124	0.467	22.347	3.077	1.232~7.685	<0.001

preoperative AHI were independent risk factors for the outcome of OSAS in children. The prevalence of obesity is increasing worldwide among children and is also increasingly becoming a serious problem affecting the health of our children, and obesity leads to an increased risk of OSAS in children [20]. Most scholars [21, 22] suggest that the etiology of OSAS in obese children may include collapse of the airway due to dysfunctional neuromotor control; narrowing of the pharyngeal lumen due to accumulation of the adipose tissue in the pharynx; and further narrowing of the airway by hypertrophic adenoids and tonsillar tissue. Adenoidectomy and tonsillectomy improves sleep apnea in most obese children, but does not completely resolve OSAS. Polysomnography is the “gold standard” for the diagnosis of OSAS in children, and surgical treatment alone may not be effective in patients with a more severe disease [23]. Some studies [24, 25] have

shown that preoperative polysomnography results in non-obese children with OSAS suggest that postoperative outcomes are often poor in children with severe OSAS. Because in children with severe OSAS with AHI > 20 times/h, the etiology may not be solely due to adenoid or tonsillar hypertrophy, the risk of residual OSAS after adenoidectomy and tonsillectomy is also increased.

In conclusion, compared with the power cutting system protocol, the use of low-temperature plasma knife surgery for OSAS in children can further improve postoperative ventilation and facilitate the postoperative recovery of the child. Although adenoidectomy and tonsillectomy can solve the sleep breathing disorder problem in most children with OSAS, it cannot yet solve all the problems of children with OSAS, especially those with obesity and severe OSAS. Therefore, in the diagnosis and treatment of OSAS in children, we should choose the appropriate treatment plan, supervise, and guide obese children to lose weight, control their weight, review polysomnography after surgery, detect residual sleep breathing disorders after surgery in time, and deal with them accordingly in order to achieve the purpose of curing the disease.

**Data Availability**

The data used in this study are available from the corresponding author upon reasonable request.

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

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