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Research Article

Effects of Nasal High-Flow Therapy after Open Chest Esophagectomy for Esophageal Cancer

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Abstract

Background: We conducted a randomized trial to determine the relationship between oxygenation and in-out fluid balance by Nasal High-Flow Therapy (NHFT) after open esophagectomy for esophageal cancer, compared with Venturi Mask (VM) therapy.

Methods: A randomized trial was conducted in two hospitals in Japan, where patients undergoing esophagectomy for esophageal cancer were randomly assigned to receive NHFT or VM in the ICU through Postoperative Day (POD) 5.

Results: Seventy-four patients were enrolled in this study. We analyzed 31 patients in the NHFT group and 32 patients in the VM group. On POD 2, PaO2 / FIO2 in the NHFT group prevented the deterioration of oxygenation compared with the VM group (262 ± 75 vs. 234 ± 60 mmHg, $P < 0.05$). The total fluid balance continued plus balance until POD 2 in both groups. A negative fluid balance was observed on POD 3 in both groups. There was no significant difference in the length of ICU and hospital stays between the two groups.

Conclusions: The NHFT group prevented the deterioration of oxygenation compared with the VM group at POD 2. The total fluid balance continued plus balance until POD 2 in both groups.

Keywords: Nasal high-flow oxygen therapy; Open esophagectomy; Oxygen therapy; Venturi mask

Introduction

Open chest esophagectomy for esophageal cancer performed through a right thoracotomy and laparotomy is a major invasive surgery [1,2]. The surgical stress of radical esophagectomy induced the release of interleukin-6 and interleukin-8 and the overproduction of these cytokines induces systemic inflammatory response syndrome [3]. Therefore, open esophagectomy has a higher risk of intraoperative and postoperative complications. There were no reports of relationship between in-out fluid balance and oxygenation by nasal high-flow therapy (NHFT) after operation. Postoperative pulmonary complications have been reported in 18 % to 38 % of patients who underwent esophagectomy for cancer [4-9] and have been associated with adverse short-term outcomes and decreased long-term survival [4]. Oxygen is commonly administered after extubation of the endtracheal tube after operation. NHFT is a novel treatment delivering heated and humidified oxygen via a nasal cannula at a maximum flow of 60 L/min. NHFT reduced the work of breathing, improved gas exchange, helped decrease dead space, increased mucus clearance, and prevents atelectasis [10]. A Venturi mask (VM) provides higher gas flow at a predetermined fraction of inspired oxygen (F_IO_2). From Maggiore et al's report [11], device discomfort was significantly lower in the NHFT group than in the VM group. Our first objective was to determine the relationship between in-out fluid balance and oxygenation by Nasal High-Flow Therapy (NHFT) after open esophagectomy for esophageal cancer, compared with Venturi Mask (VM) therapy. The secondary objective was to compare the postoperative pulmonary complications, the length of stay in the ICU and hospital between two groups.

Methods

The Ethics Committees at the Juntendo University Hospital and Juntendo University Shizuoka Hospital approved these double-center, prospective studies. We registered our clinical trial (the University Hospital Medical Information Network, UMIN000023617). We conducted a randomized controlled, open-label trial on 74 patients between February 2017 and January 2019. We obtained written informed consent from all 74 patients enrolled in this study. We enrolled nonsmoking patients aged 20–80 years with an American Society of Anesthesiologists (ASA) Physical Status Classification score of 1–2. Patients with a known history of chronic obstructive pulmonary disease, renal or heart failure, obesity (defined as a body mass index [BMI] ≥ 30 kg/m^2), refusal of informed consent, pregnancy, or any nasal/facial defect that could impede NHFT or VM use were excluded from this study. No premedication was given. We prospectively enrolled patients who were undergoing open esophagectomy (a right-thoracotomy and laparotomy) for esophageal cancer.

All Patients were extubated in the operating room after esophageal surgery. Those qualifying for extubation met the following criteria: No atelectasis was observed on chest radiograph. Consciousness was clear. Spontaneous respiration was regular and respiratory frequency ranged between 10 and 25 breaths/min. PaO_2 /F_IO_2 > 300 mmHg. Hemodynamic stability was observed (heart rate <120 beats/min; systolic blood pressure between 90 and 160 mmHg; no signs of cardiac ischemia, no hemodynamically significant arrhythmias and absence of catecholamines); body temperature ≥ 36 °C; adequate cough reflex; and absence of copious secretions.

In the NHFT （Nasal High Flow™, Fisher & Paykel Healthcare. Inc. Tokyo, JAPAN） group, we set F_IO_2 at 0.45 and flow at 50 L/min. In the VM (Inspiron Nebulizer™, Next Japan Inc. Tokyo, JAPAN) group, we set the oxygen flow rate at 6 L/min (F_I0_2 0.44) in the ICU. At this flow rate in the VM group, oxygen concentration level was approximately 44%. Arterial blood gases, White Blood Cell (WBC) count, C-Reactive Protein (CRP), total fluid balance (total fluid in − total fluid out) per day were measured each day to Postoperative Day (POD) 5. We measured the length of ICU and hospital stays (from operation day to discharge hospital day). We asked the patient to rate their discomfort related both to the interface (face mask or nasal cannula) and to the symptoms of airway dryness (mouth, throat, and nose dryness; difficulty in swallowing; and throat pain). Postoperative pulmonary complications were checked for presence such as pleural effusion, atelectasis, pneumonia, acute exacerbation of interstitial pneumonitis and aspiration pneumonitis. Chest radiography was performed each day to POD 5 and assessed for atelectasis severity using the Radiological Atelectasis Score (RAS) [12]. RAS is a 5-point scale: 0 = clear lung fields, 1 = plate like atelectasis or slight infiltration, 2 = partial atelectasis, 3 = lobar atelectasis and 4 = bilateral lobar atelectasis. From Maggiore et al.'s report [11], PaO_2 /F_IO_2 was higher with the NHFT group than with the VM group at the 24th hour after extubation. We hypothesized that NHFT would have improved the PaO_2 /F_IO_2 at 24 hours, as compared with the VM. With a type 1 error of 0.05 and a power of 80% we calculated a sample size of 100 patients (50 patients in each arm).

We analysed data using the repeated measures analysis of variance, Scheffé test, Mann–Whitney U-tests and χ^2 test. We considered P values < 0.05 as statistically significant. All statistical calculations and data analysis were performed using Stat View 5.0™ (SAS Institute Inc., Cary, NC).

Results

Seventy - four patients were enrolled in this study (Figure 1). In the NHFT group, two patients were excluded due to low F_IO_2 (< 0.45) and five patients were switched to the Venturi mask (four patients complained of hot airflow: one patient complained of pain due to sinusitis and nasal pain). In the VM group, three patients were moved to NHFT because of worsening oxygenation and one patient disliked the mask. No patients were moved to Noninvasive Positive Pressure Ventilation (NPPV) or mechanical ventilation until POD 5. The VM group (n = 32) or NHFT (n = 31) mechanisms were applied until POD 5. The heights, weights, BMIs, age, length of anesthesia and total fluid balance during anesthesia did not significantly differ between the three groups (Table 1). Compared with the VM group, the NHFT group experienced better oxygenation in the ICU. At the POD 2, the NHFT group's PaO_2 / F_IO_2 was higher than in the VM group (262 ± 75 vs. 234 ± 60 mmHg, P < 0.05; Figure 2). The VM group's PaO_2 / F_IO_2 at POD 2 significantly decreased from POD 1 (234 ± 60 vs. 298 ± 97 mmHg, P < 0.05, Figure 2). The NHFT group had a significantly lower respiratory rate than the VM group at POD 3 (18 ± 2 vs 19 ± 2 breaths/min: P < 0.05, Table 2). There was no significant difference in the length of ICU and hospital stays between the two groups. However, at over POD 40, the patients in the VM group had significantly increased the length of the hospital stays than that of the NHFT group (4 patients in the VM group and no patient in the NHFT group; p < 0.05, Table 3).

CONSORT Flow Diagram

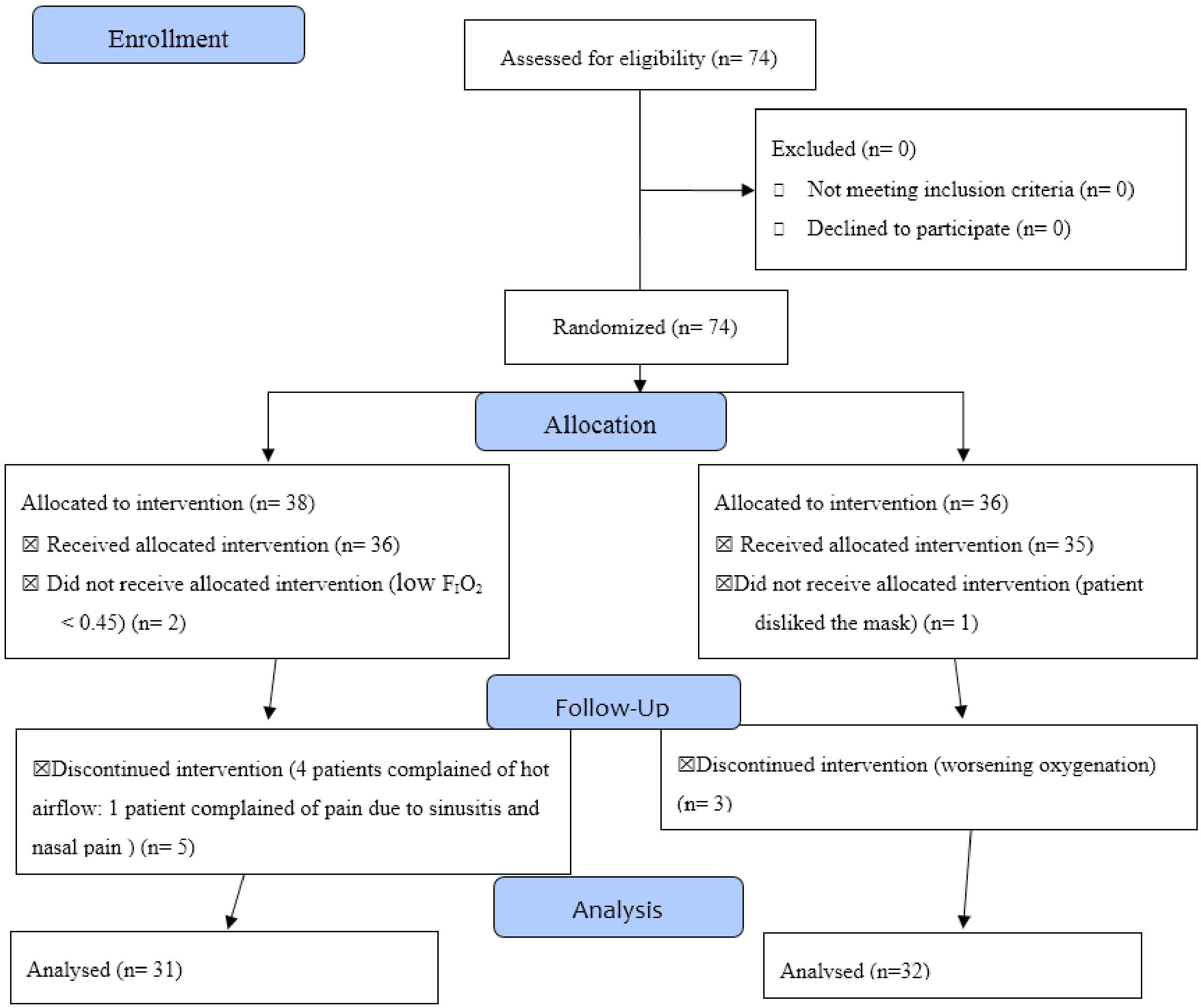

Figure 1: CONSORT Flow Diagram.

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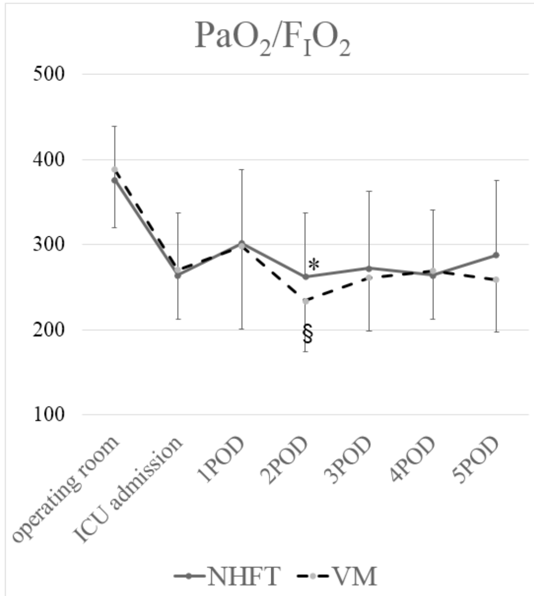

Figure 2: PaO_2/F_IO_2 after operation; All data are presented as means ± standard deviations. NHFT: Nasal High-Flow Therapy Group, VM: Venturi Mask Oxygen Therapy Group. POD: postoperative day, * P < 0.05 vs VM group. § P < 0.05 vs POD1.

	NHFT group	VM group	P
N	31	32	
Height (cm)	165±8	163±7	0.5264
Weight (kg)	56±11	58±11	0.6011
BMI (kg/m^2)	20.4±3.4	21.5±3.0	0.1818
age (years)	66±8	67±6	0.3534
male; female	23; 8	26 ; 6	
anaesthesia time (min)	549±74	557±78	0.7156
in-out balance during anaesthesia (ml)	4268±1002	4283±908	0.9475

Table 1: Baseline characteristics of the study; All data are presented as means ± standard deviations. NHFT: nasal high-flow therapy group, VM: Venturi mask oxygen therapy group.

		POD 1	POD 2	POD 3	POD 4	POD 5
$PaCO_2$ (mmHg)	NHFT group	40±7	40±6	41±5	41±4	40±5
	VM group	40±5	39±5	40±5	40±4	38±5
	P	0.7815	0.2328	0.5338	0.2398	0.09274
Respiratory rate (/min)	NHFT group	19±0	19±3	18±2	19±0	18±0
	VM group	19±0	19±2	19±2	19±0	19±0
	P	0.1649	0.9201	0.0427	0.4328	0.3293
WBC (/μL)	NHFT group	10277±3057	11480±4303	9083±3196	7410±2526	6920±2319

	VM group	11675±5456	13256±5939	10266±3716	7859±2628	7350±2436
	P	0.1935	0.154	0.1476	0.4091	0.4798
CRP (mg/dL)	NHFT group	9.55±3.29	16.37±6.011	14.12±5.84	11.11±5.92	9.62±5.77
	VM group	9.60±2.83	17.68±5.393	15.73±6.018	12.3±5.32	9.55±5.512
	P	0.8417	0.2926	0.217	0.2616	0.7505
Atelectasis Score	NHFT group	1±0.7	1.6±0.7	1.6±0.6	1.4±0.8	1.2±0.8
	VM group	1±0.7	1.5±0.7	1.5±0.7	1.5±0.7	1.3±0.7
	P	1	0.588	0.7078	0.5075	0.5117

Table 2: $PaCO_2$, Respiratory rate, WBC, CRP and Atelectasis Score after operation. All data are presented as means ± standard deviations. NHFT: Nasal High-Flow Therapy Group, VM: Venturi Mask Oxygen Therapy Group. WBC: white blood cell, CRP: C-reactive protein; RAS: Radiological Atelectasis Score; RAS is a 5-point scale: 0 = clear lung fields, 1 = plate like atelectasis or slight infiltration, 2 = partial atelectasis, 3 = lobar atelectasis and 4 = bilateral lobar atelectasis.

	NHFT group	VM group	P
lengths of ICU stays (d)	7±1	7±11	0.3534
lengths of admission (d)	20±5	28±20	0.4401
lengths of admission <40 days	31cases	28cases	
lengths of admission ≥40 days	0	4cases	χ2 test. 0.0419

Table 3: lengths of ICU stays, lengths of hospital stays, lengths of hospital stays <40 days, lengths of hospital stays≧40 days. All data are presented as means ± standard deviations. NHFT: nasal high-flow therapy group, VM: Venturi mask oxygen therapy group.

There were no significant differences in $PaCO_2$, WBC counts and CRP values among the two groups from POD 1 to 5 are provided in Table 2. There were no significant differences in total fluid in volume between the NHFT and VM groups at POD 1 (2883 ± 512 vs 2819 ± 381ml, Table 4). The total fluid balance in the NHFT group increased significantly more than in the VM group at POD 1 (1348 ± 590 vs 964 ± 510 ml: $P < 0.05$). The total fluid balance decreased as PODs increased in both groups. A negative fluid balance was observed on POD 3 in both groups.

		POD 1	POD 2	POD 3	POD 4	POD 5
fluid in	NHFT group	2883 ± 512	2658 ± 413	2270 ± 259	2095 ± 293	2030 ± 341
	VM group	2819 ± 381	2560 ± 284	2321 ± 362	2222 ± 307	2186 ± 257
	P	0.551	0.4612	0.44	0.1859	0.0471
in out balance	NHFT group	1348 ± 590	607 ± 512	-365 ± 689	-372 ± 579	-41 ± 589
	VM group	964 ± 510	531 ± 666	-13 ± 800	-131 ± 564	-23 ± 615
	P	0.0118	0.611	0.0701	0.1011	0.9088
fluid out	NHFT group	1588 ± 464	2047 ± 611	2630 ± 638	2468 ± 550	2072 ± 598
	VM group	1820 ± 531	2094 ± 554	2341 ± 665	2355 ± 665	2211 ± 645
	P	0.0512	0.9239	0.1312	0.3823	0.3773

Table 4: Total fluid in, total fluid balance and total fluid out after operation. All data are presented as means ± standard deviations. NHFT: nasal high-flow therapy group, VM: Venturi mask oxygen therapy group.

Postoperative pulmonary complications are observed in Table 5. There were fewer postoperative pulmonary complications in the NHFT group than in the VM group. There were no different RAS between the two groups (Table 2). In almost half of the patients in both groups, a left side pleural effusion compressing the left lung was detected and increased after POD 2. But no patients in either group were moved to mechanical ventilation until POD 5. A persistent right pleural effusion was found in one NHFT group patient (Table 5). Persistent pleural effusions were found in two patients in the VM group. One patient experienced acute exacerbation of interstitial pneumonitis and one patient experienced a chylothorax in the VM group. The patient with exacerbation of pneumonitis in the VM group died in the hospital. One patient in the VM group experienced aspiration pneumonitis after being discharged from the ICU. Other postoperative complications (Table 5) were as follows: cervical lymph leakage found in a patient in the NHFT group. Surface surgical site infections were found in three patients in the NHFT group. Deep surgical site infections were found in two patients in the VM group. One patient in the VM group experienced a cerebral infarction.

NHFT	VM
continuous pleural effusion：1	continuous pleural effusion: 2
cervical lymphorrhear: 1	aspiration pnuemonitis: 1
bilateral recurrent laryngeal nerve palsy: 1	acute excerbration of interstinal pnemonitis: 1
surgical site infection(surface): 3	chest lymphprrhea: 1
	cerebral infarction: 1
	surgical site infection(deep): 4

Table 5: Postoperative complication. NHFT: Nasal High-Flow Therapy Group, VM: Venturi mask oxygen therapy group.

Discussion

Our first objective was to determine the relationship between in-out fluid balance and oxygenation by Nasal High-Flow Therapy (NHFT) after open esophagectomy for esophageal cancer, compared with Venturi Mask (VM) therapy. Regarding the effects of the VM and the NHFT on oxygenation for ICU patients compared with the VM group, oxygenation was better for the patients in the NHFT group. The NHFT group prevented the deterioration of oxygenation compared with the VM group at POD 2. Positive total fluid balance continued until POD2. Negative total fluid balance was observed on POD 3 in both groups. These results indicate that the increased vascular permeability continued until POD 2. The Positive End-Expiratory Pressure (PEEP) like effect of NHFT improved oxygenation more in the NHFT group than in the VM group at POD 2. In the VM group, three patients were moved to NHFT because of worsening oxygenation. This complication resolved for all three after being moved to NHFT. RAS is the same among the two groups. These results indicate that the NHFT improved oxygenation more than the Ventri mask after open esophagectomy for esophageal cancer. By delivering the gas at flow rates that exceed the patient's peak inspiratory flow rate, NHFT provides a constant F_IO_2. With NHFT, the final concentration of oxygen truly delivered to the patient is equivalent to the F_IO_2 SET [13]. The NHFT can deliver high F_IO_2, while the Venturi mask can deliver F_IO_2 under 60% [14].

NHFT reduces the work of breathing, improves gas exchange, helps decrease dead space, increases mucus clearance, and prevents atelectasis[10]. In addition, the high flow rate of gas provides a continuous positive airway pressure like effect that helps to improve overall oxygenation and ventilation [15]. As a result, the NHFT group experienced significantly lower respiratory rates than the VM group at POD 3. This was explained that NHFT reduced the work of breathing and helped decreasing dead space. These mechanisms improved oxygenation more in the NHFT group than in the VM group. However, the NHFT is not necessary for all patients who undergo open esophagectomy for esophageal cancer. The NHFT may be necessary if the patient experiences worsening oxygenation after surgery, typically on POD 1 to 3.

The secondary objective was to compare the postoperative pulmonary complications, the length of stay in the ICU and hospital between two groups. The length of ICU stay was the same among the two groups. But over POD 40, VM group patients experienced significantly longer hospital stays than those in the NHFT group. Postoperative pulmonary complications have been associated with adverse short-term outcomes and decreased long term survival [4]. Postoperative pulmonary complications have been reported in 17.7% to 38.0% of patients who underwent esophagectomy for cancer [4-9]. Postoperative pulmonary complications were defined as respiratory insufficiency requiring intubation, pneumonia, aspiration pneumonitis, atelectasis, pleural effusion and acute exacerbation of interstitial pneumonitis. Postoperative pulmonary complications were associated with worse short- and long-term outcomes after extended oesophagectomy [16]. Univariable analysis found that patients who developed postoperative pulmonary complications had increased cumulative fluid balance in day 1 to 2. Positive fluid balance at POD 1 was predictive of pulmonary complications in patients after esophagectomyr [17]. In our study, total fluid in volumes in the NHFT group on POD 1 to 2 were at almost the same volumes as those in the VM group. However, the total fluid balance in the NHFT group at POD 1 significantly increased more than that of the VM group. Despite the volume load, improved oxygenation was achieved through the PEEP effect of the NHFT. In our study, left-side the pleural effusions occurred in almost half of the patients in both groups after POD 2. The left pleural effusion compressed the left lung, caused atelectasis and increased RAS. Pleural effusions after esophagectomy frequently occur on the left side, because the esophagus is located on the left side of the mediastinum and esophagectomy with lymphadenectomy induces inflammation mainly to the left side of the mediastinum [18]. But RAS was the same among two groups. The NHFT group experienced better oxygenation than the VM group despite the pleural effusion.

A persistent pleural effusion was found in one patient in the NHFT group and in two patients in the VM group. One patient experienced acute exacerbation of interstitial pneumonitis and one patient experienced pleural effusion by lymphorrhea andaspiration pneumonitis were admitted in the VM group. Patients in the VM group experienced more postoperative pulmonary complications than those in the NHFT group. This results in a longer hospital stays for the VM group patients than the NHFT group over 40 days. Noninvasive Positive Pressure Ventilation (NPPV) is not suitable for patients with increased secretions, decreased airway self-clearance ability, and a recent history of esophageal surgery. By using NPPV, in the early postoperative period, the delivery of positive pressure in the airways and eventual patient-ventilator asynchronies during assisted ventilation may pose a risk to the pressure of the cervical esophagus to gastric tube reconstruction anastomosis. But esophageal surgery may not be an absolute contraindication for NPPV. NPPV used for Acute Respiratory Distress Syndrome (ARDS) following esophagectomy for esophageal cancer prevented the need for intubation in half of the ARDS patients [19]. So NHFT may be an effective first option for the treatment of worsening oxygenation after esophagectomy. From Maggiore et al.'s report[11], discomfort related to the interface was significantly lower in the NHFT group than the VM group. They observed that the use of the NHFT was associated with less discomfort due to mouth dryness, and throat dryness, difficulty to swallowing and throat pain as compared with the VM group. But in our study, four patients in the NHFT group complained of hot airflow and one complained of pain from sinusitis. In our study, we informed the patients before surgery that they would receive either the NHFT or the VM. If they could not tolerate the NHFT or the VM, they could move to another method. At the start of oxygen therapy, not all the patients experienced benefits from NHFT. The NHFT group had significantly lower respiratory rates than the VM group at POD 3. At spontaneous ventilation, tidal volume does not measure at normal. There were not significantly different values of $PaCO_2$ between the two groups until POD 5. This was because the NHFT reduced the work of breathing and helped decrease dead space. At POD 3, we found that the NHFT group patients were more comfortable on respiration than the patients in the VM group.

Limitations

The number of this study was small. During this study, video-assisted thoracotomy/ laparotomy was begun for esophageal cancer. So we could not study afterward.

Conclusions

Compared with the VM group, the NHFT group prevented the deterioration of oxygenation compared with the VM group at POD 2. The total fluid balance continued plus balance until POD 2 in both groups. There were fewer postoperative pulmonary complications in the NHFT group than in the VM group.

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