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Examination of the Ability of N-acetylcysteine Administration during Anesthesia to Prevent Perioperative Deterioration of Pulmonary Function in Patients Undergoing Nephrectomy

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Background: Postoperative pulmonary complications are associated with significant morbidity and mortality in patients undergoing major surgeries. Acetylcysteine is a known antioxidant and is also used as a mucolytic agent to reduce hypersecretion and the viscosity of mucus secretions by the lung. Several studies have revealed that high doses of N-acetylcysteine can significantly prevent pulmonary complications. However, it has not yet been established whether low doses of N-acetylcysteine are also of clinical benefit. Here, we investigated the efficacy of a low dose of N-acetylcysteine, which was administered intravenously to patients under general anesthesia, in preventing perioperative deterioration of pulmonary function.
Methods: A total of 52 patients who were scheduled for nephrectomy were randomly assigned to receive either 600 mg of intravenous N-acetylcysteine or the same volume of normal saline. Patient hemodynamic and pulmonary parameters and the incidence of pulmonary complications were recorded and compared between the groups.
Results: No significant pulmonary complications occurred in either group. Moreover, no significant differences were observed regarding either patient characteristics or hemodynamic parameters between the two groups. Contrary to our expectations, the pulmonary parameters were also not significantly different between the two groups.
Conclusion: A low dose of N-acetylcysteine appears to have only limited value in preventing perioperative pulmonary complications.

Key Words: Pulmonary system, N-acetylcysteine, Nephrectomy, Perioperative complications

INTRODUCTION

Chest and abdomen surgeries induce transient acute restrictive ventilatory dysfunction. Within 24 hours of surgery, the patient's vital capacity and functional residual capacity decrease; however, these capacities gradually return to normal by approximately two weeks postsurgery. Due to the reduction in these capacities, patients are at high risk of pulmonary complications such as atelectasis, pneumonia, hypoxia, and hypercapnia. Particularly in surgeries that take longer than two hours under general anesthesia, bronchial ciliary function is reduced by a depressed coughing mechanism; moreover, the decline in excretory function may create a mucus plug consisting of residual dried bronchial secretions, which may contribute to the higher frequency of pulmonary complications [1-5].

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N-acetylcysteine (NAC) has long been used clinically as a mucolytic agent, since it does not possess any significant contraindications, with the exception of a history of hypersensitivity. N-acetylcysteine has been shown to dilute mucus secretion for better excretion, maintain airway space, and facilitate ventilation [6-8].

Here, we investigated the efficacy of two clinical doses of NAC, which were administered to patients undergoing nephrectomy under general anesthesia, in preventing perioperative pulmonary complications. As a control group, patients were treated under identical conditions, but given a placebo. The results of the groups were then compared.

MATERIALS AND METHODS

The patients included in this study were all over 50 years old and underwent planned elective nephrectomy. This study was approved by our institution's ethical committee, and informed consent was obtained from all patients who agreed to participate in the study. All patients were classified as physical status 1 or 2, as defined by the American Society of Anesthesiologists. Any patient who had taken NAC due to prolonged pulmonary disease, had a history of chronic obstructive pulmonary disease (COPD), had been diagnosed with COPD after a pulmonary function test, exhibited symptoms of acute upper respiratory infection, had a smoking history, or had a history of adverse reaction to NAC was excluded from this study. In addition, any patient who experienced an adverse effect such as rash, pruritus, angioedema, bronchospasm, tachycardia, or hypotension was excluded. In total, 56 enrolled patients were included in the final analysis. A computer was used to randomly assign patients to group M, which received NAC, or to group C, which received an identical amount of placebo. Group M included 28 patients; the remaining 28 patients were assigned to group C.

No premedication was given to any patient. Noninvasive blood pressure, electrocardiogram, and pulse oximetry devices were applied and monitored during the operation. General anesthesia was induced intravenously by using thiopental sodium and vecuronium bromide. After intubation, anesthesia was maintained with an inhalation anesthetic, such as sevoflurane or desflurane, in addition to continuous remifentanil infusion. An arterial catheter was inserted into the radial artery of each patient, and a central venous catheter was also inserted into the internal jugular vein. Arterial blood gas and central venous pressures were measured after insertion of the catheters, and their initial values were set as T0. Prior to switching to the lateral position, 600 mg of NAC diluted in 100 mL of normal saline was injected into the patients in group M. Patients in the control group received the same volume of normal saline alone. This treatment was defined as the first administration. Repair of the patient's skin was defined as the end of the operation. At this time, arterial blood gas and central venous pressures were measured again, and these values were set as T1. Also, a second administration of an identical amount of NAC (or normal saline, as appropriate) was given to each group at this time, using the same procedure as for the first administration. Vital signs and arterial blood gas were measured again at 1 and 12 hours postoperation; these values were set as T2 and T3, respectively.

Postoperative pulmonary function was evaluated with respect to the partial pressure of oxygen (PaO_2), the ratio of the pressure of arterial oxygen to the fractional inspired oxygen concentration (PaO_2/FiO_2), the difference in alveolar-arterial oxygen tension ($AaDO_2$), and the percentage of available hemoglobin that was saturated with oxygen (SaO_2). In addition, the mean arterial pressure (MAP), heart rate (HR), and central venous pressure (CVP) were also compared and analyzed. The presence of perioperative pulmonary complications was evaluated by listening to chief complaints, auscultation, gathering evidence regarding pulmonary symptoms, and performing simple chest radiograms.

Statistical comparison of patient sex distribution in the two groups was performed using the chi-square test, whereas the two-sample *t*-test was used to compare patient age, weight, height, MAP, HR, PaO_2, PaO_2/FiO_2, $AaDO_2$, and SaO_2 values. For within-group comparisons of changes in the values of MAP, HR, PaO_2, PaO_2/FiO_2, $AaDO_2$, and SaO_2, repeated measures ANOVA was used. p-values less than 0.05 were considered statistically significant.

RESULTS

A total of 52 patients were included in this study (Group

Table 1. Patient characteristics

	Group M	Group C
ASA class		
1	4	1
2	23	24
Sex		
Male	23	22
Female	4	3
Age (yr)	60.26 ± 10.574	64.36 ± 8.669
Weight (kg)	69.15 ± 10.143	63.50 ± 9.374
Height (cm)	164.96 ± 8.235	163.46 ± 6.086
Anesthesia time (min)	320.04 ± 73.033	331.20 ± 68.103
Operation time (min)	240.11 ± 68.616	251.72 ± 74.360

Values are expressed as numbers of patients or means ± standard deviations.
ASA: American Society of Anesthesiologists.
No significant differences were observed between the two groups regarding any of the parameters.

M: 27 patients, Group C: 25 patients). The two groups were not significantly different with respect to ASA class, sex, age, weight, height, or total operation time (Table 1). No NAC-related complications occurred in any patient.

Regarding PaO_2, the values of the two groups were not significantly different ($p = 0.9396$); however, intra-group comparisons revealed that the PaO_2 values at T2 were significantly lower than the values at T0 ($p < 0.0001$) (Fig. 1A). Similarly, the $AaDO_2$ values were not significantly different between the two groups ($p = 0.5751$), but each group showed significantly lower $AaDO_2$ at T2 compared with T0 (Fig. 1C). The values of PaO_2/FiO_2 ($p = 0.6207$) (Fig. 1B) and SaO_2 ($p = 0.35$) (Fig. 1D) were not significantly different between the two groups. Moreover, no significant differences in MAP values were observed, either when comparisons were made between the two groups (Fig. 1E) or between different time points within each group (Fig. 1G). The HR values were also not significantly different between the two groups (Fig. 1F) ($p = 0.5641$); however, within each group, the HR values were significantly increased at T2 and T3 compared with T0 ($p < 0.01$).

DISCUSSION

Previous studies have presented many measures for reducing postoperative pulmonary complications. Kim et al. [9] suggested that continuous administration of NAC during surgery reduces signs of acute pulmonary injury, and Zingg et al. [10] also reported a decrease in perioperative pulmonary complications when patients undergoing esophagectomy received 150 mg/kg of NAC. However, the dose used in the study by Zingg et al. is recommended for treating acetaminophen toxicity. The dosage recommendations for NAC to be used in adults as a mucolytic agent are 600 to 900 mg of NAC, two to three times daily [11]. Patients with chronic bronchitis generally receive a daily total of 400 to 1200 mg of NAC, which is administered two to three times orally or intravenously, whereas patients with COPD are advised to receive 600 mg of NAC for more than 6 months. Since these studies used higher doses of NAC than are clinically recommended during surgery, we investigated whether a low dose of NAC could prevent perioperative pulmonary complications. In our study, 600 mg of NAC was administered twice by intravenous injection to patients who underwent elective nephrectomy, once immediately after anesthetic induction and then again at the end of the operation. The effects of the medication on perioperative pulmonary complications were then investigated.

Nephrectomy is generally performed in the lateral decubitus position with the use of a kidney bar. The use of this position has significantly different postoperative consequences compared with surgeries that are performed in the supine position. First, in the lateral decubitus position, the position and the force of gravity differentiate a patient's lungs into a dependent and a nondependent lung. Postoperatively, the dependent lung is more likely to exhibit increased pulmonary circulation and secretion deposition. In addition, pulmonary ventilation, which is assisted by positive pressure ventilation during general anesthesia, is performed mainly by the nondependent lung. Thus, the dependent lung generally exhibits a higher incidence of atelectasis. In addition, the dependent lung exhibits reduced reaction to hypoxic vasoconstriction under general anesthesia, which also contributes to the increased risk of postoperative pulmonary complications. Many studies have described a considerable number of pulmonary complications in the dependent lung after surgeries in the lateral decubitus position. For example, Modi et al. [12] reported a case of pulmonary edema in the dependent lung of a patient with a kidney transplant, and the development of atelectasis in the dependent lung of an-

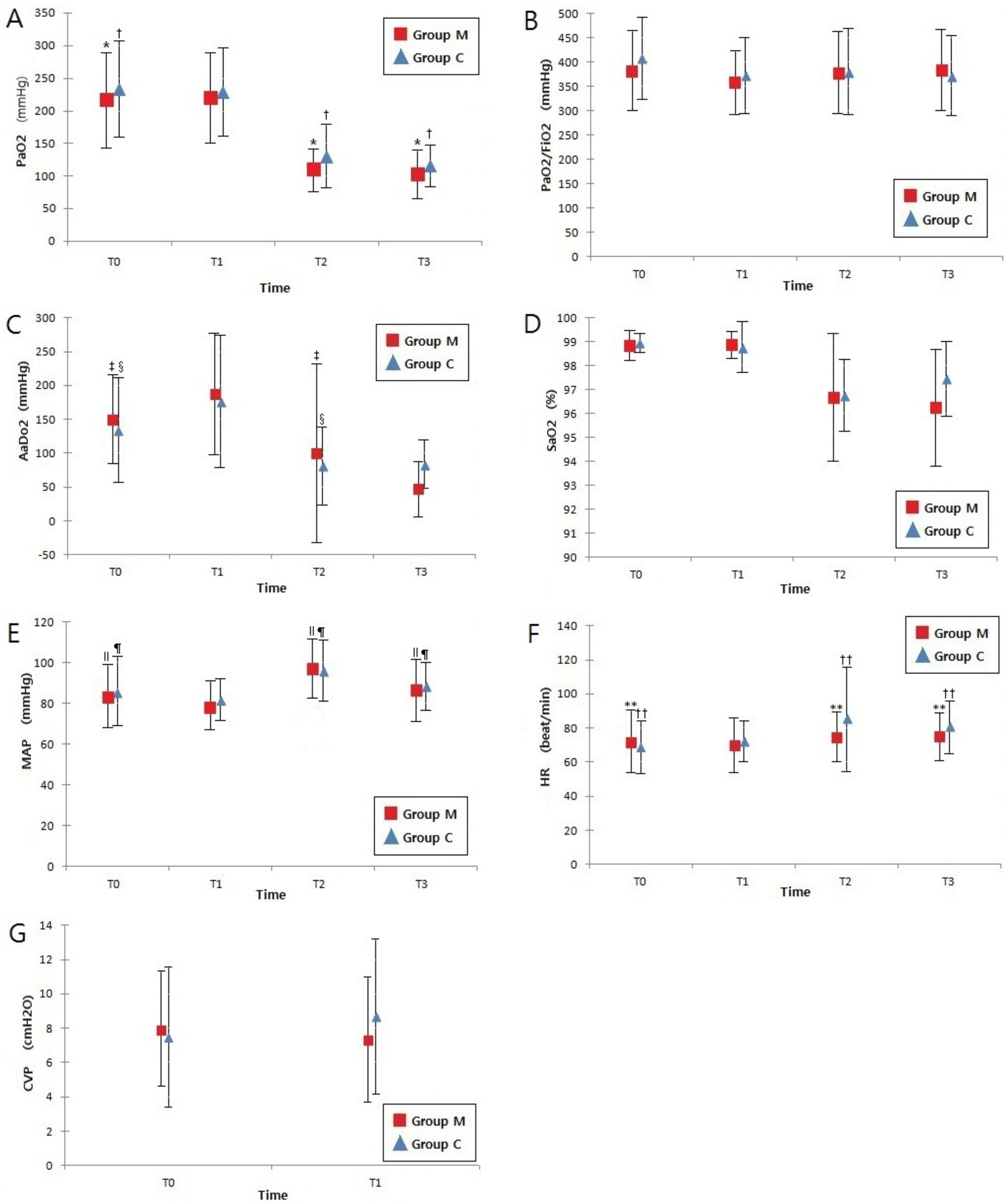

Fig. 1. Time-dependent changes in the measured parameters. (A) PaO_2: partial pressure of oxygen in the blood (mmHg). *In group M, the T2 and T3 values were significantly lower than the T0 value. †In group C, the T2 and T3 values were significantly lower than the T0 value. (B) PaO_2/FiO_2: index of arterial oxygenation efficiency, which corresponds to the ratio of the partial pressure of arterial O_2 to the fraction of inspired O_2 (mmHg). (C) $AaDO_2$: difference in alveolar-arterial oxygen tension (mmHg). ‡In group M, the T2 value was significantly lower than the T0 value. §In group C, the T2 value was significantly lower than the T0 value. (D) SaO_2: percentage of available hemoglobin that is saturated with oxygen (%). (E) MAP: mean arterial pressure (mmHg). ‖In group M, the T2 and T3 values were significantly higher than the T0 value. ¶In group C, the T2 and T3 values were significantly higher than the T0 value. (F) HR: heart rate (beats/min). **In group M, the T2 and T3 values were significantly higher than the T0 value. ††In group C, the T2 and T3 values were significantly higher than the T0 value. (G) CVP: central venous pressure (cmH_2O). T0: after arterial and central venous cannulation. T1: end of operation. T2: 1 hour postoperation. T3: 12 hours postoperation. Values are expressed as means ± standard deviations. $p < 0.05$.

other patient with a kidney transplant was also reported in a study by Kabaria et al. [13]. We hypothesized that postoperative pulmonary complications are more prominent in patients who undergo surgery in the lateral decubitus position. Thus, we selected patients who underwent nephrectomy in the lateral decubitus position to determine whether NAC administration could prevent perioperative pulmonary complications.

Many studies have used pulmonary function tests to evaluate respiratory capacity postoperatively. However, since postoperative pain may affect the exertional effort of a patient's respiration, we decided that this methodology may not yield the most accurate results in postoperative pulmonary function tests. Moreover, the results of pulmonary function tests can also be affected by the patient's level of cooperation; thus, varying levels of cooperation could affect the results. Hence, we employed an arterial blood gas test, which is a more objective evaluation of ventilatory capacity. This test also has another important advantage over the pulmonary function test in that it does not require the patient to be in an alert state to be performed. Since the air pumped into a patient during surgery has a higher content of oxygen than atmospheric air, we included PaO_2 as a ventilatory parameter in addition to pulse oximetry. Also, in order to reduce the variations resulting from different levels of oxygenation in each patient, we compared and analyzed the PaO_2/FiO_2 values. Diagnostic criteria of acute respiratory distress syndrome (ARDS) were used as an oxygenation parameter; these criteria were also used to make decisions regarding extubation or the implementation of mechanical ventilation. Since Choi et al. [14] suggested that a low oxygenation parameter score is predictive of an increased risk of ARDS, we also considered this parameter as an important prognostic factor for perioperative pulmonary complications.

In previous studies by Tse et al. [15], David et al. [16], and van Overveld et al. [17], 600 mg of NAC was administered twice daily. All three studies reported positive results, including improved small airway function, lowered incidence of disease aggravation, and improvement in symptoms. These improvements were demonstrated by increased forced vital capacity and inspiratory capacity on the pulmonary function test. Therefore, we predicted that the same amount of NAC would prevent the development of perioperative pulmonary complications. However, we did not observe any significant differences between the NAC group and the placebo group, at least with respect to the parameters studied in this investigation.

Since we did not observe any significant differences in the levels of PaO_2/FiO_2, we hypothesize that the decreases in the levels of PaO_2 and $AaDO_2$ at the end of the surgery compared with their initial values are due to the increased amount of dissolved oxygen in the blood. This increase is the result of enhanced alveolar oxygenation, since air with higher oxygen content is administered during induction and operation. Also, elevated MAP and HR levels are believed to be caused by physiologic responses to the removal of cardiopulmonary depression and the pain sensations that are triggered when the effects of the anesthesia wear off.

In conclusion, this study did not find any evidence to support the idea that a low dose of NAC is protective against perioperative pulmonary complications. However, a study by Stey et al. [18] did conclude that the effect of NAC is dose-dependent. Our results are generally consistent with those reported in a study by Kim et al. [9], in which NAC was administered to patients without COPD. The Kim et al. study found similar results between study and control groups, with the exception that a reduction in acute pulmonary injury was observed in the NAC treatment group. This discrepancy could be explained by several possibilities. First, NAC has been found to have a stronger effect in patients with COPD compared with healthy individuals. Second, NAC clearly has preventative effects on healthy individuals; however, a large dose must be administered to exert the same preventative effect. Lastly, our data analysis and interpretation were limited due to our small sample size. To comprehensively determine the effects of a low dose of NAC, future studies with a larger sample size will be required. These studies should compare the effects of a low dose of NAC on patients with COPD vs healthy individuals, and also determine the precise dose for NAC to have a preventative effect in healthy individuals.

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