Nitric Oxide Inhalation therapy for Pulmonary Hypertension After Mitral Valve Surgery Does Not Shorten the Intubation Period and Length of Stay in the Intensive Care Unit: A Retrospective Study

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Abstract

Background

Inhaled nitric oxide (NO) is often used postoperatively for pediatric pulmonary hypertension (PH). Although the use of postoperative inhaled NO for adult cases has become prevalent, the Asian data of such cases are limited. This study aimed to evaluate the safety and effectiveness of NO inhalation therapy for PH in adult patients after mitral valve surgery.

Methods

In this retrospective study, we enrolled 24 adult patients with a mean pulmonary artery pressure (mPAP) > 25 mmHg after mitral valve surgery at our institution from January 2017 to September 2020. Among these patients, NO was used postoperatively (NO group) in 13, whereas NO was not used in 11 (non-NO group). We compared the clinical data, such as age, preoperative echocardiogram, cardiac catheterization results, perioperative information, postoperative Swan-Ganz catheter data, tracheal intubation time, and length of stay in the intensive care unit (ICU).

Results

The NO group had higher tricuspid regurgitation pressure gradient, right atrial pressure, and pulmonary artery wedge pressure, as well as more surgically complex cases, than the non-NO group. There were no differences in operative and aortic cross-clamp time, tracheal intubation duration, or length of ICU stay. In the NO group, the mPAP decreased and the cardiac index increased after postoperative NO inhalation. However, there were no significant differences in the mPAP and cardiac index between the NO and non-NO groups.

Conclusions

Our results suggest that NO inhalation therapy was not associated with shorter postoperative intubation and ICU stay in adult patients with PH after mitral valve surgery. These findings support those of studies from other countries, yet they do not clarify the usefulness of inhaled NO in these cases. Optimal NO therapeutic strategies should be reconsidered with the goal of reducing intubation time and length of stay in the ICU.

Background

Nitric oxide (NO), a selective pulmonary vasodilator, is an inhaled drug that decreases afterload in the right heart system and increases preload in the left heart system [1]. NO inhalation therapy has been widely used for pulmonary hypertension (PH) after pediatric cardiac surgery [2, 3]. In recent years, NO

inhalation therapy has been used in adults who have undergone cardiac surgery [4–6]. Some patients who undergo cardiac valve surgery develop PH postoperatively [7]; therefore, as postoperative PH portends worse outcomes, research and use of NO inhalation therapy in adult patients have attracted attention. However, evidence of improved outcomes with the use of NO in adults with PH after mitral valve surgery is insufficient. In particular, little data are available on the Asian population [8]. The purpose of this single center retrospective study was to validate the usefulness of NO inhalation therapy for PH in adult patients after mitral valve surgery.

Methods

Patients

The institutional board of Hirosaki University approved this study. In this retrospective study, a total of 85 patients underwent mitral valve surgeries at our hospital from January 2017 to September 2020. Of these, 24 patients (12 men and 12 women) without preoperative PH who developed postoperative PH were included in the study. We defined PH as a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg. Patients who did not develop PH postoperatively, as well as cases of reoperation and emergency surgery were excluded. We divided the patients into the following two groups: those who received NO inhalation therapy postoperatively (NO group; n = 13) and those who did not (non-NO group; n = 11). NO inhalation therapy was administered according to surgeon's preference. The patient characteristics are listed in Table 1.

Table 1
Patient characteristics

Variables	NO group	Non-NO group	P-Value
Sex, male:female	8:5	4:7	0.219
Age (years)	62.6 ± 10.3	64.9 ± 11.0	0.622
BMI (kg/m ²)	25.1 ± 4.0	24.4 ± 3.4	0.671
NYHA classification	2.64 ± 0.8	2.3 ± 0.6	0.259
Chronic A	8	6	0.552
Echocardiogram			
LVEF (%)	57.5 ± 16.0	63.9 ± 7.4	0.229
TRPG (mmHg)	45.1 ± 15.4	27.5 ± 8.8	0.017
Catheterization findings			
mPAP (mmHg)	41.1 ± 14.4	28.9 ± 10.0	0.89
PCWP (mmHg)	29.9 ± 14.9	16.6 ± 5.0	0.029
RAP (mmHg)	12.6 ± 7.2	4.4 ± 2.3	0.022
Perioperative data			
Operative method, MVR: MVP	6: 7	0: 11	0.016
Concomitant surgery	8	3	0.093
Operative time (min)	446.8 ± 89.1	387.1 ± 117.1	0.201
CPB time (min)	269.9 ± 52.8	227.3 ± 67.5	0.121
Aortic cross clamp time (min)	172.4 ± 36.7	144.5 ± 34.6	0.082
Data are expressed in numbers or mean ± standard deviation			
Abbreviations: AF, atrial fibrillation; BMI, body mass index; CPB, cardiopulmonary bypass; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; MVP, mitral valve prolapse; MVR, mitral valve regurgitation; NO, nitric oxide; PCWP, pulmonary capillary wedge pressure; NYHA, New York Heart Association; RAP, right atrial pressure; TRPG, tricuspid regurgitation pressure gradient			

Intraoperative and postoperative management

After induction of general anesthesia, a Swan-Ganz catheter was inserted through the internal jugular vein, and pulmonary artery and central venous pressures were continuously measured in all patients. The pulmonary artery catheter was usually removed on the third postoperative day. Systemic arterial pressure was monitored with an arterial pressure line placed in the radial artery.

Immediately after admission to the intensive care unit (ICU), hemodynamics was monitored, and blood gas analysis was performed. NO inhalation therapy was started for patients with mPAP > 25 mmHg. NO for inhalation used in the study was supplied by INOflo (Mallinckrodt Pharmaceuticals, Tokyo, Japan). The initial dose of NO was 20 ppm. About 12 h after the initiation of therapy, NO was gradually tapered (from 20 to 10, 5, 2, and 1 ppm) if the patient's hemodynamics were stable. Then, NO inhalation therapy was stopped temporarily (on-off test). If there is no worsening of PH again, NO inhalation therapy was terminated before extubation. The maximum dose of NO was 20 ppm.

Primary and secondary outcomes

The primary outcome of this study was the length of ICU stay. The secondary outcomes included preoperative echocardiography and catheterization findings, operative procedure including concomitant surgery (aortic valve replacement and coronary artery bypass grafting), operative time, cardiopulmonary bypass (CPB) time, aortic cross-clamp time, postoperative Swan-Ganz catheter findings, and postoperative intubation time.

Statistical analysis

The data were processed using IBM SPSS Statistics software, version 22 (IBM, Armonk, NY, USA). All continuous values are expressed as mean $\pm$ standard deviation or median and interquartile range. Categorical variables are expressed as the number and frequency (%).

For comparison of continuous data, the Mann-Whitney U test was performed. For comparison of categorical data, a chi-square test was performed. Differences were considered statistically significant at $P < 0.05$.

Results

Table 1 shows patient characteristics. There was no significant difference in the mean age (62.6 ± 10.3 [NO group] vs 64.9 ± 11.0 [non-NO group] years; $P = 0.622$) and number of patients who underwent concomitant surgery (8 (61.5%) vs 3 (27.2%); $P = 0.093$) between the NO and non-NO groups, respectively. For the NO and non-NO groups, the systolic tricuspid regurgitation pressure gradient (TRPG) was 45.1 ± 15.4 and 27.5 ± 8.8 mmHg ($P = 0.017$), right atrial pressure was 12.6 ± 7.2 and 4.4 ± 2.3 mmHg ($P = 0.022$), and pulmonary capillary wedge pressure was 29.9 ± 14.9 and 16.6 ± 5.0 mmHg ($P = 0.022$), respectively, with the NO group showing significantly higher values. The mPAP was higher in the NO group, but this difference was not significant (41.1 ± 14.4 vs 28.9 ± 10.0 ; $P = 0.89$). There was no significant difference between the two groups in operative time ($P = 0.201$) or aortic cross-clamp time ($P = 0.082$). However, there were significantly more MVR cases in the NO group than in the non-NO group (6 vs 0; $P = 0.016$).

Table 2 shows the patients' postoperative data. There was no significant difference in mPAP between the NO and non-NO groups immediately after surgery (30.7 ± 4.8 vs 28.6 ± 3.7 mmHg; $P = 0.269$) before NO use, and at 24 hours after surgery (24.7 ± 3.2 vs 21.6 ± 6.6 mmHg; $P = 0.2$). There was no significant

difference in the cardiac index either immediately after surgery (3.3 ± 0.4 vs 2.9 ± 0.4 L/min/m²; $P = 0.48$) or at 24 hours after surgery (3.2 ± 0.5 vs 2.8 ± 0.5 mmHg; $P = 0.08$) between the NO and non-NO groups. Similarly, there was no significant difference in postoperative tracheal intubation time (44.0 ± 26.7 vs 23.5 ± 23.8 hours, $P = 0.085$) and ICU stay (6.5 ± 2.4 vs 6.7 ± 6.9 days, $P = 0.935$) between the two groups. There were no postoperative deaths and no adverse events attributable to the use of NO.

Table 2
Postoperative data

Variable	NO group	Non-NO group	P-Value
Immediately after surgery			
CVP	10.8 ± 3.8	10.9 ± 3.8	0.969
mPAP (mmHg)	30.7 ± 4.8	28.6 ± 3.7	0.269
Cardiac index (L/min/m ²)	3.3 ± 0.5	2.9 ± 0.5	0.48
P/F	257.9 ± 76	299.8 ± 123.6	0.363
At 24 hours after surgery			
CVP	8.5 ± 3.9	7.4 ± 3.9	0.515
mPAP (mmHg)	24.7 ± 3.2	21.6 ± 6.6	0.2
Cardiac index (L/min/m ²)	3.3 ± 0.5	2.9 ± 0.5	0.08
P/F	313.0 ± 74.1	294.2 ± 70.9	0.549
Tracheal intubation duration (hours)	43.9 ± 26.7	23.5 ± 23.8	0.085
ICU stay (day)	6.5 ± 2.4	6.7 ± 6.9	0.935
Data are presented as mean $\pm$ standard deviation			
Abbreviations: CVP, central venous pressure; ICU, intensive care unit; mPAP, mean pulmonary artery pressure; P/F			

Discussion

This study evaluated the clinical outcomes of 24 adult patients who developed PH after mitral valve surgery and found that NO inhalation did not decrease tracheal intubation time or ICU stay and that no in-hospital deaths occurred.

NO inhalation therapy has been used for many years, mainly in pediatric cardiac surgery. Although NO inhalation therapy improves hemodynamics after pediatric cardiac surgery, Wong and other researchers reported that NO inhalation therapy does not reduce ICU length of stay nor improve mortality [9]. In recent years, NO inhalation therapy has gained popularity in the field of adult cardiac surgery. A meta-analysis

of randomized controlled studies showed that NO inhalation therapy had no or minimal benefit in patients with PH after pediatric and adult cardiac surgeries [10]. Our results support these findings. In our study, the NO group had higher preoperative TRPG, right atrial pressure, and pulmonary capillary wedge pressure than the non-NO group. The NO group included more complex surgical cases requiring concomitant surgery, such as aortic valve replacement. Nevertheless, the postoperative course of the two groups, including duration of tracheal intubation and length of ICU stay did not differ. After NO inhalation, the mPAP decreased and the cardiac index increased, but these values did not differ significantly from those of the non-NO group. We believe that since the NO group included more severe PH cases than the non-NO group, NO inhalation therapy worked well, leading to the same postoperative course and hemodynamics. There are limited Asian data, including those in Japan, on NO inhalation therapy after adult cardiac surgery. Nakane et al. reported that, in adult valvular surgery, NO inhalation therapy improved PH and postoperative respiratory, coagulation, and renal function, but it did not reduce intubation time or ICU length of stay [8]. Our study is unique in that we included only mitral surgery cases to decrease the variability in surgical procedures as much as possible. Although patients with mitral stenosis may develop PH postoperatively, it has been reported that patients with mitral regurgitation developed PH at a rate of 20%-30% after mitral valve surgery [11–13]. Therefore, it is important to study PH and NO levels after mitral valve surgery. We believe that sub-analyses of more severe PH (mPAP > 30 mmHg) cases are necessary because NO worked well in some cases in this study. Optimal NO therapeutic strategies should be reconsidered to establish an appropriate treatment for PH after mitral valve surgery that will shorten intubation time and length of ICU stay. In the field of pediatric cardiac surgery, Tominaga et al. reported that the duration of postoperative intubation and the length of hospital stay were shorter in patients who received NO inhalation therapy with a high-flow nasal cannula after extubation than in those who did not [14]. The report describes NO inhalation therapy based on the Fontan procedure, in which the use of NO via a high-flow nasal cannula after extubation shortened the tracheal intubation time in half. We have started this treatment strategy for the delivery of inhaled NO by using a high-flow nasal cannula after extubation in adults. In addition, the study of a new NO inhalation strategy is under consideration.

This study has some limitations. This was a single-center retrospective study with a small number of patients. There was a selection bias because the NO group included more severe cases than the non-NO group. Therefore, further multicenter clinical studies are required.

Conclusion

Our results suggest that NO inhalation therapy does not shorten postoperative intubation and ICU stay in the postoperative management of adult patients with PH after mitral valve surgery. A larger number of cases and reconsideration of the NO postoperative treatment strategy are necessary in the future.

Abbreviations

AF

atrial fibrillation
BMI
body mass index
CPB
cardiopulmonary bypass
ICU
intensive care unit
LVEF
left ventricular ejection fraction
mPAP
mean pulmonary artery pressure
MVP
mitral valve prolapse
MVR
mitral valve regurgitation
NO
nitric oxide
PCWP
pulmonary capillary wedge pressure
PH
pulmonary hypertension
NYHA
New York Heart Association
RAP
right atrial pressure
TRPG
tricuspid regurgitation pressure gradient

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Institutional Review Board of Hirosaki University Hospital [approval number: 2021-146]. All methods were performed in accordance with the Declaration of Helsinki. All patients got written informed consent and agreed the publication.

Consent for publication Not applicable.

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article.

Competing interests

Not applicable

Funding

There are no grant numbers or funding information to disclose.

Author's contributions

HS collected the data, conceived and wrote the manuscript. RK designed this study. RK, KD and MM reviewed the manuscript. All authors read and approved the final manuscript.

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