Author Contributions

Conceived and designed the experiments: K. Murase K. Mori KC. Performed the experiments: K. Murase CY KA YC MA YH. Analyzed the data: K. Murase K. Mori. Contributed reagents/materials/analysis tools: YT KT T. Handa T. Hitomi TO MM. Wrote the paper: K. Murase K. Mori KC.

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Flexible Positive Airway Pressure Improves Treatment Adherence Compared with Auto-adjusting PAP

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Study Objectives: There are no clinical data comparing adherence and quality of life between auto-adjusting positive airway pressure (APAP) and two different flex positive airway pressure (PAP) devices (A-Flex, C-Flex) in patients with obstructive sleep apnea (OSA).

Design and Setting: Ninety-three patients in whom OSA was newly diagnosed were randomly assigned to receive 3 mo of APAP (n = 31), APAP with C-Flex (n = 31), or APAP with A-Flex (n = 31). Objective adherence was determined after 3 mo of CPAP treatment, and the Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), and Calgary Sleep Apnea Quality of Life Index (SAQLI) were examined at baseline and after 3 mo. After 3 mo, patients in the APAP with A-Flex group and those in the APAP with C-Flex group were crossed over and those in the APAP group were switched to A-Flex for an additional 3 mo.

Measurements and Results: The groups were similar demographically. Treatment adherence during the first 3 mo was significantly greater in the APAP with C-Flex group (APAP with C-Flex: 5.19 ± 1.84 h/night versus APAP: 3.96 ± 1.66 h/night versus APAP with A-Flex: 4.27 ± 2.12 h/night, P = 0.04). There was a significant improvement in two of four of the SAQLI domain scores and in the ESS and PSQI in the APAP with C-Flex group. Adherence significantly improved among the poor compliers (< 4 h/night of use) in the APAP group after change to APAP with A-Flex (P = 0.01).

Conclusions: Of these three modes of PAP delivery, adherence was greatest with APAP with C-Flex.

Clinical Trial Registration: URL: http://www.clinicaltrials.gov. Unique identifier: NCT00873977.

Keywords: A-Flex, C-Flex, continuous positive airway pressure, obstructive sleep apnea, treatment adherence

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INTRODUCTION

Continuous positive airway pressure (CPAP), the mainstay of treatment for moderate to severe obstructive sleep apnea (OSA), has been shown to normalize sleep architecture, reduce daytime sleepiness, enhance daily function, and decrease cardiovascular events.[1-3] Although CPAP is a highly effective treatment, adherence is suboptimal. To improve patient comfort and treatment adherence, various CPAP modalities have been developed. Auto-adjusting positive airway pressure (APAP) devices continuously adjust the pressure in real time according to that required to maintain upper airway patency. It has been reported that treatment compliance with APAP was equivalent to that with fixed PAP therapy.[4-6] Adherence with flexible CPAP (C-Flex; Philips Respironics, Murraysville, PA, USA), which flexes airway pressure on exhalation and inhalation on a breath-by-breath basis to reduce the work of breathing, has been reported to be significantly better compared with fixed PAP therapy in one study.[7] However, other studies reported that adherence with C-Flex and fixed positive airway pressure (PAP) therapy was similar.[8-11] To our knowledge, a comparison of treatment adherence of APAP with APAP with C-Flex has not been reported. Because the use of APAP for the treatment of OSA has increased, a prospective randomized study comparing APAP to APAP with C-Flex with respect to CPAP adherence is needed. In addition, a new CPAP device (A-Flex; Philips Respironics) is designed to further improve breathing comfort. Like C-Flex, A-Flex flexes pressure at the beginning of exhalation but also has a fixed 2 cm H_2O pressure difference between inspiration and expiration.

The aim of this study was to compare objective adherence to CPAP between APAP, APAP with C-Flex, and APAP with A-Flex over an initial 3-mo period. We also investigated daytime sleepiness, sleep quality, and quality of life (QOL). Additionally, after 3 mo, patients in the APAP with A-Flex group and the APAP with C-Flex groups were crossed over to use the alternate mode (C-Flex or A-Flex) to compare adherence. In addition, the APAP group was crossed over to the A-Flex for these final 3 mo.

METHODS

Study Participants

Patients in whom OSA was newly diagnosed (apnea-hypopnea index [AHI] > 20) were enrolled in the current study according to the Japanese Health Insurance System. Patients were excluded if they were younger than 20 y, had a major medical or psychiatric condition that would interfere with the demands of the study and adherence to PAP, or had ever used CPAP therapy. This study was approved by the Ethics Committee of Kyoto University. All patients gave written informed consent to participate.

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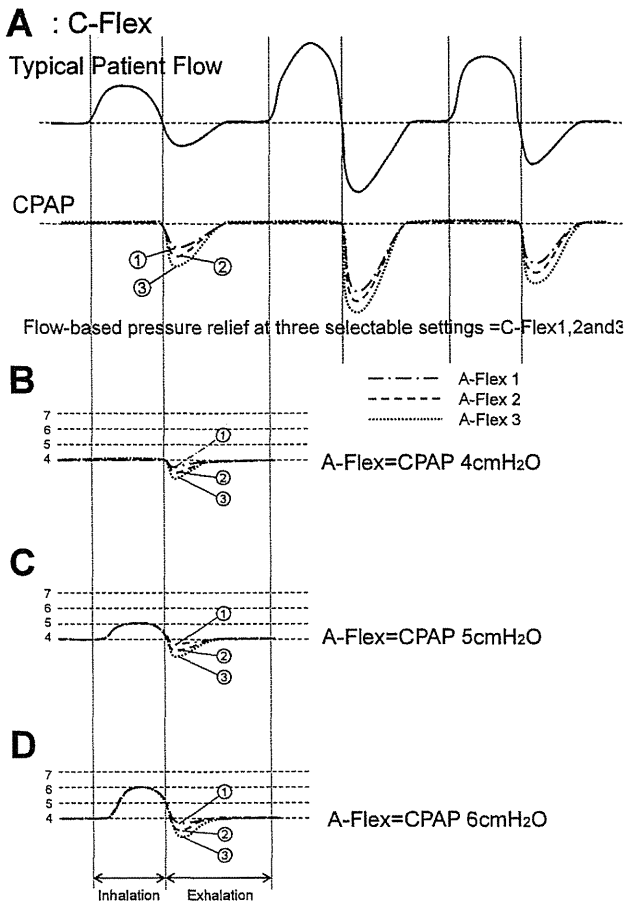

Figure 1—(A) C-Flex pressure relief reduced pressure at the beginning of exhalation and returned to the therapeutic pressure just before inhalation. The level of pressure relief varies based on the patient's expiratory flow and which of the three C-Flex settings (1, 2, and 3) has been selected. **(B-D)** A-Flex has the same function as C-Flex during expiration. At 4 cm H_2O CPAP, the A-Flex PAP machine is same as the C-Flex machine PAP **(B)**. At 5 cm H_2O CPAP, the A-Flex PAP machine can provide 1 cm H_2O pressure support at the inspiration **(C)**. From 6 or more cm H_2O CPAP, A-Flex machine can make 2 cm H_2O pressure supports at the inspiration **(D)**.

C-Flex and A-Flex PAP Machines

C-Flex pressure relief was developed to make CPAP therapy more comfortable by reducing pressure at the beginning of exhalation and returning to the therapeutic pressure just before inhalation (Figure 1A). The level of pressure relief varies based on the patient's expiratory flow and which of the three C-Flex settings (1, 2, and 3) has been selected.

Like C-Flex, A-Flex provides flow-based pressure relief at the beginning of exhalation. At 4 cm H_2O CPAP, the A-Flex PAP machine is the same as the C-Flex machine PAP (Figure 1B). However, at 5 cm H_2O CPAP, the A-Flex PAP machine can provide 1 cm H_2O pressure support at inspiration (Figure 1C). From 6 cm or more H_2O CPAP, the A-Flex machine can provide 2 cm H_2O pressure support at inspiration (Figure 1D). A-Flex has the same function as C-Flex during expiration (Figure 1B-D).

Study Design

The study was a randomized single-blind (patients blinded) crossover trial of APAP versus APAP with C-Flex (set to dip level 3) versus APAP with A-Flex (set to dip level 3). The dip level is the level of pressure reduction during expiration, and dip level 3 is the greatest pressure reduction during expiration. Data were collected at baseline and after 3 and 6 mo of PAP treatment. At baseline, we recorded the patients' demographic characteristics and polysomnographic data. In addition, subjective sleepiness, sleep quality, and health-related QOL were measured using the Epworth Sleepiness Scale (ESS),[12] Pittsburgh Sleep Quality Index (PSQI),[13] and Calgary Sleep Apnea Quality of Life Index (SAQLI).[14,15] The SAQLI consists of five domains: daily functioning (domain A), social interactions (domain B), emotional functioning (domain C), symptoms (domain D), and treatment-related symptoms (domain E). The total SAQLI score for domains A through D was obtained before and after CPAP treatment, and the score for domain E was factored in after the patient received CPAP. CPAP titration was performed with autotitration during full-night polysomnography (PSG) attended by sleep technicians and the pressure range was between 4 and 20 cm H_2O. For CPAP titration, each patient underwent full-night PSG on the allocated CPAP mode (i.e., APAP with C-Flex group underwent full-night PSG on APAP with C-Flex). The attending technicians checked for abnormal movements of the titrated PAP machine. However, they could not find any trouble during this trial.

The primary outcome was objective adherence after 3 mo of CPAP treatment. Objective adherence was downloaded from the memory card (Encore Pro Smartcard; Philips-Respironics) located in the PAP device. Secondary outcomes were ESS, PSQI, and SAQLI at 3 mo after the beginning of CPAP treatment.

Additionally, after 3 mo of PAP treatment, the APAP with A-Flex group and the APAP with C-Flex group were crossed over to the alternate mode (C-Flex or A-Flex) and the APAP group was switched to A-Flex for an additional 3 mo. The evaluations performed at 3 mo were repeated 6 mo after the start of CPAP treatment.

Polysomnography

The diagnosis of OSA was confirmed by PSG (SomnoStar Pro, Cardinal Health, Dublin, OH, USA), which was started at 22:00 and ended at 6:00 the following morning. Surface electrodes were attached using standard techniques to obtain an electrooculogram, electromyogram of the chin, and 12-lead electroencephalograph. Sleep stages were defined according to the criteria of Rechtschaffen and Kales.[16] Ventilation/respiratory effort was monitored by inductive plethysmography (Respitrace QDC, Viasys Healthcare, Palm Springs, CA, USA). Airflow was monitored by a nasal pressure transducer (PTAFlite, Pro-Tech Services Inc., Mukilteo, WA, USA) and supplemented by an oronasal thermal sensor (Sleepmate Technologies, Midlothian, VA, USA). Arterial oxygen saturation (SaO_2) was monitored continuously with a pulse oximeter (Adult Flex System, Nonin Medical, Plymouth, MN, USA).

Apnea was defined as the complete cessation of airflow and hypopnea as a clear decrease in airflow of 50% or more lasting for 10 sec or more accompanied by a decrease in SpO_2 of at least 3% and/or associated with arousal.[17] All AHI values were expressed as the number of episodes of apnea and hypopnea per h over the total sleep time. The lowest SpO_2 during sleep was calculated in each patient.

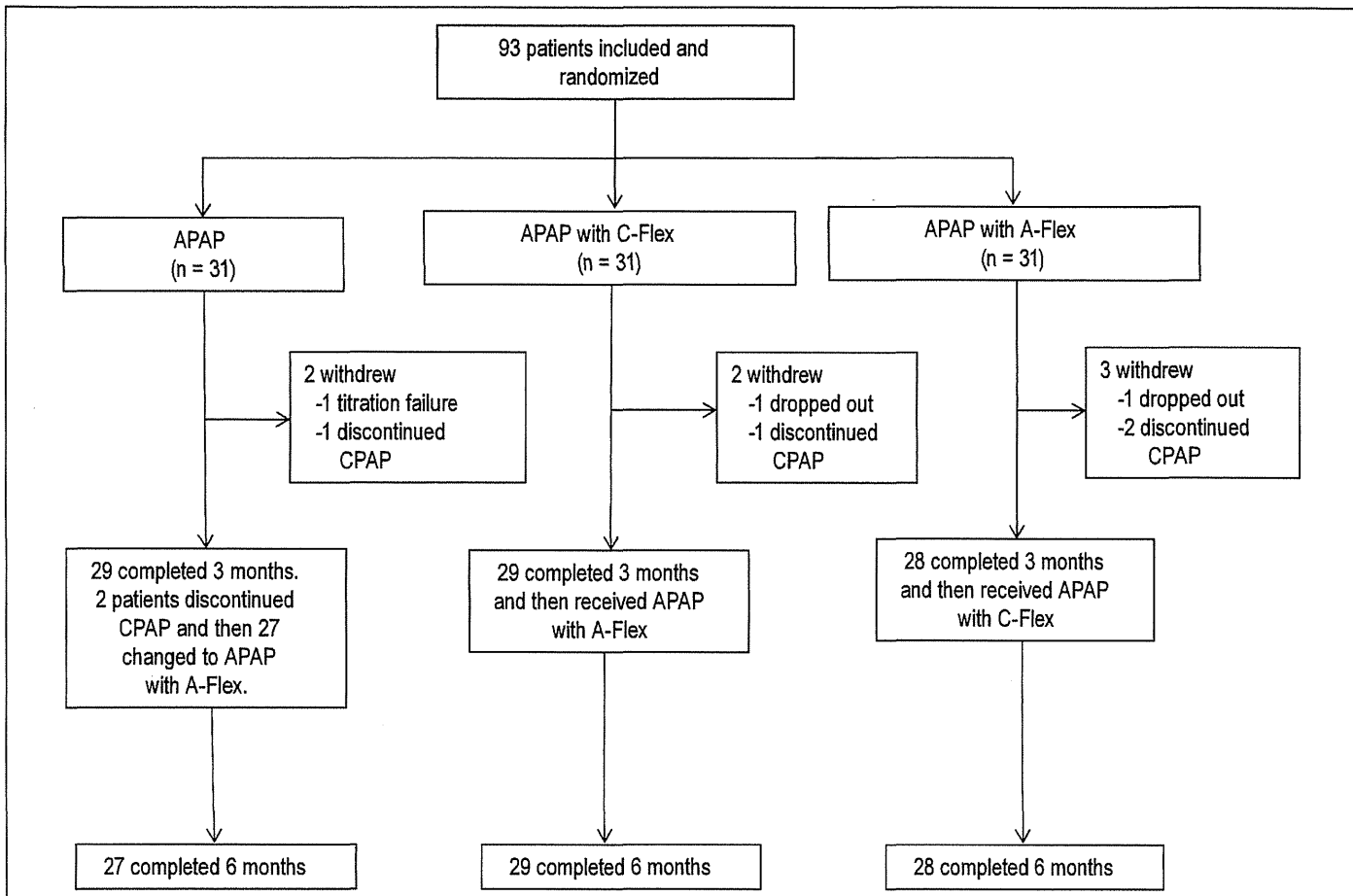

Figure 2—Flow chart of the study population. APAP, auto-adjusting positive airway pressure; CPAP, continuous positive airway pressure.

Randomization

This study was randomized via blinded envelope prior to the beginning of the study.

Power Analysis

Based on a previous study,[7] differences of 1 h/night of PAP adherence between each group were decided to be clinically significant, and standard deviation (SD) of 1.5 h/night was expected. The sample size was set to achieve 80% power at a 5% significance level. The calculated sample size in each group was 36 patients.

Statistical Analysis

Data analysis was conducted using a statistical software program (Statview, version 5.0; SAS Institute Inc., Cary, NC, USA). Data were expressed as mean ± SD or absolute numbers and percentages in each study group. The patients' demographic characteristics, polysomnographic data, responses to three questionnaires at baseline and after 3 mo of CPAP treatment, and adherence after 3 mo of CPAP treatment were compared among the three groups using a one-way analysis of variance. When a significant difference was observed, we used the Bonferroni/Dunn method to identify where the differences were significant. For categorical variables, the χ^2 test was used. Within the group, comparisons of adherence (3 mo versus 6 mo) or of results from the three questionnaires (baseline versus 3 mo, 3 mo versus 6 mo) were analyzed using a paired *t* test. In all analyses, $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Assessments

Figure 2 shows the study flow chart. Ninety-three patients in whom OSA was newly diagnosed were randomly assigned to receive 3 mo of APAP (n = 31), APAP with C-Flex (n = 31), or APAP with A-Flex (n = 31). During the first 3 mo, two patients withdrew from the APAP group (one discontinued PAP, one had Cheyne-Stokes breathing during PAP titration), two patients withdrew from the APAP with C-Flex group (one dropped out, one discontinued PAP), and three patients withdrew from the APAP with A-Flex group (one dropped out, two discontinued PAP). Data on patients who dropped out during the first 3 mo were excluded from the analysis.

Tables 1 and 2 summarize baseline characteristics and polysomnographic data, respectively, on study participants. Patients were predominantly male, middle-aged, and had moderate to severe OSA. Neither baseline characteristics nor polysomnographic data differed among the three groups.

Effects of CPAP Treatment on PSG Variables

Table 3 shows the polysomnographic data on the PAP night. Compared with the baseline PSG, significant changes in polysomnographic variables such as the AHI and arousal index were

Table 1—Baseline characteristics of study participants[a]

	All (n = 86)	APAP (n = 29)	APAP with C-Flex (n = 29)	APAP with A-Flex (n = 28)	P value
Age (y)	59.3 ± 10.8	56.9 ± 8.8	61.0 ± 10.7	59.8 ± 12.6	0.33
Sex (male/female)	72/14	25/4	24/5	23/5	0.90
BMI (kg/m^2)	27.1 ± 4.7	27.4 ± 5.5	27.4 ± 4.2	26.6 ± 4.4	0.77
Living alone	11 (12.8)	6 (20.7)	3 (10.3)	2 (7.1)	0.29
Hypertension	50 (58.1)	14 (48.3)	20 (69.0)	16 (57.1)	0.28
Dyslipidemia	42 (48.8)	14 (48.3)	13 (44.8)	15 (53.6)	0.80
Diabetes mellitus	27 (31.4)	11 (37.9)	7 (24.1)	9 (32.1)	0.52
ESS	9.2 ± 4.4	9.5 ± 4.6	9.2 ± 4.5	8.9 ± 4.3	0.88

[a]Mean ± SD or number (%). APAP, auto-adjusting positive airway pressure; BMI, body mass index; ESS, Epworth Sleepiness Scale.

Table 2—Baseline polysomnographic data on study participants[a]

	APAP (n = 29)	APAP with C-Flex (n = 29)	APAP with A-Flex (n = 28)	P value
Sleep efficiency, %	75.1 ± 11.9	72.2 ± 12.7	70.6 ± 15.0	0.43
S1, %	26.6 ± 13.7	26.8 ± 14.2	27.2 ± 14.2	0.98
S2, %	52.0 ± 11.8	54.2 ± 13.5	52.7 ± 11.0	0.78
S3/4, %	6.4 ± 8.9	4.4 ± 6.2	6.3 ± 8.6	0.57
REM, %	15.0 ± 5.0	14.6 ± 5.0	13.9 ± 6.7	0.73
Arousal, events/h	34.1 ± 12.4	36.3 ± 14.7	36.2 ± 14.2	0.79
Central apnea, events/h	2.9 ± 5.0	2.3 ± 3.7	3.3 ± 5.2	0.69
AHI, events/h	40.8 ± 12.4	43.3 ± 15.2	45.7 ± 15.9	0.46
Mini SpO_2 (%)	77.0 ± 7.4	75.2 ± 12.8	78.4 ± 6.5	0.44
SpO_2 < 90% (% TST)	16.2 ± 14.9	14.9 ± 16.6	18.4 ± 23.2	0.77

[a]Mean ± SD or number (%). AHI, apnea-hypopnea index; APAP, auto-adjusting positive airway pressure; REM, rapid eye movement; SpO_2, percutaneous oxygen saturation; TST, total sleep time.

Table 3—Polysomnographic data on study participants upon CPAP titration[a]

	APAP (n = 29)	APAP with C-Flex (n = 29)	APAP with A-Flex (n = 28)	P value
Sleep efficiency, %	77.2 ± 11.4	76.5 ± 7.9	72.0 ± 11.5	0.14
S1, %	15.7 ± 7.7	16.2 ± 9.9	16.9 ± 9.5	0.89
S2, %	57.3 ± 8.0	60.7 ± 11.8	57.1 ± 9.3	0.29
S3/4, %	6.9 ± 8.3	4.4 ± 5.3	6.6 ± 7.3	0.34
REM, %	20.1 ± 5.0	18.7 ± 6.1	19.5 ± 5.8	0.63
Arousal, events/h	20.2 ± 9.0	19.7 ± 9.4	20.7 ± 9.7	0.93
Central apnea, events/h	1.4 ± 1.6	1.4 ± 1.8	2.5 ± 2.9	0.09
AHI, events/h	4.0 ± 3.7	3.8 ± 4.7	6.0 ± 4.5	0.11
Mini SpO_2 (%)	90.2 ± 3.9	87.5 ± 9.4	88.8 ± 4.5	0.27
SpO_2 < 90% (% TST)	0.2 ± 0.6	2.1 ± 6.2	1.2 ± 4.8	0.30

[a]Mean ± SD or number (%). AHI, apnea-hypopnea index; APAP, auto-adjusting positive airway pressure; CPAP, continuous positive airway pressure; REM, rapid eye movement; SpO_2, percutaneous oxygen saturation; TST, total sleep time.

noted in all three groups. There were no significant differences among the three groups in the polysomnographic data on CPAP titration. Also, the number of patients who used hypnotic agents during CPAP titration did not differ significantly among the three groups (APAP with C-Flex: 7 of 29, 24.4% versus APAP: 11 of 29, 37.9% versus APAP with A-Flex: 9 of 28, 32.1%; P = 0.52).

After 3 mo of treatment, the 90th percentile PAP, leak, and mean AHI were downloaded and recorded from the memory card located in the PAP device. There were no significant differences among the three groups in terms of residual AHI (APAP with C-Flex: 3.4 ± 2.2 events/h versus APAP: 3.5 ± 2.0 h/night versus APAP with A-Flex: 4.6 ± 2.9 h/night; P = 0.11), 90th percentile PAP (APAP with C-Flex: 8.4 ± 1.7 cm H_2O versus APAP: 8.2 ± 1.3 cm H_2O versus APAP with A-Flex: 8.8 ± 1.7 cm H_2O; P = 0.32), or 90th percentile leak (APAP with C-Flex: 45.7 ± 7.0 L/min versus APAP: 49.7 ± 13.1 L/min versus APAP with A-Flex: 46.5 ± 11.5 L/min; P = 0.34).

Primary Outcome: Adherence Over 3 Mo

Figure 3 shows a comparison among the three groups with regard to adherence to CPAP treatment over a 3-mo period. Median adherence was significantly greater in the APAP with C-Flex group, especially compared with the APAP group (APAP with C-Flex, n = 29: 5.19 ± 1.84 h/night versus APAP, n = 292 9: 3.96 ± 1.66 h/night versus APAP with A-Flex, n = 28: 4.27 ± 2.12 h/night; P = 0.04). In the *post hoc* analysis, adherence to APAP with C-Flex was significantly greater in comparison with APAP (P = 0.01). In addition, there were significant differences among the groups in percentage of days PAP was used (APAP with C-Flex: 91.9 ± 10.6% versus APAP: 79.4 ± 21.8% versus APAP with A-Flex: 82.5 ± 22.9%; P = 0.04) but not in percentage of days PAP used > 4 h (APAP with C-Flex: 66.6 ± 29.8% versus APAP: 54.8 ± 27.9% versus APAP with A-Flex: 57.6 ± 32.7%; P = 0.30). *Post hoc* testing revealed that the percentage of days PAP was used in the APAP with C-Flex group was significantly higher than in the APAP group (P = 0.02).

Secondary Outcomes: ESS, PSQI, and SAQLI After 3 Mo of CPAP Treatment

Table 4 details the effect of CPAP treatment on ESS, PSQI, and SAQLI in the three groups. For the entire group, ESS (P = 0.004) and domain A (P = 0.04), domain C (P = 0.006), and domain D (P < 0.0001) in the SAQLI questionnaire were significantly improved after 3 mo of PAP. Differences in responses to these three questionnaires were not statistically significant among the three groups at baseline, but after 3 mo of PAP treatment differences were noted. ESS and PSQI scores were significantly improved using APAP with C-Flex (ESS, 9.2 ± 4.5 to 7.3 ± 3.8, P = 0.01; PSQI, 7.2 ± 3.6 to 6.1 ± 2.8, P = 0.04), whereas significant improvements with APAP and APAP with A-Flex were not observed. In the SAQLI questionnaire, two domains were significantly improved and the other two domains trended toward improvement in the APAP with C-Flex group. On the other hand, the APAP and APAP with A-Flex groups had a significant improvement only in one domain of the SAQLI. However, as to the changes in the values for ESS, PSQI, and SAQLI among the three groups between before and after 3 mo of CPAP, the APAP with C-Flex group tended to have greater improvement in PSQI (P = 0.08) than the other two groups, whereas differences in the ESS and SAQLI were not significantly different among the three groups (Table 5).

Crossover in CPAP Mode

After 3 mo, two patients discontinued PAP treatment in the APAP group. The change in the CPAP mode did not have a significant effect on PAP adherence in any group (from APAP to APAP with A-Flex, n = 27, from 4.15 ± 1.51 h/night to 4.12 ± 1.16 h/night, P = 0.89; from APAP with C-Flex to APAP with A-Flex, n = 29, from 5.19 ± 1.84 h/night to 4.95 ± 1.94 h/night, P = 0.17; from APAP with A-Flex to APAP with C-Flex, n = 28, from 4.27 ± 2.12 h/night to 4.15 ± 1.99 h/night, P = 0.56). Although the group of patients moving from APAP to APAP with A-Flex tended to show improvement in domain B of the SAQLI (P = 0.07), ESS, PSQI, and SAQLI scores did not significantly change in any group (results not shown).

In a subgroup analysis of poor compliers (< 4 h/night of PAP use), there was a significant increase in PAP adherence in the patients moving from APAP to APAP with A-Flex (n = 10, from 2.55 ± 0.76 h/night to 3.20 ± 0.85 h/night, P = 0.01) (Figure 4). In contrast, adherence did not change between 3 and 6 mo in the other groups.

DISCUSSION

The current study is the first to show a significant superiority of APAP with C-Flex on treatment adherence during the first 3 mo of use compared with APAP. Also, only patients using APAP with C-Flex had a significant improvement in subjective sleepiness and sleep quality. These results suggest that APAP with C-Flex may be a superior CPAP modality for the initial treatment of moderate to severe OSA.

To date, it has not been shown that PAP adherence can be improved by using different pressure applications of PAP. A meta-analysis of a number of published studies comparing

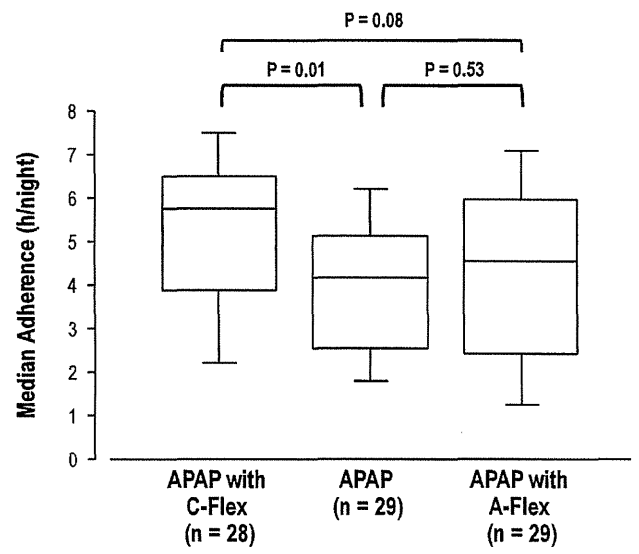

Figure 3—CPAP adherence with APAP with C-Flex, APAP, and APAP with A-Flex after 3 mo of treatment. Data are shown as a bow-whisker plot with median and 25th percentile of CPAP adherence. APAP, auto-adjusting positive airway pressure.

Table 4—Analysis of health-related quality of life and sleep related questionnaires[a]

	APAP (n = 29)			C-Flex (n = 29)			A-Flex (n = 28)		
	BL	3 mo	P value	BL	3 mo	P value	BL	3 mo	P value
ESS	9.5 ± 4.6	8.2 ± 4.0	0.12	9.2 ± 4.5	7.3 ± 3.8[b]	0.01	8.9 ± 4.3	8.1 ± 4.3	0.34
PSQI	6.0 ± 2.5	6.1 ± 2.9	0.72	7.2 ± 3.6	6.1 ± 2.8[b]	0.04	6.3 ± 3.2	5.8 ± 2.3	0.21
SAQLI									
Domain A	5.6 ± 1.1	5.7 ± 1.2	0.56	5.2 ± 1.3	5.5 ± 1.1[c]	0.08	5.4 ± 1.1	5.6 ± 1.3	0.37
Domain B	5.6 ± 0.9	5.7 ± 1.0	0.70	5.3 ± 1.1	5.7 ± 1.0[b]	0.02	5.8 ± 1.1	5.8 ± 0.8	0.89
Domain C	5.1 ± 0.9	5.3 ± 1.1	0.11	4.9 ± 1.0	5.2 ± 1.0[c]	0.06	5.1 ± 0.9	5.3 ± 0.9	0.26
Domain D	2.7 ± 1.1	3.7 ± 1.4[b]	0.0009	2.6 ± 1.2	3.5 ± 1.6[b]	0.001	2.3 ± 1.2	3.8 ± 1.7[b]	< 0.0001
Domain E		4.7 ± 1.2			4.3 ± 1.1			4.6 ± 1.2	
Total	4.8 ± 0.7	4.7 ± 1.2	0.71	4.5 ± 0.8	4.5 ± 1.1	0.83	4.7 ± 0.7	4.8 ± 1.1	0.65

[a]Mean ± SD. [b]P < 0.05 versus BL. [c]P < 0.10 versus BL. APAP, auto-adjusting positive airway pressure; BL, baseline; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; SAQLI, Calgary Sleep Apnea Quality of Life Index. Domain A, daily functioning; Domain B, social interactions; Domain C, emotional functioning; Domain D, symptoms; Domain E, treatment-related symptoms.

APAP with fixed CPAP revealed that there was no difference between the two modalities regarding subjective sleepiness and adherence to PAP.[4,18] The difficulty of exhaling against a fixed positive pressure is a common complaint when using CPAP, so C-Flex was developed, which reduces pressure at the beginning of exhalation and increases pressure to a level determined to be therapeutic for the latter part of exhalation. Aloia et al.[7] demonstrated that use of a C-Flex device provided a significant improvement in CPAP adherence (1.7 h/night of additional use after a 12-wk follow-up period compared with a fixed PAP therapy). However, this study was not a randomized trial. Thereafter, Marshall et al.[19] reported that in a 4-wk randomized study there was a trend toward greater CPAP adherence with C-Flex compared with fixed PAP therapy (C-Flex, 4.7 ± 2.9 h/night versus fixed PAP, 3.0 ± 2.1 h/night), but the difference was not statistically significant because of the small sample size. A meta-analysis also found that C-Flex does not provide any significant benefit over fixed PAP in terms of treatment adherence.[20]

Table 5—Changes in values of ESS, PSQI, and SAQRI among the three groups from before and after 3 mo of CPAP[a]

	APAP (n = 29)	APAP with C-Flex (n = 29)	APAP with A-Flex (n = 28)	P value
ESS	-1.3 ± 4.3	-2.2 ± 3.9	-0.8 ± 4.3	0.45
PSQI	0.2 ± 2.5	-1.3 ± 2.9	-0.5 ± 2.1	0.08
SAQLI				
Domain A	0.1 ± 0.8	0.1 ± 1.7	0.2 ± 1.0	0.97
Domain B	0.1 ± 0.7	0.1 ± 1.5	0.03 ± 1.1	0.94
Domain C	0.2 ± 0.6	0.1 ± 1.2	0.2 ± 0.7	0.89
Domain D	1.0 ± 1.4	0.8 ± 1.4	1.5 ± 1.7	0.26
Domain E	–	–	–	–
Total	-0.1 ± 0.9	-0.1 ± 1.3	0.1 ± 1.0	0.73

[a]Mean ± SD. APAP, auto-adjusting positive airway pressure; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; SAQLI, Calgary Sleep Apnea Quality of Life Index.

In the current study, we confirmed that APAP with C-Flex was associated with significantly greater CPAP adherence than APAP. Many studies suggested that APAP reduces the mean PAP requirements, which are thought to influence CPAP adherence.[4-6] C-Flex is designed to flexibly deliver pressure on a breath-by-breath basis by adjusting pressure within exhalation, which may be a more important variable for treatment adherence than the overall PAP level. This C-Flex technology may be responsible for the significant superiority of treatment adherence with APAP with C-Flex compared with APAP. Our study also showed that adherence in the APAP with A-Flex group did not improve after changing to the use of APAP with

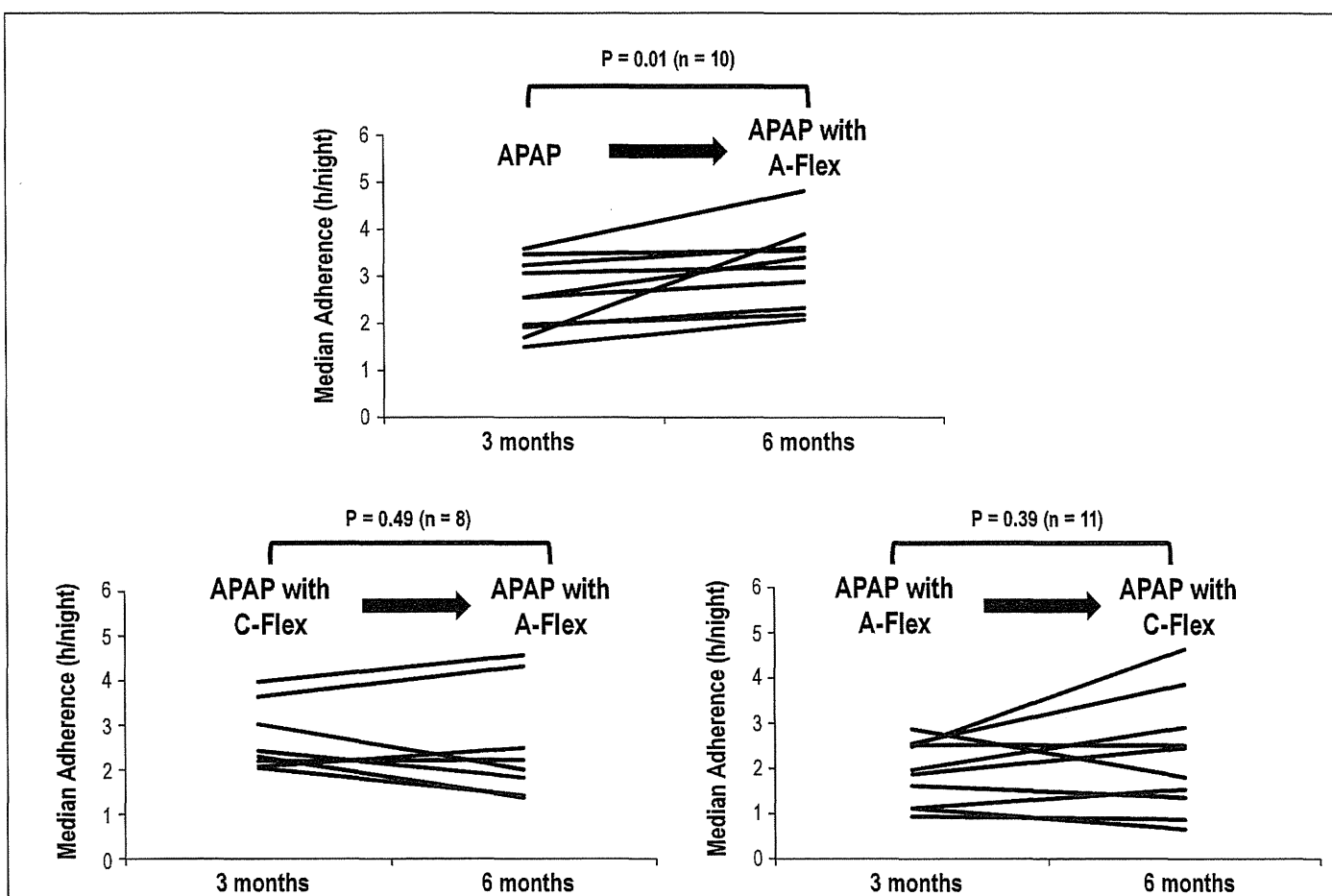

Figure 4—Analysis of poor compliers (< 4 h/night of CPAP use) between 3 and 6 mo. Individual data are presented.

C-Flex. CPAP adherence within the first 3 mo has been described as a strong predictor of long-term CPAP use.[21]

CPAP adherence is a key issue in OSA, as greater improvements in daytime sleepiness, blood pressure, and QOL occur with greater CPAP use.[22-25] A number of different variables independent of the CPAP mode can influence CPAP adherence. Older age, the use of lipid-lowering medications, the use of sedative/hypnotic agents on CPAP titration, a higher AHI, and greater daytime sleepiness were all factors shown to increase CPAP adherence.[21,26-30] In contrast, a lower body mass index (BMI) ($\leq$ 30 kg/m^2) and psychosocial factors such as living alone have been shown to be associated with poor CPAP adherence.[31,32] In the current study, there was no significant difference in these variables among the three groups. Also, all study patients received the same education on CPAP treatment. In addition, no humidification was used in any participant and their interfaces for CPAP treatment did not change during the study period. Therefore, we think that the CPAP mode was the main driver of the results of our study.

Pépin et al.[10] reported that after changing the CPAP mode from a fixed PAP to C-Flex, CPAP adherence was significantly improved in patients with low adherence (< 4 h/night of CPAP use) during the initial 3 mo, whereas this improvement did not occur in patients who were already using CPAP for > 4 h/night. These results suggest that C-Flex is an effective modality for improving adherence. Compared with patients in previous reports,[8-11] our patients had relatively low CPAP adherence (mean ± SD: 4.5 ± 1.9 h/night). Several reasons could account for this finding. As described previously, our study population had a low BMI (27.1 ± 4.7) and mild to moderate daytime sleepiness (mean ESS:,9.2 ± 4.4). It has already been described that a lower BMI and less daytime sleepiness were associated with poor CPAP adherence.[21,31] In addition, poor sleep quality and QOL were only minimally abnormal in our patients compared with previous reports.[20,32,33] Improving sleep-related QOL after CPAP in patients already having comparatively high sleep quality and QOL would seem to be difficult. Wells et al.[34] demonstrated that patients who experienced greater improvements in daily functioning had higher levels of CPAP adherence. Therefore, the absence of improvement in subjective symptoms makes it unlikely that high levels of CPAP adherence would be achieved. Taken together, our patients had several traits that could be associated with poor CPAP compliance. This might explain why C-Flex had a significant effect on CPAP adherence in the current study.

We also demonstrated that the use of APAP with A-Flex significantly improved some QOL factors and that CPAP adherence in the APAP with A-Flex group was not greater than in the APAP group. On the other hand, a significant improvement in CPAP adherence was observed in the subgroup of poor compliers who were moved from APAP to APAP with A-Flex. This result suggests that A-Flex may be an alternative CPAP mode for improving adherence in patients with poor compliance. However, further studies using randomized prospective designs are needed to confirm this result. In addition, a future study that investigates the change in PAP adherence after a switch from APAP to APAP with C-Flex is warranted.

This study had some limitations. First, our study population was Asian, and their BMI was comparatively low. Therefore, it might be difficult to apply the results of the current study to all patients with OSA. Second, this was not a double-blind but a single-blind (patients blinded) randomized study. The investigators might be influenced in their assessments by knowing the treatment received. However, the same education on PAP therapy and follow-up methods after randomization were conducted for all patients. Thus, we think this possible limitation had a minimal effect on the study outcomes.

In conclusion, this prospective, randomized study demonstrated that APAP with C-Flex led to significantly greater adherence than APAP. APAP with C-Flex is a potentially superior CPAP mode among the three tested. Although we did not observe significant changes in PAP adherence after the switch from APAP to APAP with C-Flex, A-Flex seemed to be an effective CPAP approach in patients with poor adherence to APAP.

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DISCLOSURE STATEMENT

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LIVER TRANSPLANTATION 18:1217-1225, 2012

ORIGINAL ARTICLE

Use of Noninvasive Ventilation for Pediatric Patients After Liver Transplantation: Decrease in the Need for Reintubation

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Noninvasive ventilation (NIV) refers to ventilation delivered through a noninvasive interface (a nasal or face mask) rather than an invasive interface (an endotracheal tube or tracheostomy). The role of NIV in preventing reintubation after abdominal surgery in pediatric patients is uncertain. Therefore, we evaluated the role of NIV for this purpose in pediatric patients after liver transplantation. We successfully started using NIV for respiratory complications (RCs) in pediatric patients undergoing liver transplantation in 1999. For this report, we screened all medical records of patients under the age of 12 years who underwent liver transplantation between 2001 and 2009, and we retrieved data for cases at high risk of extubation failure. We retrospectively compared the clinical outcomes of patients who received NIV during their intensive care unit (ICU) stay and patients who did not. Data for 94 cases (92 patients) were included in this analysis. NIV was used in 47 patients during their ICU stay. The rate of reintubation for RCs was significantly lower in NIV patients versus non-NIV patients [3/47 (6.4%) versus 11/47 (23.4%), $P = 0.02$]. Furthermore, the discharge rate from the ICU was significantly better for NIV patients versus non-NIV patients. The use of NIV after extubation prevented the worsening of atelectasis and stabilized respiratory conditions in this cohort. No major changes in operative procedures or other treatments during the examined period were found. In conclusion, NIV is acceptable and promising for the respiratory management of pediatric patients undergoing liver transplantation. Its use may stabilize respiratory conditions and decrease the need for reintubation in pediatric liver transplant patients, and it may also facilitate an early ICU discharge. *Liver Transpl 18:1217-1225, 2012.* © 2012 AASLD.

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Orthotopic liver transplantation (OLT) has become the standard of care for many pediatric patients with fatal liver diseases. In pediatric OLT patients, respiratory complications (RCs) are among the most frequently encountered early postoperative complications, and they have been reported as important causes of postoperative morbidity and mortality.[1,2]

Abbreviations: ABG, arterial blood gas; CMV, conventional mechanical ventilation; CXR, chest X-ray; EPAP, expiratory positive airway pressure; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; IPAP, inspiratory positive airway pressure; NIV, noninvasive ventilation; OLT, orthotopic liver transplantation; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of arterial oxygen; PS, pressure support; RC, respiratory complication; RCT, randomized controlled study; SaO_2, arterial oxygen saturation.

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Noninvasive ventilation (NIV) refers to ventilation delivered through a noninvasive interface (a nasal or face mask) rather than an invasive interface (an endotracheal tube or tracheostomy). NIV is effective for respiratory insufficiency in various situations. In particular, the use of NIV to wean patients from conventional mechanical ventilation (CMV) by early extubation or to prevent reintubation has attracted much attention lately.[3-5] However, NIV has been used for this purpose only to a very small extent in pediatric populations. Although data supporting this technique in children have emerged during the last few years, experience with children has typically been restricted to case series and has mainly involved the long-term use of NIV.[6] We successfully started using NIV for RCs in OLT pediatric patients in 1999.[7] We have subsequently had many more OLT cases, and some have presented difficulties such as RCs. Therefore, we have retrospectively examined patient data to elucidate the benefits of NIV use for preventing reintubation after surgery in pediatric OLT patients, and we have compared the clinical outcomes of NIV patients and non-NIV patients.

PATIENTS AND METHODS

Subjects

We screened all medical records of patients less than 12 years old who underwent OLT between 2001 and 2009, and we identified patients at high risk for extubation failure after the operation as follows. First, we excluded patients from the analysis for the following reasons: (1) death or transfer to another hospital without extubation, (2) reintubation after extubation within the previous 3 months, (3) accidental extubation, and (4) the performance of OLT concurrently with other organ transplants. Thereafter, on the basis of previous reports on extubation failure, every patient who fulfilled at least 1 of the following criteria at extubation was included in the analysis: (1) CMV use for more than 1 week, (2) a partial pressure of arterial oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio < 250 mm Hg, (3) a partial pressure of carbon dioxide ($PaCO_2$) > 45 mm Hg, and (4) atelectasis of more than 1 lobe.[8-10] The data collection and analysis were performed only by authors of this article, and the use of these data was approved by the institutional review board of kyoto university hospital.

Criteria for Extubation After Operation

Details for the treatments (except for respiratory management) were reported previously by our group.[11] Although decisions about respiratory management were based on clinical judgment, the following factors were considered to be indications for extubation: (1) clinical stability and no major abdominal complications from the operation, (2) no markedly disturbed consciousness, (3) well-maintained spontaneous breathing, and (4) a PaO_2/FiO_2 ratio > 200 mm Hg under minimal ventilator support [eg, pressure support (PS) < 5 cm H_2O and expiratory positive airway pressure (EPAP) < 4 cm H_2O]. Because immunosuppressants were given to all patients, we were eager to perform extubation as early as possible to prevent ventilator-associated pneumonia. After extubation, chest X-rays (CXRs) and arterial blood gas (ABG) data were evaluated repeatedly according to the patient's respiratory condition.

NIV Technique and Oxygen Supplementation

In patients whose respiratory condition was deteriorating after extubation, the use of NIV (VPAP, ResMed, North Ryde, Australia) was considered (Fig. 1). Although decisions about the implementation of NIV were also dependent on clinical judgment, patients who fulfilled at least 1 of the following criteria were considered to be candidates for NIV application: (1) arterial oxygen saturation (SaO_2) < 90% despite maximal oxygen administration (oxygen flow rate = 15 L/minute with a simple mask or a mask with a reservoir bag), (2) hypercapnia ($PaCO_2$ > 45 mm Hg), (3) pulmonary edema, (4) worsening atelectasis, and (5) respiratory distress [eg, tachypnea and/or respiratory muscle fatigue]. PS ventilation was delivered with a nasal or face mask. After the mask was secured, the levels of PS and EPAP and the amount of oxygen were progressively increased according to the judgment of the attending physician until (1) SaO_2 was >95% and (2) the respiratory rate was decreased and/or thoracic and abdominal paradoxical movement was reduced. After NIV was introduced, the patient's condition was assessed repeatedly, and adjustments were made to NIV and oxygen settings. When NIV was initially applied, the goal was to continue its use as long as the patient could tolerate it or it appeared to no longer be necessary. When we administered only oxygen, the amount of oxygen was adjusted to keep SaO_2 > 95%. Sedative medications were not given during NIV use.

Criteria for Reintubation

Patients whose respiratory conditions deteriorated despite NIV treatment or oxygen therapy or who were intolerant of NIV treatment were reintubated and managed with CMV. The predetermined criteria for reintubation were as follows: (1) a failure to maintain an SaO_2 level > 90% with adjusted NIV and/or maximal oxygen settings, (2) the development of copious tracheal secretions that could not be expectorated, (3) an increase in $PaCO_2$ accompanied by a pH ≤ 7.30 even after adjusted metabolic acidosis (suggesting rapid worsening of respiratory acidosis), (4) impaired consciousness necessitating endotracheal intubation to protect the upper airway (eg, seizure or hepatic coma), and (5) severe hemodynamic instability (defined as a systolic blood pressure < 70 mm Hg) even with inotropic drugs. If the patient was reintubated for any of the first 3 items, we counted the event as reintubation due to an RC.

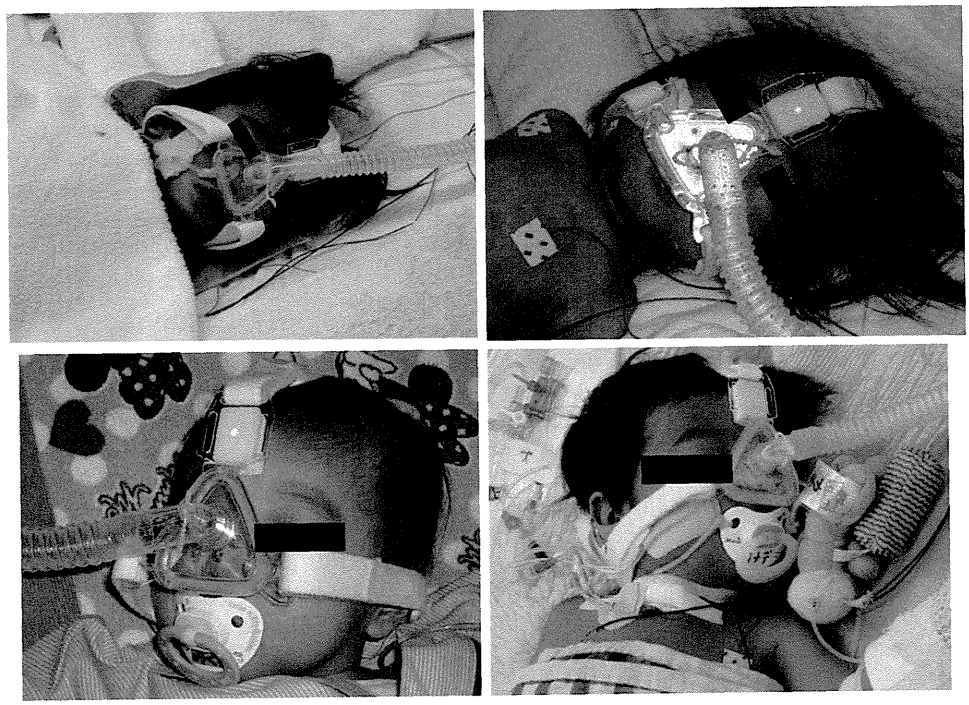

Figure 1. Pictures of pediatric patients receiving NIV in this study.

Data Analysis

We compared the clinical outcomes of the NIV and non-NIV cohorts during their intensive care unit (ICU) stays. The evaluation of outcomes was based on the following factors: reintubation in the ICU, the length of stay in the ICU and in the hospital after extubation, and survival. In each case, the timing and duration of NIV use, the initial NIV settings, the reason for reintubation, the reason for NIV use, and the cause of death were clarified. Sequential ABG data and CXR findings for patients receiving NIV were recorded before and after NIV use at 12- to 24-hour intervals. The CXR findings were reviewed by 2 respiratory physicians (K.M and Y.C.) who were blinded to clinical information.

The outcomes and background demographic data for the 2 cohorts were compared with the unpaired t test or the Mann-Whitney U test for continuous variables and with the chi-square test for categorical variables. A comparison of the ICU discharge rates for the 2 cohorts was made with Kaplan-Meier curves and a log-rank test. If a patient died or was reintubated for reasons other than respiratory problems, we did not include any further data on that patient in our analysis. Changes in ABG data were assessed with the Wilcoxon signed-rank test. Two-tailed P values < 0.05 were considered statistically significant. All statistical analyses were performed with JMP 7.0.2 statistical software (SAS Institute, Inc., Cary, NC).

RESULTS

Between 2001 and 2009, pediatric OLT was performed 251 times. After the records were screened for those cases, we found that 94 cases fulfilled the criteria for this study, and they were included in the analysis (Fig. 2). Two patients underwent retransplantation during this period. This cohort included 9 patients managed with NIV who were also included in our previous case series.[7,12] NIV was used for 47 cases during their ICU stay (Fig. 2). We compared the perioperative clinical backgrounds of NIV patients and non-NIV patients. No significant differences between the 2 cohorts were found with respect to patient characteristics, preoperative disease severity, operative conditions, or the administration of immunosuppressants (Table 1). At extubation, the vital signs and the ABG data did not differ significantly between the 2 cohorts. However, the number of patients with atelectasis was greater in the NIV cohort, and the hemoglobin level was lower (Table 2). No major changes in operative procedures were identified during the examined period.

Seven of the 47 NIV patients (14.9%) required reintubation, and 3 were reintubated because of RCs. On the other hand, 15 of the 47 non-NIV patients (31.9%) required reintubation, and 11 of these patients were reintubated because of RCs. The rate of reintubation due to RCs was significantly lower for the NIV patients ($P = 0.02$). No statistically significant differences were found between these 2 cohorts with respect to the rate of reintubation under all circumstances, the length of the hospital stay, or survival (Table 3). During the 9-year study period, the annual rate of NIV use for the cases in our analysis increased from 8.3% in 2001 to more than 80% in 2009. On the other hand, the annual rate of reintubation due to RCs decreased from 25% in 2001 to 0% in 2009 (Fig. 3).

The major reasons for NIV use were worsening atelectasis and the development of respiratory distress. Detailed reasons for NIV use, the time from extubation to NIV use, and the initial NIV settings are shown

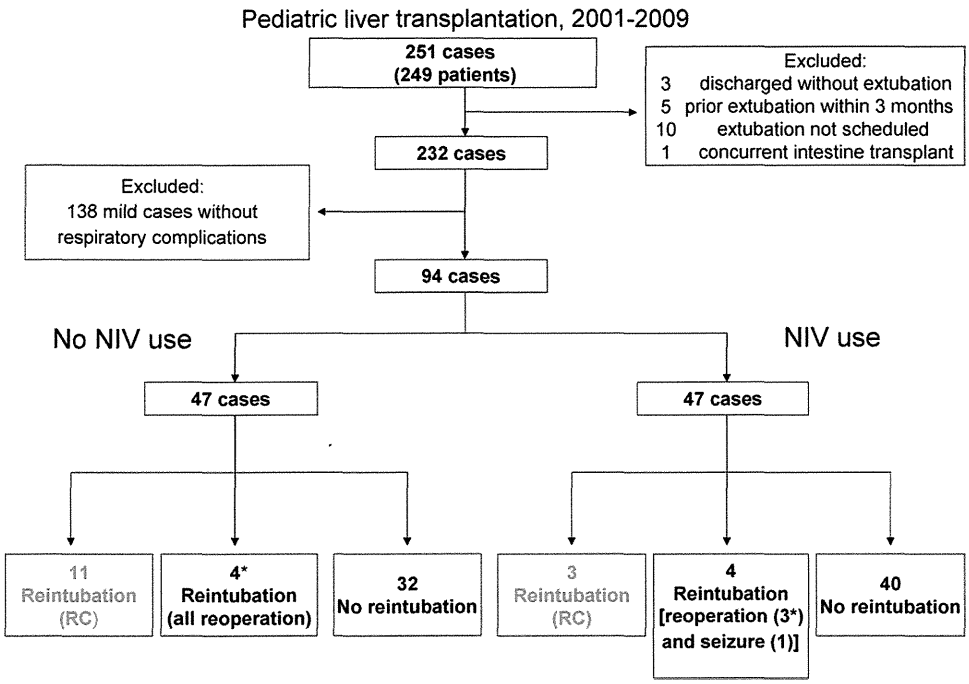

Figure 2. Patient selection and respiratory management of the study patients during their ICU stay. *Seven patients (4 in the non-NIV group and 3 in the NIV group) were reintubated because of reoperation for abdominal complications such as intra-abdominal bleeding, hepatic artery thrombosis, and bile leakage.

TABLE 1. Patient Characteristics and Perioperative Conditions

	No NIV Use (n = 47)	NIV Use (n = 47)	*P* Value
Background			
Male sex [n (%)]	20 (42.6)	20 (42.6)	>0.89
Age (months)*	10 (7-63)	10 (7-87)	0.87
Age < 1 year [n (%)]	21 (44.7)	25 (53.2)	0.54
Height (cm)*	72 (63-105)	67 (63-109)	0.60
Body weight (kg)*	8.5 (6.8-18.9)	7.5 (5.9-17)	0.16
Etiology [n (%)]			
Biliary atresia	31 (66.0)	29 (61.7)	0.09
Fulminant hepatitis	3 (6.4)	1 (2.1)	
Wilson's disease	2 (4.3)	0	
Hepatoblastoma	3 (6.4)	0	
Congenital portosystemic shunt	0	4 (8.5)	
Retransplantation	3 (6.4)	7 (14.9)	
Other	5 (10.6)	6 (12.8)	
Preoperative factors*			
Total bilirubin (mg/dL)	9.7 (1.9-18.6)	11.9 (4.3-17.4)	0.75
Albumin (g/dL)	3.4 (3.0-3.9)	3.3 (2.9-3.8)	0.32
Prothrombin time (seconds)	14.3 (12.8-18.5)	14.6 (13.1-16.7)	0.85
Time from onset to transplantation (months)	8 (3-38)	8 (4-54)	0.82
Pediatric End-Stage Liver Disease score	18.8 (1.3-26.7)	16.7 (7.5-26.2)	0.95
Operative factors			
Incompatible donor blood type [n (%)]	6 (12.8)	11 (23.4)	0.18
Blood loss/body weight (mL/g)*	0.09 (0.03-0.20)	0.13 (0.06-0.21)	0.27
Graft liver/body weight (%)*	2.57 (1.57-3.16)	2.82 (1.76-3.46)	0.49
Immunosuppressants [n (%)]			
Tacrolimus	47 (100)	47 (100)	>0.88
Steroid	47 (100)	47 (100)	>0.88
Mycophenolate mofetil	9 (19.1)	10 (21.3)	0.80

*The data are expressed as medians and first and third quartiles.

in Table 4. Because it was occasionally difficult for the spontaneous-timed mode of our device to trigger a patient's breathing and to achieve sufficient ventilator support for tachypneic breathing, we basically applied the timed mode for patients less than 1 year old.[7]

TABLE 2. Condition of the Patients at Extubation

	No NIV Use (n = 47)	NIV Use (n = 47)	*P* Value
Time from operation to extubation (days)*	1 (1-2)	1 (1-3)	0.11
Vital signs at extubation			
Systolic blood pressure (mm Hg)	102.8 ± 15.7	99.2 ± 15.5	0.25
Diastolic blood pressure (mm Hg)	49.5 ± 10.3	53.7 ± 13.6	0.40
Heart rate (beats/minute)	105.7 ± 23.9	111.1 ± 21.7	0.23
Body temperature (°C)	36.9 ± 0.8	37.0 ± 0.7	0.41
Respiratory rate (breaths/minute)	29.3 ± 11.6	26.5 ± 6.7	0.70
ABG data at extubation			
PaO_2/FiO_2 ratio (mm Hg)	282.7 ± 114.5	281.8 ± 103.8	0.99
$PaCO_2$ (mm Hg)	41.4 ± 8.2	40.0 ± 6.0	0.89
pH	7.40 ± 0.06	7.39 ± 0.05	0.19
Imaging findings for atelectasis [n (%)]	23 (48.9)	35 (74.5)	0.01
Blood examination data on extubation			
White blood cells ($\times 10^3/\mu L$)	9.7 ± 4.7	10.7 ± 5.0	0.33
Hemoglobin (g/dL)	9.9 ± 1.5	8.9 ± 1.8	<0.01
Platelets ($\times 10^4/\mu L$)	10.2 ± 7.6	9.1 ± 6.1	0.64
Total bilirubin (mg/dL)	5.2 ± 5.4	5.9 ± 4.7	0.20
Direct bilirubin (mg/dL)	2.6 ± 5.1	3.0 ± 3.6	0.40
Blood urea nitrogen (mg/dL)	9.7 ± 6.5	11.1 ± 7.9	0.27
Creatinine (mg/dL)	0.19 ± 0.15	0.17 ± 0.13	0.56
Albumin (g/dL)	3.03 ± 0.55	2.96 ± 0.53	0.45
C-reactive protein (mg/dL)	3.6 ± 2.7	4.1 ± 3.6	0.23

NOTE: The data are expressed as means and standard deviations unless otherwise noted.
*The data are expressed as medians and first and third quartiles.

TABLE 3. Clinical Outcomes

	No NIV Use (n = 47)	NIV Use (n = 47)	*P* Value
Reintubation in ICU due to RCs [n (%)]	11 (23.4)	3 (6.4)	0.02
Reintubation in ICU [n (%)]	15 (31.9)	7 (14.9)	0.05
Death in hospital [n (%)]	5 (10.6)	5 (10.6)	>0.98
Hospital stay (days)*	80.7 ± 10.3	75.8 ± 10.3	0.74

*The data are expressed as means and standard deviations.

The reasons for reintubation and death are shown in Table 5. All but 1 of the reintubations and 43 of the 47 NIV introductions (91.5%) in the ICU were performed within 72 hours of extubation. Sequential ABG data for the 47 NIV patients showed significant improvements in PaO_2, $PaCO_2$, and pH after NIV use (Fig. 4). Fourteen of the 21 patients who were administered NIV because of worsening atelectasis showed improvements in atelectasis (as shown by CXRs) after NIV use. Changes in CXRs for typical cases are shown in Fig. 5. Furthermore, the discharge rate from the ICU was significantly better for NIV patients versus non-NIV patients (Fig. 6).

All patients tolerated NIV, and no severe complications from NIV use occurred. Nasal bridge ulcers and gastric distension were prevented by soft silicone seals and nasogastric tubes, respectively.

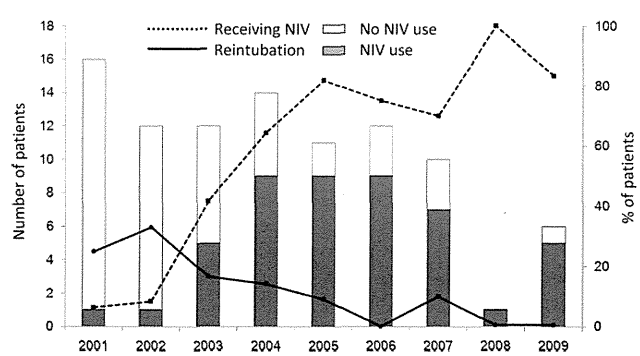

Figure 3. Rates of NIV use and reintubation and numbers of patients included in the analysis by year during the 9-year study period. The gray columns represent the annual number of patients who received NIV, and the white columns represent the annual number of patients who did not. The dashed line represents the percentage of patients treated with NIV with respect to the total number of patients included in the analysis. The solid line represents the percentage of patients who required reintubation because of RCs with respect to the total number of patients included in the analysis.

DISCUSSION

Studies of postextubation NIV use in children are scarce. According to our literature survey, no studies

TABLE 4. Reasons for Implementing NIV, Timing and Duration of NIV Use, and Initial NIV Settings (n = 47)

Reasons for NIV use [n (%)]	
Worsened atelectasis	21 (44.7)
Respiratory distress	19 (40.4)
Hypercapnia	5 (10.6)
Pulmonary edema	2 (4.3)
Time from extubation to NIV use (hours)*	2 (0-44)
Time from extubation to NIV use < 72 hours [n (%)]	43 (91.5)
Duration of NIV use (days)*	9 (2-17)
Initial NIV settings	
IPAP (cm H_2O)†	7.6 ± 1.7
EPAP (cm H_2O)†	3.9 ± 1.0
Respiratory rate (breaths/minute)†	25.2 ± 7.0
Spontaneous-timed mode/timed mode (n/n)	27/20

*The data are expressed as medians and first and third quartiles.
†The data are expressed as means and standard deviations.

TABLE 5. Reasons for Reintubation and Death

Reasons for Reintubation*	No NIV Use (n = 11)	NIV Use (n = 3)
Worsened atelectasis	3 (27.3)	2 (66.7)
Massive airway secretions	2 (18.2)	0 (0)
Hypercapnia	6 (54.5)	1 (33.3)

Reasons for Death	No NIV Use (n = 5)	NIV Use (n = 5)
Graft failure	4 (80)	4 (80)
Intra-abdominal bleeding	0	1 (20)
Pneumonia	1 (20)	0

NOTE: The data are presented as numbers and percentages.
*The time from extubation to reintubation was 7.9 ± 7.5 hours for the non-NIV group and 19.2 ± 8.6 hours for the NIV group ($P = 0.06$).

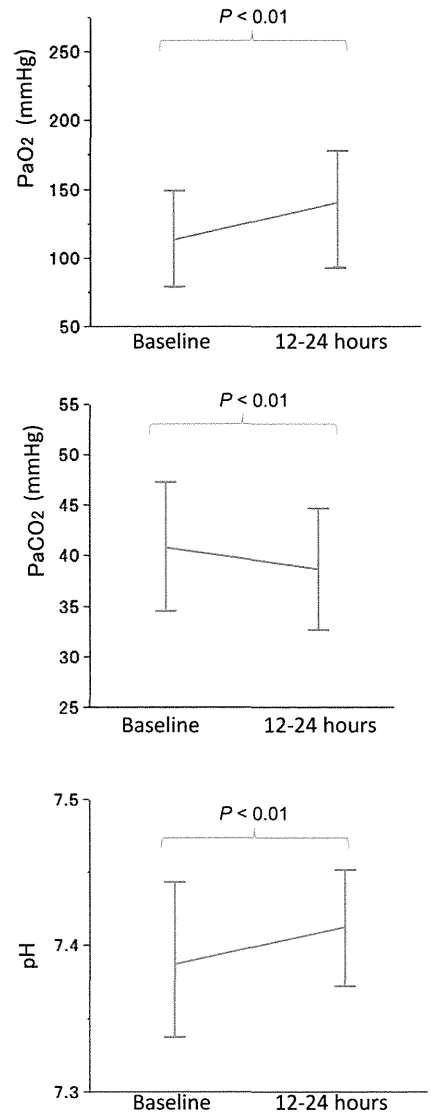

Figure 4. Changes in ABG analyses before and after NIV use.

have systematically investigated the effects of NIV use in pediatric patients after abdominal surgery. The results of the current study showed that the need for reintubation due to RCs after surgery was significantly lower for pediatric OLT patients receiving NIV versus those not receiving NIV. The differences in the clinical backgrounds of the 2 cohorts imply that the NIV cohort had more severe conditions than the non-NIV cohort. In addition, the fact that the treatment modalities for RCs during the screening period did not change provides support for the strong association of NIV use with the reduction in the number of patients requiring reintubation. Furthermore, as we show in Fig. 3, the annual changes in the rates of NIV use and reintubation also seem to imply an association of NIV use with the reduction in reintubation.

The improvements in ABG data after NIV use suggest that NIV stabilized patients' respiratory conditions and gave them time to respond to other treatments. This may have allowed them to avoid reintubation and may have facilitated early discharge from the ICU. In this study, the major reasons for the implementation of NIV were worsened atelectasis and the development of respiratory distress. Atelectasis is a common postoperative complication after abdominal surgery.[13-15] In particular, children are at increased risk for the development of atelectasis because of anatomical factors (eg, a lack of collateral pathways for ventilation and low conductance of the central airways).[15] Because airway patency is lost abruptly after extubation, the aspiration of small amounts of mucus and oropharyngeal or gastric secretions may occlude a bronchus or bronchiole in a child, and atelectasis

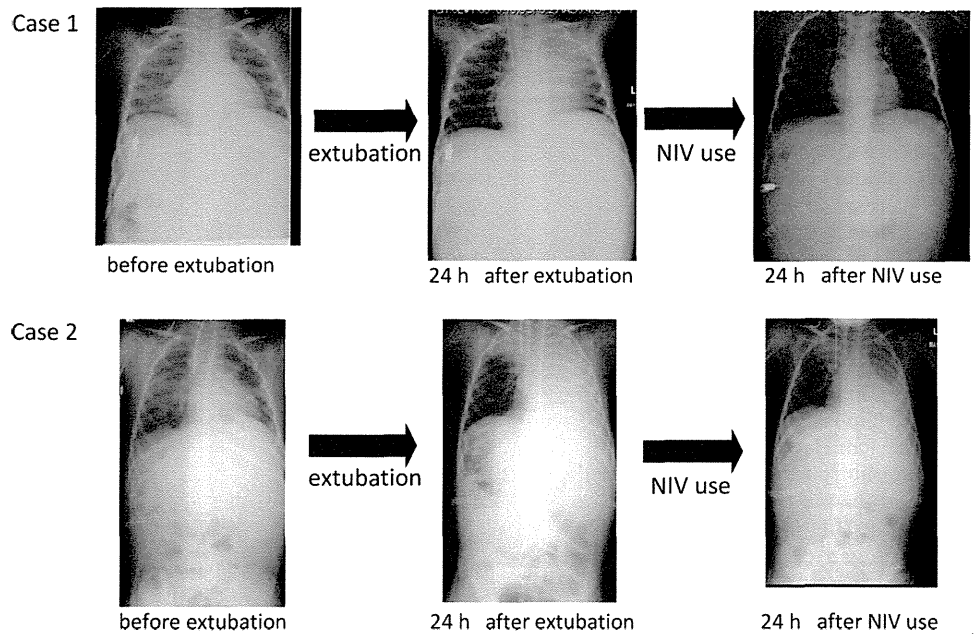

Figure 5. Typical examples of CXRs showing the deterioration of atelectasis after extubation and the amelioration of atelectasis after NIV use.

may develop or, if already present, may worsen.[16] The developed atelectatic lung area decreases the functional residual capacity and increases the ventilation-perfusion mismatch. Subsequently, hypoxemia may either develop or deteriorate.[17] In adult patients with postoperative hypoxemic respiratory failure, it has been shown that NIV improves ventilation, minimizes atelectasis formation, and increases the functional residual capacity.[18,19] Squadrone et al.[20] showed in their prospective randomized controlled study (RCT) that NIV can decrease the need for reintubation in adults after major abdominal surgery. This benefit of NIV can be just as valid for pediatric patients.

On the other hand, the effects of NIV on postextubation respiratory distress are controversial. Keenan et al. performed an RCT in a heterogeneous adult population and found no differences in the rates of reintubation for the NIV and control groups.[21] Esteban et al.[4] also performed an RCT to investigate whether NIV could prevent the need for reintubation in patients with respiratory failure after extubation. Although NIV was introduced because of respiratory distress in most of their cases, they were not able to show a benefit from NIV. However, in these 2 trials, the majority of the acute respiratory failures were medical in origin, and there were a limited number of postoperative patients who had undergone abdominal surgery. In these previous trials, the efficacy of NIV appeared to differ markedly and to depend on the backgrounds of the subjects and the criteria for the initiation of NIV.

It is noteworthy that in our study, most reintubations and NIV introductions were performed within 72 hours of extubation. In cases of extubation failure, most reintubations are reported to be required within 48 to 72 hours of extubation, as in our study.[22-24] Therefore, NIV use during this period appears to have a strong benefit in stabilizing a patient's respiratory condition.

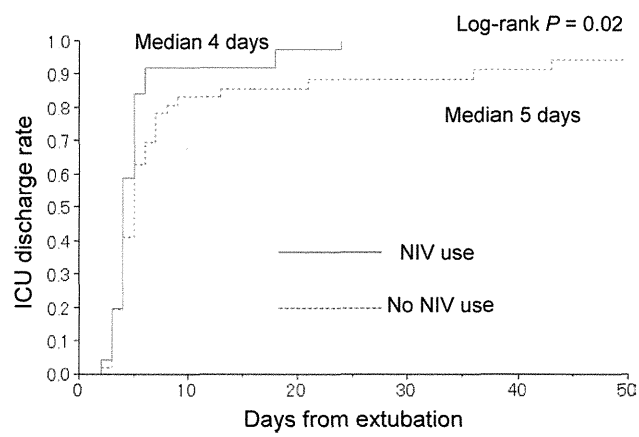

Figure 6. Kaplan-Meier analysis of rates of discharge from the ICU.

Because prospective RCTs of the respiratory management of severely ill pediatric patients are ethically difficult to perform, published reports of NIV use in children with acute respiratory failure are not abundant and are not systematic. Yañez et al.[25] showed in their RCT that NIV improved hypoxemia and decreased the need for intubation in pediatric patients with acute respiratory failure. In another RCT, Mayordomo-Colunga et al.[10] found that postextubation NIV was useful in preventing reintubation when it was applied immediately after extubation, whereas NIV was more likely to fail when acute respiratory failure had already developed. Although both studies reported the efficacy of NIV for pediatric patients with respiratory failure, the study patients' clinical backgrounds were not uniform. In this study, even though it was retrospective, we aimed to include patients with similar clinical backgrounds by investigating only OLT patients. Because an evaluation of the role of NIV

in supporting extubation in a clinically unified pediatric population is rare, this study can be regarded as clinically significant.[26]

This study has some limitations. First, because of its retrospective design, the judgments about when to initiate NIV use and perform reintubation were not randomized. Even though the criteria for NIV implementation were not changed during the study period, not all patients who met the criteria for NIV implementation received NIV, and these patients composed the non-NIV cohort. It may be considered that the patients receiving NIV were somewhat sicker than the others (eg, they were more anemic or had more extensive atelectasis; Table 2). In addition, the rate of NIV use increased as the years passed, and this suggests that the attending physicians did not use NIV as readily in the early years because the technique for pediatric patients had not yet been well established. Furthermore, because ABG and CXR analyses were not performed as often in the non-NIV group, a full comparison of such data with the NIV group over a comparable time period was not possible. There is the possibility that the observed changes in ABG and CXR results in the NIV group were related to the usual clinical course rather than NIV implementation. However, the respiratory conditions (PaO_2/FiO_2 ratio, $PaCO_2$, and degree of atelectasis) of these patients had worsened before NIV implementation. We evaluated data before and after NIV implementation at 12- to 24-hour intervals, and it seems unlikely that the ABG data and the CXR findings would have improved significantly in such a short period without any intervention related to respiratory management. Second, during the use of NIV in our pediatric patients, we could not precisely determine oxygen concentrations with our NIV device. Therefore, when we were evaluating the ABG data, we could not calculate the PaO_2/FiO_2 ratio. Third, for the cases with atelectasis, it was impossible to judge whether they had pneumonia. Thus, we could not address the efficacy of NIV in patients with pneumonia.

In conclusion, NIV is an acceptable and promising method of respiratory management in pediatric OLT patients with respiratory failure after extubation. An NIV trial may prevent the worsening of atelectasis and contribute to the stabilization of a patient's respiratory condition. Consequently, it may decrease the need for reintubation during the postoperative period and lead to an early discharge from the ICU. It is possible that all extubated pediatric patients should be placed on NIV after abdominal surgery to prevent the development and deterioration of RCs for a short period of time. Prospective RCTs, although ethically difficult to perform, would help us to confirm these results and are warranted.

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INTERNAL MEDICINE

□ CASE REPORT □

Transient Increase in Epileptiform Discharges after the Introduction of Nasal Continuous Positive Airway Pressure in a Patient with Obstructive Sleep Apnea and Epilepsy

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Abstract

In patients with obstructive sleep apnea (OSA) and epilepsy, the frequency of generalized spike and wave complexes (GSWCs) usually decreases after the initiation of nasal continuous positive airway pressure (nCPAP) therapy. However, we herein report a patient who had a transient increase in GSWCs following nCPAP treatment. A woman with epilepsy underwent polysomnography, who showed severe OSA and 30 GSWCs during the sleep study. Polysomnography at the introduction nCPAP showed that the GSWCs increased to 94 times during the monitoring period, despite improvement of her OSA. Polysomnography was again performed four months later, and the GSWCs had decreased to 23 times. Physicians should therefore be cautious regarding a possible increase in epileptiform discharges and seizures immediately after the introduction of nCPAP.

Key words: transient increase in epileptiform discharges, epilepsy and obstructive sleep apnea, nasal continuous positive airway pressure (nCPAP) introduction

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Introduction

Both sleep disordered breathing (SDB) and epilepsy are common disorders. SDB was observed in 24% of adult men and 9% of adult women (1) and the prevalence of epilepsy in the general population is approximately 1% (2). Therefore, epilepsy is often accompanied by SDB, mainly obstructive sleep apnea (OSA). In one study, one-third of medically intractable epilepsy patients had a respiratory disturbance index greater than 5 (3), and another study showed that about 10% of the adult epilepsy patients had OSA (4). In patients with SDB and epilepsy, the frequencies of seizures (5-7) and epileptiform discharges (8) are usually decreased after the treatment of SDB, such as by nasal continuous positive airway pressure (nCPAP) and other means. This secondary beneficial effect of SDB treatment on epilepsy may be associated with a decrease in sleep fragmentation, sleep stage transition, and desaturation, since focal and generalized seizures are more likely to occur during light sleep or soon after awakening (9) and epileptiform discharges tend to be activated by sleep in some epilepsy patients.

As mentioned above, treatment for SDB usually ameliorates not only SDB, but also epilepsy, in patients with both conditions. However, we herein report a patient who experienced a transient increase in epileptiform discharges immediately after beginning nCPAP treatment.

Case Report

An 18-year-old woman began to have monthly complex

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