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Smoking is Associated with the Severity of Rhododendrol-induced Leukoderma and with the Occurrence of Leukomelanoderma

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Abstract

Background

Rhododendrol (RD) is a skin whitening ingredient that was developed in Japan. Among the 800000 users of RD-containing cosmetics, 20000 patients developed localized leukoderma (RD-induced leukoderma). Forty-two % of those users showed perilesional hyperpigmentation (leukomelanoderma), and 14% of them were associated with vitiligo vulgaris afterwards.

Methods

For this retrospective cohort study, we abstracted data from our dermatology medical records of 101 patients who developed leukoderma after using the cosmetics containing RD from July 2013 to December 2014. Age, BMI, the number of RD-containing products they used, smoking history, and depigmentation scores at their baseline visit as well as blood test data for anti-nuclear and/or anti-thyroid antibodies were analyzed. Multivariable logistic regression and linear regression were used for analyses of leukomelanoderma, vitiligo vulgaris and characteristics at the baseline visit.

Results

Age, the number of RD-containing products used, BMI, anti-nuclear, and anti-thyroid antibodies were not significantly correlated with the presence of leukomelanoderma, but it appeared that leukomelanoderma was more likely to occur in patients with current smoking. In addition, smokers showed a significant increase in their depigmentation score at the baseline visit.

Conclusions

Our study demonstrates that smoking is associated with the severity of RD-induced leukoderma and the occurrence of leukomelanoderma.

Key Words: Rhododendrol; Leukoderma; Vitiligo vulgaris; Leukomelanoderma; Smoking

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Introduction

Rhododendrol (RD, 4-[4-hydroxyphenyl]-2-butanol) is a skin whitening ingredient that was developed in 2006 by Kanebo Cosmetics. Cosmetics containing RD were on sale from 2008 in Japan. However, it turned out that among the users of RD-containing cosmetics, a considerable number of users developed leukoderma in 2013. As many as 20000 users, approximately 2% of the 800000 users of RD-containing cosmetics, developed RD-induced leukoderma. After discontinuing use of those cosmetics, most leukodermas showed spontaneous repigmentation. However, some users noted that their leukodermas still persisted for several years, and new leukodermas appeared in non-RD exposed skin areas, suggesting the development of vitiligo vulgaris[1].

The Japanese Dermatological Association (JDA) established a Special Committee on the Safety of Cosmetics Containing Rhododendrol and reported a nationwide epidemiological survey[2-4] after developing a scoring system to evaluate the severity of leukodermas. The median depigmentation score at the baseline visit was 6 (range 0-48) among the 1315 patients whose questionnaire of the second nationwide survey was available, and most of those were at a relatively lower score[3]. Hyperpigmentation in depigmented or surrounding area was observed in 42% of 1235 patients whose responded to the questionnaire, and one third of them improved afterward[3].

Fourteen % of patients who were subjects of the third nationwide survey observed, expansions of the areas of depigmentation or the development of vitiligo vulgaris at non-exposed areas[4]. RD was developed and was thought to reduce melanin synthesis, as a competitive inhibitor of tyrosinase, the enzyme critical to melanin synthesis[5,6]. RD itself is degraded by tyrosinase and gives rise to harmful metabolites that are toxic to melanocytes[7]. In susceptible subjects, the damaged melanocytes induced T-cell responses which activated site-specific cytotoxic lymphocytes (CTLs). Those, CTLs may cause the spread of depigmentation to non-exposed sites[8].

Cigarette smoke contains a variety of reactive oxygen species (ROS) such as superoxide and hydroxyl radicals and other chemicals that increase the burden of oxidative stress[9]. Oxidative stress induced by ROS has been implicated in the pathogenesis of autoimmune diseases because it may damage autoimmune target cells and produce novel antigens[10]. It has also been reported that vitiligo vulgaris develops due to the overproduction of ROS in melanocytes[11].

In this retrospective cohort study, we collected data of patients who visited our institution for the treatment of RD-induced leukoderma. Their data was analyzed to identify risk factors of the severity of RD-induced leukoderma and the occurrence of perilesional hyperpigmentation (leukomelanoderma).

Methods

Patients

After approval by the Institutional Review Board of Osaka City University Medical School (#3810), we assembled a retrospective cohort of 101 patients with RD-induced leukoderma, who had visited our Dermatology Department from July 2013 to December 2014. From their medical records, we collected their age, BMI, the number of RD-containing products used, smoking history, and depigmentation scores at their baseline visit. Blood tests were conducted to assess whether they had anti-nuclear and/or anti-thyroid antibodies at their baseline visit. In addition, whether the patients developed vitiligo vulgaris or hyperpigmentation at surrounding areas (i.e. leukomelanoderma) during the course of treatment was also recorded.

Evaluation of the depigmentation score and leukomelanoderma

The Depigmentation score as defined by the JDA was calculated as the sum of the six parts of individual area scores: forehead, periorbital areas, cheeks (right and left sides), nose and mouth, neck and hands. Each individual area score was the multiplication of the degree (i.e. complete depigmentation: 2, incomplete depigmentation: 1) and the area of depigmentation: 0 (0%), 1 (1%-25%), 2 (26%-50%), 3 (51%-75%) and 4 (76%-100%). The maximum total depigmentation score was 48. The presence or absence of leukomelanoderma was visually assessed independently by two dermatologists using photographs.

Statistical analysis

We assessed the factors associated with 1) the severity of the leukoderma, which is quantified by the depigmentation score at the baseline visit, 2) the occurence of leukomelanoderma, and 3) the occurrence of vitiligo vulgaris. Multivariable logistic regression was used for binomial outcomes of the occurrence or non-occurrence of leukomelanoderma as well as vitiligo vulgaris during the treatment course. Multivariable linear regression was used for continuous outcome of the first depigmentation score to assess the effects of various risk factors including age, smoking history, number of RD-containing roducts used, BMI, anti-nuclear, and anti-thyroid antibodies. The depigmentation score at the baseline visit was natural log-transformed to provide normality in the residuals, and coefficients obtained by the regression model were back-transformed indicating the % increase in the first depigmentation score by an interquartile range (IQR) increase in corresponding covariates. The non-linearity of continuous risk factor variables was assessed using a restricted cubic spline. No significant non-linearity was observed. Missing data were imputed using the multiple imputation method because the exclusion of patients who had missing data might cause a selection bias. Demographic and clinical characteristics of the patients were presented using median and IQR for continuous variables and frequencies and percentages for categorical variables. All statistical analyses used a two tailed significance level of 0.05. All statistical calculations were performed using R software, version 3.5.1 (www.r-project.org).

Results

Characteristics of the patients

We enrolled 101 patients who developed leukoderma after using cosmetics containing RD, and their demographics are listed in Table 1. It shows median or percentage value of each risk factor that we hypothesize, depigmentation score, and complication with vitiligo vulgaris and leukomelanoderma. Regarding smoking history, twelve of patients (12%) had it, however, there was no former-smoker but current-smoker.

Depigmentation scores at the baseline visit

Histogram plots of depigmentation scores at the baseline visit are shown in Figure 1. The median value of the depigmentation score at the baseline visit was 14 (IQR, 4-32) (Table 1).

Development of leukomelanoderma and vitiligo vulgaris

Results of the multivariable logistic regression are shown in Figure 2. We analyzed the association of leukomelanoderma and vitiligo vulgaris with each of the candidate risk factors. Age, number of RD-containing products used, BMI, anti-nuclear, and anti-thyroid antibodies were not significantly correlated with the outcome, but it appeared that leukomelanoderma was more likely to occur in patients with current smoking (odds ratio 21.53, 95% CI 2.39-193.78; p=0.006).

Table 1. Demographic and clinical characteristics of patients at the baseline visit

Variable	N=101
Age in years, median (IQR)	60 (48, 70)
Female, n (%)	101 (100)
Smoking, n (%)	12 (12)
Number of products, median (IQR)	9.5 (5, 17)
BMI, median (IQR)	21.6 (19.58, 23.48)
Positive for anti-nuclear antibody, n (%)	11 (12)
Positive for anti-thyroid antibody, n (%)	26 (28)
Depigmentation score, median (IQR)	14 (4, 32)
Complication of vitiligo vulgaris, n (%)	10 (10)
Complication of leukomelanoderma, n (%)	48 (48)

IQR, interquartile range.

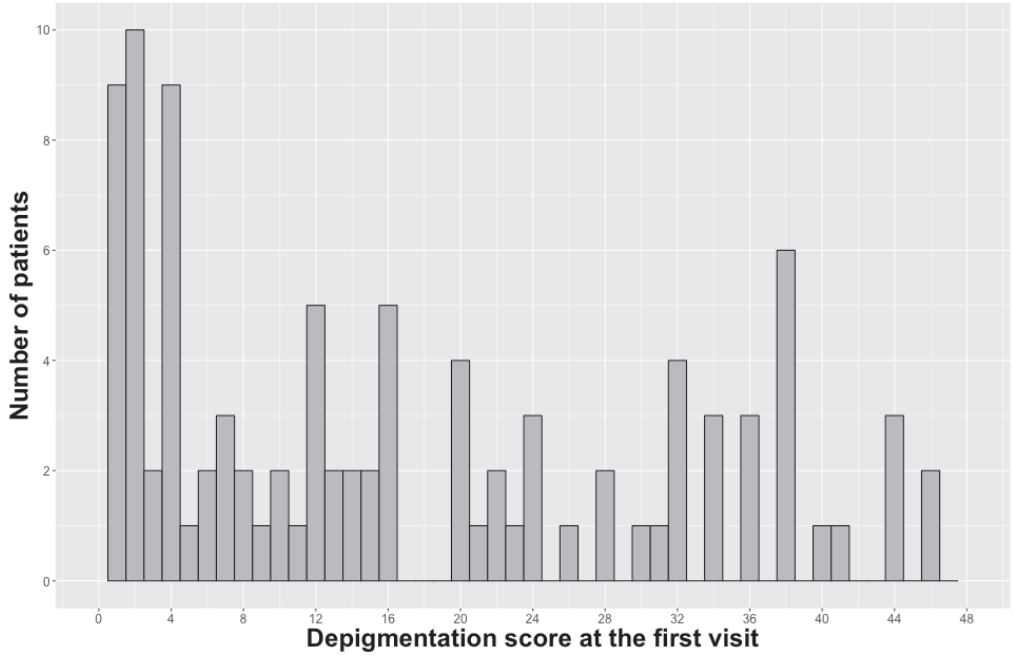

Figure 1. Histograms of depigmentation scores at the baseline visit (n=101). Most patients presented with a relatively low depigmentation score.

The effect of smoking

As indicated by linear regression analysis (Table 2), patients who have smoking history had significant increases in the depigmentation score at the baseline visit (coefficient 1.239, p=0.012). The other factors such as age, the number of RD-containing products used, BMI, anti-nuclear, and anti-thyroid antibodies did not appear to show a significantly different effect on the first depigmentation score at the baseline visit. Box plots were used to compare the depigmentation scores at the baseline visit between smokers and non-smokers (Fig. 3). That analysis showed that the median of the depigmentation score at the baseline visit was significantly higher among patients with a smoking history (median score 26 for the smokers, 13 for non-smokers, p=0.03).

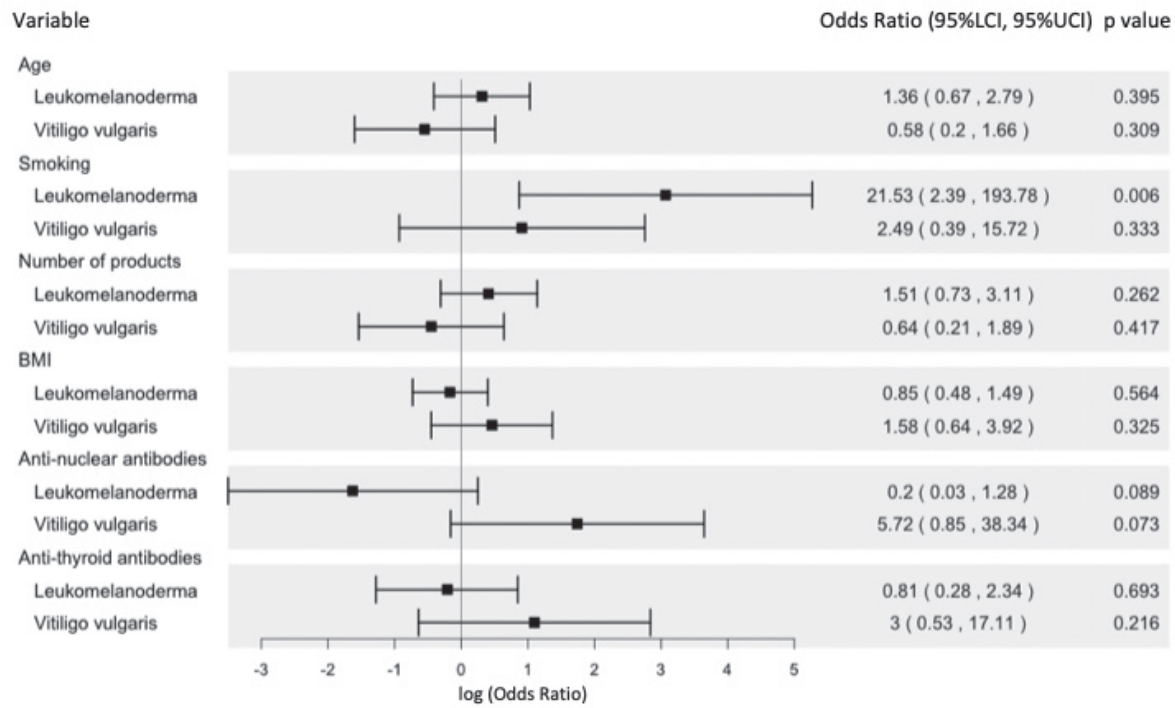

Figure 2. Result of multivariable logistic regression for leukomelanoderma and vitiligo vulgaris including age, smoking, number of rhododendrol (RD) -containing products used, BMI, anti-nuclear, and anti-thyroid antibodies. Odds ratios reflect a comparison between the 25th and the 75th percentile values for each variable. Age, smoking, number of RD-containing products used, BMI, anti-nuclear, and anti-thyroid antibodies were not significantly correlated with leukomelanoderma and/or vitiligo vulgaris, but leukomelanoderma was likely to occur in patients who had a smoking history (odds ratio 21.53, 95% CI 2.39-193.78; p=0.006).

Table 2. Linear regression analysis of the effect of each factor on the depigmentation scores at the baseline visit

Variable	Coefficient	95% CI	p value
Age (IQR: 48-70)	1.295	[0.897, 1.869]	0.165
Smoking	1.239	[1.239, 5.505]	0.012
Number of products (IQR: 5-17)	1.004	[0.856, 1.177]	0.960
BMI (IQR: 19.6-23.5)	0.915	[0.685, 1.223]	0.546
Positive for anti-nuclear antibody	0.788	[0.387, 1.644]	0.522
Positive for anti-thyroid antibody	1.258	[0.695, 2.277]	0.444

Coefficients are indicated as % increase in depigmentation scores at the baseline visit by IQR increase in the corresponding covariates. IQR, interquartile range.

Discussion

This study shows that smoking is associated with the increase of the depigmentation score at the baseline visit and also the development of leukomelanoderma. To the best of our knowledge, only one clinical study exists regarding the risk factors related to RD-induced leukoderma[12]. Patients with a history of atopic dermatitis or patients who had a higher depigmentation score at the baseline visit significantly developed vitiligo vulgaris after the RD-induced leukoderma[12]. However, this is the first report referring to an association between smoking and RD-induced leukoderma.

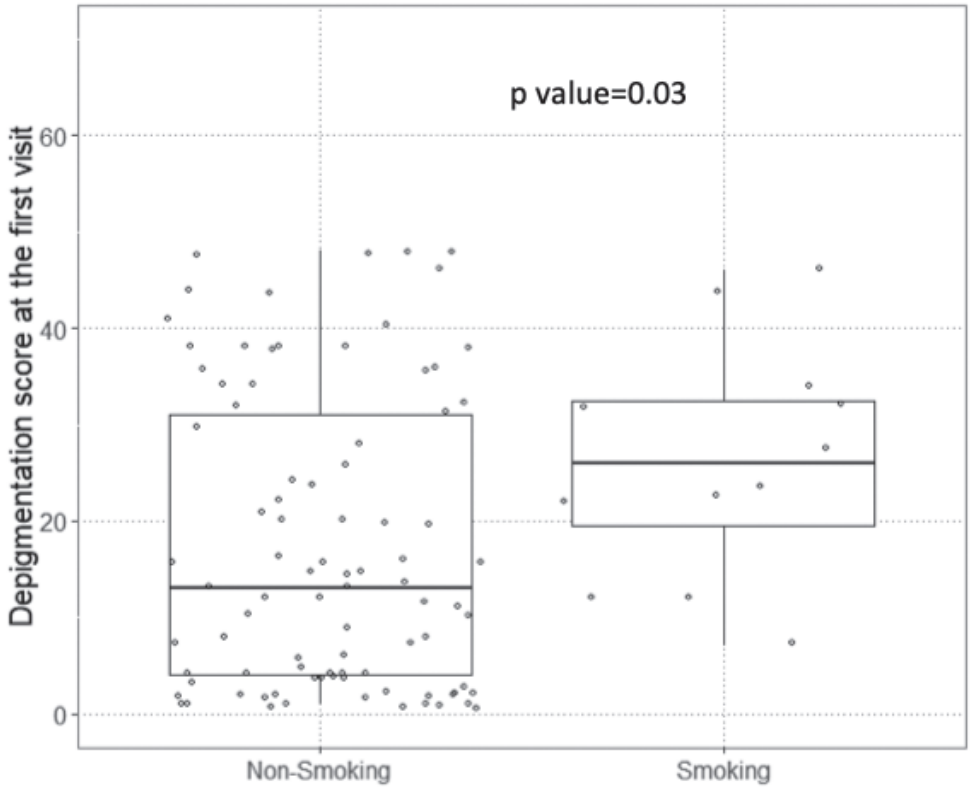

Figure 3. Box plots of depigmentation scores at the baseline visit by smokers and non-smokers. Mann-Whitney U test showed the median depigmentation score of smokers at the baseline visit is higher than non-smokers (median score 26 for smokers, 13 for non-smokers, p=0.03).

RD is a competitive inhibitor of tyrosinase and reduces melanin production, but it is also cytotoxic to human melanocytes[5]. One of the mechanisms for its cytotoxicity is the effect of RD-quinone through binding with sulfhydryl proteins, and the other is the pro-oxidant activity of RD-derived melanins that leads to oxidative stress[13]. Within human melanocytes, tyrosinase oxidizes RD to RD-quinone and RD-cyclic-quinone which is cytotoxic to melanocytes. When these toxic substances combine with thiol-containing chemicals such as glutathione (GSH) and cysteine (Cys), they will be detoxified to RS-catechol and RS-cyclic-catechol[7,14,15]. RD-catechol and RD-cyclic catechol which are metabolites of RD-quinone generate superoxide in the process of their oxidization. It has also been reported that superoxide dismutase (SOD) oxidizes superoxide to hydrogen peroxide (H_2O_2) and oxygen. H_2O_2 which is one type of ROS, is detoxified by combining with a thiol group[14]. In smokers, the plasma levels of GSH and Cys have been shown to be significantly lower than in nonsmokers[16]. Thus, metabolites of RD and ROS are supposed to be less detoxified in smokers, given that GSH and Cys are exhausted from the detoxification of smoking-related chemicals.

Leukomelanoderma is a combined form of dyspigmentation, composed of speckled pattern of hyperpigmentation along with wider areas of hypopigmentation (Fig. 4). Leukomelanoderma can be caused by the medication history, such as oral thiazide-based diuretics[17,18], and by the application of hydroquinone[19]. The mechanism of leukomelanoderma induced by medication may be due to sun exposure, the color of the skin and the genetic predisposition, however, none of these are obvious[18].

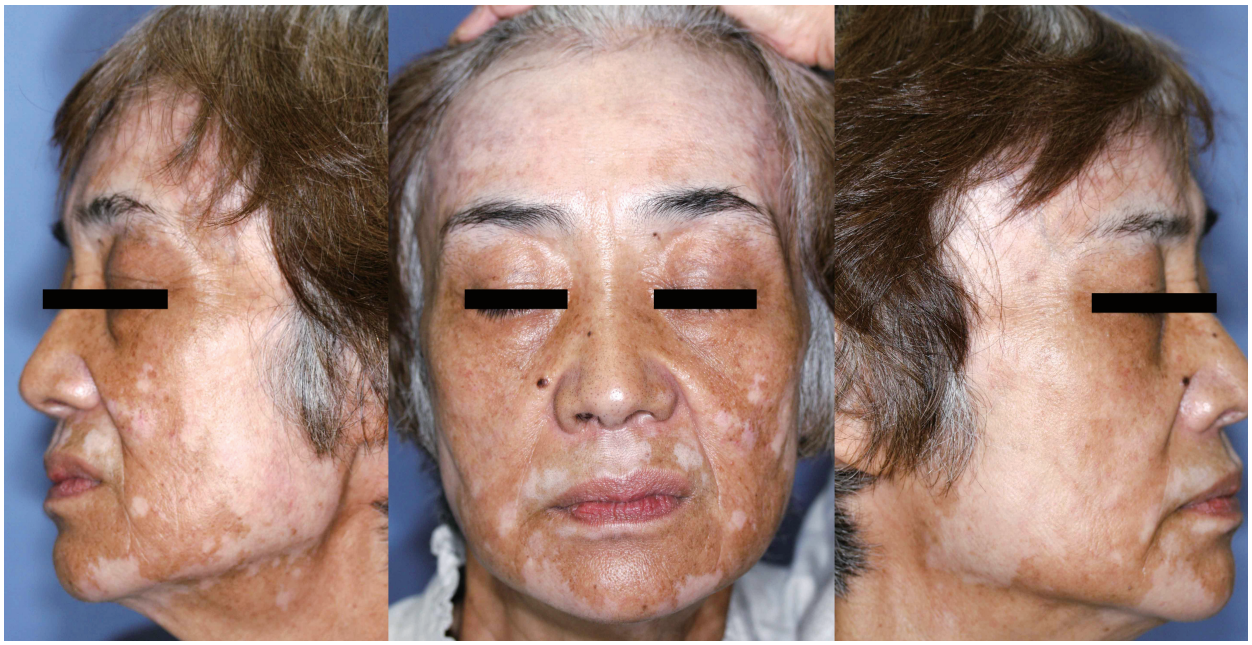

Figure 4. Clinical appearance of leukomelanoderma. Speckled hyper- and hypo-pigmentation are intermixed on a relatively wide range of the skin. This patient was 69-year-old woman who had a smoking history at the first visit. Her depigmentation score was 28.

In regard to hydroquinone, the combination of post-inflammatory pigmentation induced by contact dermatitis and hydroquinone-induced leukoderma has been postulated[19]. In fact, contact dermatitis due to RD was suggested by positive patch testing, as reviewed by the first epidemiological report from the JDA[2]. The presence of leukomelanoderma considerably lowers the quality of life of patients. It has been reported that perilesional hyperpigmentation was seen in 42% of patients with RD-induced leukoderma[3], and in this study cohort, 48% of the patients had leukomelanoderma.

Tobacco smoking induces several undesirable characteristics of skin aging such as wrinkles and increased skin pigmentation[20-23]. Melanin indices of the skin among current smokers are higher when compared with never and former smokers[23]. Human epidermal melanocytes are activated by water-soluble tobacco smoke through the Wnt/β-catenin signaling pathway and produce more melanin *in vitro*[24].

A limitation of this study is that the number of patients who smoked was small. Although the percentage (12%) was higher than the women's value (8.2%) of a national health and nutrition survey in 2016 in Japan, it may be difficult to generalize our results because the sample size was small.

In conclusion, our study has shown that smoking induces more severe RD-induced leukoderma. The depigmentation score at the baseline visit of smokers is higher, suggesting that cytotoxic substances may accumulate in the course of the metabolism of RD because of the low levels of GSH and Cys in the plasma[16]. In addition, smoking may lead to a higher risk of leukomelanoderma probably due to post-inflammatory pigmentation caused by contact dermatitis.

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All authors have no COI to declare regarding the present study.

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Systematic Stepwise Treatment Strategy and Its Short-term Outcomes for Patients with Corona Virus Disease 2019 Complicated by Acute Respiratory Distress Syndrome

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Abstract

Background

Corona Virus Disease 2019 (COVID-19) continues to be a global crisis, and mortality from COVID-19 remains uncontrolled in several countries. Once the patients acquire acute respiratory distress syndrome (ARDS) concomitantly and require ventilatory support, mortality is reported to reach up to 30%-90%. The aim of this study was to assess our treatment strategy and its outcomes.

Methods

This was a single-center, retrospective study, and all patients admitted due to ARDS following COVID-19 were reviewed. We administrated aggressive prolonged prone positioning with high positive end expiratory pressure. Low dose methylprednisolone was used for all patients. Extracorporeal membrane oxygenation was indicated for the patients in whom PaO_2/FiO_2 (P/F) ratio <80 under our initial treatment strategy.

Results

From March 2020 to June 2020, total of nine patients were hospitalized with polymerase chain reaction-positive Severe Acute Respiratory Syndrome Coronavirus 2 infection concomitant with ARDS. The median age was 72 (47.5-78) years old and all patients were male. The P/F ratio at the time of admission was 116 (69-140). The median Sequential Organ Failure Assessment score was 8 (7-11), and two patients were in a state of septic shock and had already been administrated vasopressors. By performing our strategic treatment, five patients were recovered from ARDS and were successfully extubated without any complications. The total in-hospital mortality rate during

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this study period was 33.3%.

Conclusions

Our systematic stepwise intensive care strategy for ARDS following COVID-19 achieved permissive outcomes compared to the high mortality rate in the world including elsewhere in Japan.

Key Words: ARDS; COVID-19; Mortality; Prone position; Methylprednisolone

Introduction

Patients with Corona Virus Disease 2019 (COVID-19), which has become a global epidemic since December 2019, are often asymptomatic or accompanied by mild fever and respiratory symptoms[1]. However, depending on the patient's background, such as older age and their underlying diseases, COVID-19 can become severe at a rate of about 5%-10%[1,2] and can develop into acute respiratory distress syndrome (ARDS) that requires precise respiratory management and extracorporeal circulation. Once these patients concomitantly acquire ARDS, the mortality rate reportedly rises to 32%-97.2%[1,3-6]. Although the use of drugs such as favipiravir and hydroxychloroquine is currently drawing attention, its effectiveness is still unestablished. And treatment for ARDS following COVID-19 must be modified based on a general ARDS strategy[7,8] because of the extremely rapid deterioration of the respiratory condition and its comorbidities such as hypercoagulopathy and organ infarctions. Furthermore, every step of all required clinical procedures such as endotracheal intubation must be thoroughly modified to avoid secondary infections of essential health care workers.

We retrospectively assessed our treatment strategy and its outcomes in patients with ARDS related to COVID-19.

Methods

In this single-center, retrospective review, we assessed patients admitted to the Trauma and Critical Care Center of Osaka City University Hospital. The records of all patients admitted with COVID-19 concomitant with ARDS were reviewed and included nine patients who were evaluated for outcomes and complications. The classification of severity of ARDS was referenced by Berlin definition[9].

Outlines of our stepwise treatment strategy for ARDS secondary to COVID-19 is shown in Figure 1.

Treatment for COVID-19

For the patients with polymerase chain reaction (PCR) -positive Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, favipiravir and hydroxychloroquine were available drugs in our institution. Favipiravir was administered 3600 mg as the initial dose on the 1st day and 1600 mg per day was continued for the next 14 days. Hydroxychloroquine was administered 400 mg per day and was continued for the next 14 days as well. In view of the potential for community-acquired pneumonia, ceftriaxone (CTRX) and azithromycin (AZM) were administered together until the sputum culture was confirmed. If the result of sputum culture was negative, we terminated these antibiotics and if causative bacteria such as methicillin-resistant staphylococcus aureus had already been detected in previous hospital, we added or continued sensitive drugs for these bacteria.

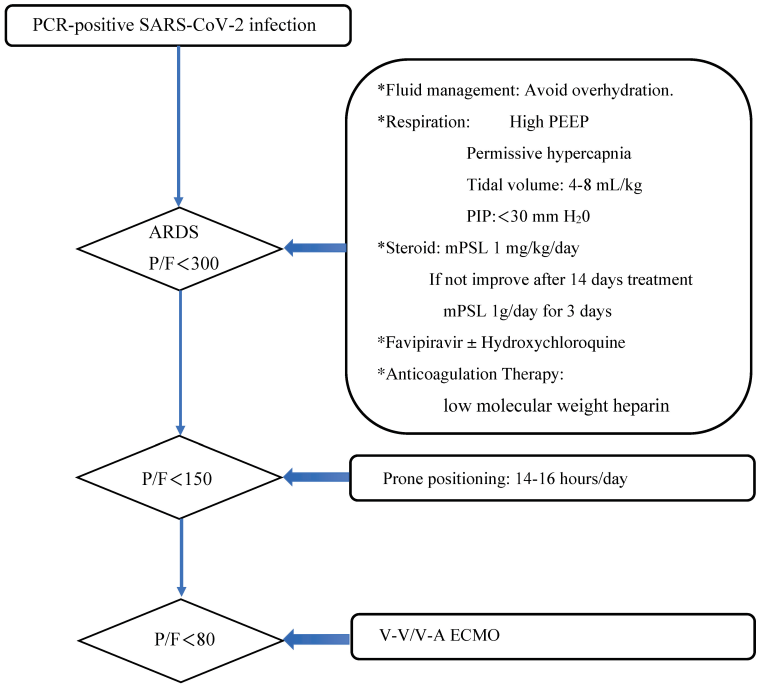


Figure 1. Our stepwise approach to treat ARDS secondary to COVID-19. ARDS, acute respiratory distress syndrome; mPSL, methylprednisolone; PCR, polymerase chain reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; PEEP, positive end-expiratory pressure; P/F, PaO_2/FiO_2; PIP, positive inspiratory pressure; and V-V/V-A ECMO, veno-venous/veno-arterial extracorporeal membrane oxygenation.

Infusion management

Infusion control was based on serum lactate level, stroke volume variation (SVV) between the range of 10%-18%, and echocardiographic evaluation such as measuring the length of left ventricular end-diastolic diameter between the range of 35-40 mm and the length of inferior vena cava diameter between the range of 8-15 mm.

If we could not obtain a sufficient mean atrial pressure despite maintaining intravenous volume, norepinephrine and/or dobutamine was administered based on the cardiac function of the patients. If the administration speed of norepinephrine exceeded 0.1 μg/kg/h, we considered adding vasopressin to control systemic peripheral vascular resistance.

Respiratory management

To limit aerosolization from the patients, we adopted a prompt endotracheal intubation strategy if the patients required oxygen at more than 5 L/min. Based on the general recommendations for ARDS, the ventilator adjustment strategy was managed by maintaining high positive end-expiratory pressure (PEEP) and low tidal volume at 4-8 mL/kg of ideal body weight, allowing permissive hypercapnia. To prevent the occurrence of ventilator-induced lung injury, maximum airway pressure was controlled so as not to exceed 30 cm H_2O[7,8,10].

Administration of spontaneous awakening trial under sedation

We used continuous intravenous administration of propofol, dexmedetomidine, midazolam, and fentanyl in combination to maintain the Richmond Agitation and Sedation Scale score at a level of −3 to −5. And we tapered the sedatives once a day to assess the best consciousness level and neurological deficits of the patients.

Administration of prolonged prone positioning

If a PaO_2/FiO_2 (P/F) ratio ≧150 could not be obtained even under maximum appropriate ventilatory support, aggressive prone position therapy was introduced (Fig. 1). To obtain maximum effects of this treatment, the prone position was continued for >14 hours but <16 hours to avoid complications such as pressure ulcers[11,12].

Administration of extracorporeal membrane oxygenation (ECMO)

In patients in whom a P/F ratio of >80 could not be obtained even with the addition of prone position therapy and there were no absolute contraindications for the patients, we introduced veno-venous ECMO as an additional treatment option.

Use of corticosteroids

We immediately started low-dose methylprednisolone at 1 mg/kg/day if the patients met the diagnostic criteria for ARDS.

On the basis of one report[13], we considered the administration of a high dose of methylprednisolone at 1 g/day for 3 days as a steroid pulse only in patients in whom we could not obtain adequate oxygenation even after administration of best current treatment strategy for 14 days (Fig. 1).

Prophylactic administration of low molecular weight heparin

If there were no hemorrhagic complications on admission, we started low molecular weight heparin from the 1st day of admission because of the reports of a high incidence of complications of hypercoagulopathy specified to COVID-19[13-15]. If the patients were complicated by disseminated intravascular coagulopathy (DIC) as calculated by acute DIC score during their clinical course[16], we converted to the use of recombinant human soluble thrombomodulin and added antithrombin (AT-Ⅲ) if the value of AT-Ⅲ in the blood examination was <70%.

Statistical analysis

Statistical values are expressed as the median (interquartile range 25%-75%) or number (%).

Results

From March 2020 to June 2020, total of nine patients were hospitalized with PCR-positive SARS-CoV-2 infection and respiratory failure associated with ARDS. The previous medical histories of the patients are shown in Table 1. The median age of the patients was 72 (47.5-78) years old, and all patients (100%) were male. The number of days from disease onset to admission to our hospital was 9 (5.5-13.5) days. All nine patients (100%) met the criteria for ARDS based on the Berlin definition. Three patients had already been treated with Ciclesonide in previous hospital. The history of smoking was the most frequent background (88.9%) and their median Sequential Organ Failure Assessment score was calculated as 8 (7-11)[17]. Three patients (33.3%) were complicated by DIC. Two patients were already suffering acute kidney failure, and two patients were in shock and had already been administered vasopressors at a previous hospital. The other comorbidities and underlying diseases detected on admission were concomitant methicillin-resistant *Staphylococcus aureus* pneumonia in one patient, massive cerebral infarction in one patient (Table 2).

The results of the main blood tests and radiological type of COVID-19 infection obtained at admission are shown in Table 3. The P/F ratio at the time of admission was 116 (69-140), and seven (77.8%) of patients had already been intubated at a previous hospital. lactate dehydrogenase (LDH) on admission was 408 (387.5-847.5) international unit (IU/L), krebs von der lungen 6 (KL-6) was 887 (466.5-2833.5) Unit/mL, and C-reactive protein (CRP) was 17.7 (8.66-25.01) mg/dL. Type of

Table 1. Demographic Data of the Patients

	N=9
Sex	9 (Male 100%)
Age, years	72 (47.5-78)
Type of admission	
Transferred from other hospital	9 (100%)
Physiological data on arrival	
GCS	6 (3-15)
HR (beats per min)	98.0 (87.5-128.5)
Systolic blood pressure (mm Hg)	158.0 (137.5-163.5)
Body temperature (℃)	37.5 (36.6-38.0)
Past medical history / Underlying disease	
Current/Ex-smoker	8 (88.9%)
Alcohol abuser	1 (11.1%)
Hypertension	3 (33.3%)
Diabetes	4 (44.4%)
Hyperlipidemia	1 (11.1%)
Stroke	0
Cardiac failure	3 (33.3%)
COPD	1 (11.1%)
Chronic kidney disease	1 (11.1%)
Post nephrectomy	1 (11.1%)
Current malignant lymphoma treatment	1 (11.1%)
SOFA score on admission	8 (7-11)

Statistical data are presented as median (25%-75% interquartile range) or number. GCS, Glasgow Coma Scale; HR, heart rate; COPD, chronic obstructive pulmonary disease; and SOFA, Sequential Organ Failure Assessment.

Table 2. Concomitant Complications on Arrival

	N=9
Concomitant complications on arrival	
ARDS	9 (100%)
MRSA pneumonia	1 (11.1%)
Massive cerebral infarction	1 (11.1%)
Cardiac failure	2 (22.2%)
Acute kidney injury	2 (22.2%)
Endotracheal intubation/Ventilator	7 (77.8%)
Septic shock requiring Vasopressor	2 (22.2%)
DIC	3 (33.3%)

Statistical data are presented as number (percent). ARDS, acute respiratory distress syndrome; MRSA, methicillin-resistant *Staphylococcus aureus*; and DIC, disseminated intravascular coagulopathy.

COVID-19 infection classified by computed tomography (CT) scan was three in Type L that showed only ground-glass densities are present, and six in Type H that showed a remarkable increase in lung weight.

The details of the clinical data were described in Table 4. Prone position therapy was performed

Table 3. Examination Results

	N=9
P/F ratio	116 (69-140)
Base excess	−4.0 (−4.9- −2.7)
pH	7.34 (7.29-7.37)
Lactate level (mmol/L)	0.9 (0.7-1.3)
WBC (/μL)	6600 (3700-16300)
Plt ($\times 10^4$/μL)	12.9 (8.05-19.5)
CRP (mg/dL)	17.7 (8.66-25.01)
Cr (mg/dL)	0.97 (0.76-1.58)
BUN (mg/dL)	19 (14.5-53)
CK (IU/L)	227 (99.5-347.0)
LDH (IU/L)	408 (387.5-847.5)
KL-6 (Unit/mL)	887 (466.5-2833.5)
HgbA1c (%)	6.1 (5.75-7.7)
T-Bil (mg/dL)	0.5 (0.35-1.0)
Fibrinogen (mg/dL)	539 (431.0-666.5)
FDP (μg/mL)	6.4 (5.1-99.2)
PT-INR	1.08 (0.98-1.4)
Type of COVID-19 infection classified by CT scan	
Type L	3 (33.3%)
Type H	6 (66.7%)

Statistical data are presented as median (25%-75% interquartile range). P/F, PaO_2/FiO_2; WBC, white blood cell count; Plt, platelet count; CRP, C-reactive protein; Cr, creatinine; BUN, Blood urea nitrogen; CK, Creatinekinase; IU/L, international unit; LDH, lactate dehydrogenase; KL-6, krebs von der lungen 6; HgbA1c, hemoglobin A1c; T-Bil, total bilirubin; FDP, fibrinogen degradation products; and PT-INR, prothrombin time-international normalized ratio.

in six (66,7%) patients, and it could be performed for 16 (14.5-16.5) hours/day. Three patients (33.3%) were received steroid pulse dose therapy for three days after being treated 14 days our best tactical treatment. The respiratory condition of two patients improved significantly shortly after administration of high-dose steroids, but ARDS in the other one patient did not show significant improvement. As the results, two of these three patients had worsened the respiratory conditions and died during admission. The concomitant complications observed during admission were ventricular fibrillation in one patient (11.1%), bacterial pneumonia in three patients (33.3%), tension pneumothorax in one patient (11.1%) and mediastinal emphysema in two patients (22.2%). One of these patients (11.1%) with mediastinal emphysema had detected tracheoesophageal fistula and treated conservatively. Acute renal injury requiring renal replacement therapy were concomitant with four patients (44.4%) and intravenous thrombosis were detected in one patient (11.1%).

One patient was considered to be indicated on ECMO therapy based on the P/F ratio at the time of admission. However, as a massive cerebral infarction was also detected by computed tomography scan on admission, we decided not to administrate ECMO, and conservative best medical treatment was continued for this patient. Thus, ECMO was not required in any patient (0%), and renal replacement therapy was administered in 3 patients due to acute kidney injury (33.3%).

Recovery from ARDS and successful extubation was achieved in five patients over 7 (5.5-10.5) days, and they were transferred to another hospital at 10 (6.5-13.5) days after admission. One

Table 4. Clinical Courses

	N=9
Successful extubation	5 (50%)
Length of ventilator support from admission, days	7 (5.5-10.5)
Length of stay in ICU, days	10 (6.5-13.5)
Length of ventilator support from admission, days	17.5 (7.5-27)
Length of stay in ICU, days	18.5 (10-27)
Required prone positioning	6 (66.7%)
Length of prone positioning, days (hours)	16 (14.5-16.5)
Requiring blood transfusion	1 (11.1%)
Low-dose steroid use	9 (100%)
High-dose steroid use after 14 days from admission	3 (33.3%)
Vasopressor use	9 (100%)
Max catecholamine index	5.5 (4.5-9)
CRRT	4 (44.4%)
ECMO	0
Tracheostomy	1 (11.1%)
Concomitant comorbidities during admission	
Ventricular fibrillation	1 (11.1%)
Tension pneumothorax	1 (11.1%)
Bacterial pneumonia	3 (33.3%)
Mediastinal emphysema	2 (22.2%)
Tracheoesophageal fistula	1 (11.1%)
Endotracheal re-intubation	1 (11.1%)
Acute kidney injury requiring CRRT	4 (44.4%)
Deep venous thrombosis	1 (11.1%)
Systemic fungal infection	1 (11.1%)
Mild pressure sore (prone-positioned patient)	3/6 (50%)
CPC grade obtained on disposition	
Ⅰ	5 (55.6%)
Ⅱ	0
Ⅲ	0
Ⅳ	1 (11.1%)
Ⅴ	3 (33.3%)
In - hospital mortality	3 (33.3%)

Statistical data are presented as median (25%-75% interquartile range) or number. CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; and CPC, Cerebral Performance Category.

patient (Patient 7 in Fig. 2) improved respiratory conditions and transferred to another hospital with intubated. Another one (Patient 6 in Fig. 2) patient was performed tracheostomy because of prolonged ventilation time on thirty-nine days after admission for treating respiratory conditions and tracheoesophageal fistula. The obtained Cerebral Performance Category (CPC) of the nine patients at the points of disposition was 1 in five patients (55.6%), 2 in zero, 3 in zero, 4 in one (11.1%), and 5 in three patients (33.3%). Mild pressure sores developed after long-term prone position therapy in three patients (50%) on the anterior lower jaw and anterior thoracic wall in all three. Eight patients (88.9%) converted to negative on a follow-up PCR SARS-CoV-2 test after 14 days of treatment. Final in-hospital mortality was three patients (33.3%) during this study period.

Figure 2 shows the timeline of all patients. We had checked PCR again after 14 days of treatment

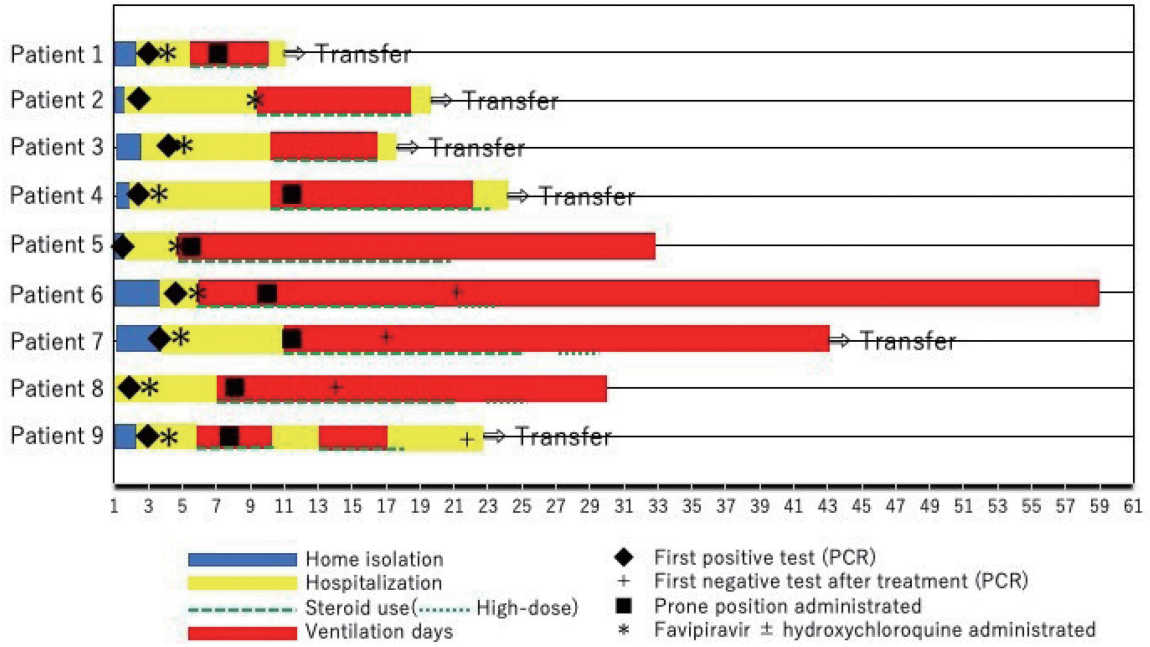


Figure 2. The timeline of all patients. PCR, polymerase chain reaction.

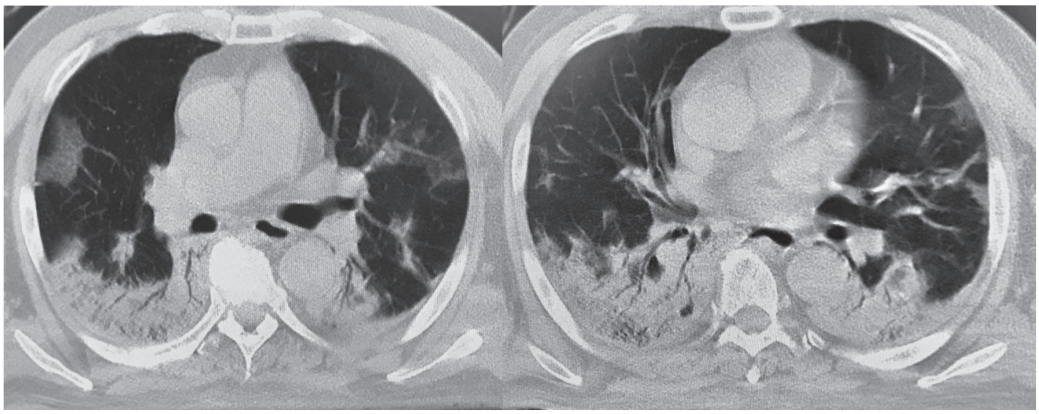
except being extubated and transferred patients. One patient (Patient 5 in Fig. 2) with a current history of lymphoma died due to multiple organ failure and recurrent exacerbation of respiratory function probably because of the patient's immunocompromised condition. The conversion of PCR-negative for SARS-CoV-2 test and viral seroconversion tested by serum antibody was not observed only this patient after 14 days of treatment. The cause of the death of another patient (Patient 8 in Fig. 2) was the result of a do not attempt resuscitation (DNAR) request obtained from the patient's family due to failure of the patient to regain consciousness following a massive cerebral infarction that was detected on admission. The other one patient (Patient 6 in Fig. 2) had once recovered from ARDS, but died because of decreased respiratory conditions due to pulmonary fibrosis and multiple organ failure including systemic fungal infection at the 57 days after admission. The CT scan of this patient at the time of admission and after 14 days treatment were shown in Figure 3.

Discussion

Although there are currently several recommended treatment strategies for COVID-19 and concomitant ARDS, the mortality rate remains high globally, especially among patients requiring mechanical ventilation. As a clinical finding, the lung compliance of our patients was significantly poor, and almost all patients required a high intra-tracheal pressure close to 30 cm H_2O to obtain the targeted tidal volume.

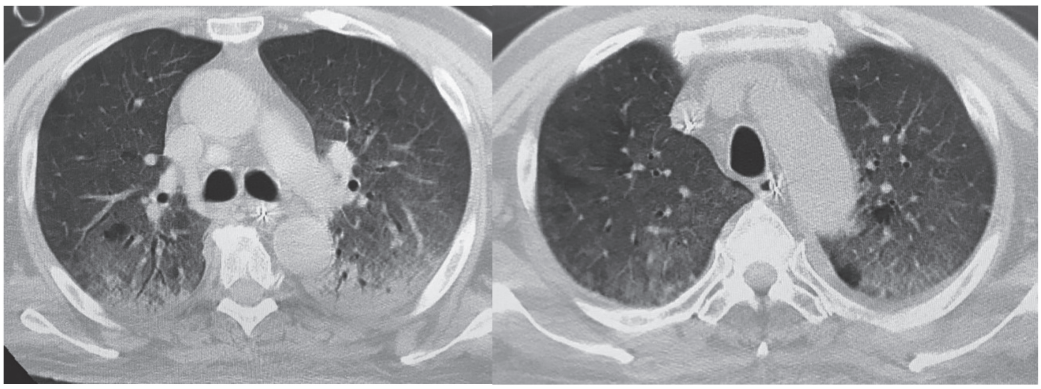
Respiratory disfunction due to ARDS is mainly due to the collapse of bilateral dorsal lung alveoli and atelectasis; hence, the prone position was recommended to correct the ventilation/perfusion (V/Q) mismatch from ARDS[7,8,15]. We also consider this positioning to allow the most invasive and secure therapy for these patients, and thus we continued the prone position for 14-16 hours if it was indicated for the particular patient. We consider this prolonged prone position strategy especially for Type H patients was the most effective and important treatment for COVID-19 patients since the

A



a b

B



a b

Figure 3. Lung computed tomography image of the same patient on the time of admission (A) and after 14 days treatment (B). (A) CT shows predominant bilateral and peripheral consolidation with areas of air bronchogram (a, b) and focal ground-glass opacities associated with smooth interlobular and intralobular septal thickening in the right lower lobes (crazy-paving pattern). (B) The CT scan of the same patient after 14 days of treatment. CT shows advanced stage of bilateral dependent consolidation and pulmonary fibrosis with bronchiectasis were detected especially in the anterior lung regions (a). A less common but bilateral and predominant peripheral consolidation pattern with round cystic changes is also detected internally (b).

respiratory condition of the patients improved significantly during prone positioning.

ECMO is always available for patients with ARDS in our institution, and we recognize that its administration is effective for acute respiratory or circulatory disfunction. For COVID-19 patients, ECMO indications were recommended as a P/F ratio of less than 60[18], but given the consideration for the difficulty of procedures in unfamiliar environments with wearing full personal protective equipment and of communication between the staffs, we defined the ECMO indication as the P/F ratio of less than 80. However, by performing our treatment strategy faithfully, no patients developed the criteria for ECMO induction during the study period.

The systemic administration of steroids for ARDS is still an issue under global discussion. The

risks and benefits of using steroids for ARDS have been discussed on a global scale, and there is still no strong recommendation for their use[19-21]. Recently, low-dose use of corticosteroid was weakly recommended for general ARDS[19] and also in association with COVID-19[22,23]. The provisional guideline issued by World Health Organization (WHO)[15] stopped recommending the administration of steroid drugs on the basis of several observational studies. However, there are several opinions indicating the usefulness of low-to-moderate doses of steroids in the acute phase[19,22,24]. Based on the findings of Meduri et al[24], we also administer a low dose of steroids in the acute phase of ARDS in our institution.

Although historically there have been some negative opinions regarding high-dose steroid administration for ARDS prolonged to over 14 days after onset[25,26], one report notes that high-dose administration of methylprednisolone permitted the patients to be weaned and the ventilator to be withdrawn[13]. In our study, we administrate high-dose methylprednisolone only for the patients without obtaining improvement after 14 days treatment. Although the respiratory condition of two patients seemed to have improved significantly shortly after administration of high-dose steroids, but the final respiratory conditions and their outcomes did not show significant improvement.

Recently the use of dexamethasone reported to decrease 28-day mortality among those who were receiving invasive mechanical ventilation[27]. Although the administration of dexamethasone for ARDS patients had not been highly recommended so far, WHO guidelines updated the recommendation for using dexamethasone for ARDS following COVID-19 on the basis of this study[15]. We have to consider the indication of dexamethasone especially for receiving invasive mechanical ventilation.

As the treatment drugs for COVID-19, after we had experienced a case of ventricular fibrillation, probably due to prominent QT interval prolongation in patients who use hydroxychloroquine in combination with AZM, and some similar reports from around the world[28], based on electrocardiography at admission and drug-induced corrected QT (QTc) interval prolongation risk score[29], concomitant use of hydroxychloroquine and AZM was discontinued in the patients with moderate risk or higher. And as the sedation strategy, because many complications of hypercoagulation and cerebral infarction in relation to COVID-19 are reported[30-32], we tapered the sedatives once a day to assess the best consciousness level and neurological deficits of the patients and no one had fresh cerebral complications during admission. The incidences of mediastinal emphysema and tracheoesophageal fistula were considered to be occurred due to long-term intubation with high intra tracheal pressure and direct cuff pressure of endotracheal tube to wall of trachea[33,34]. Normally, the cuff pressure is controlled at 20-25 mm Hg[35], but the cuff pressure of this patient was recorded up to 30 mm Hg in order to limit the aerosolization and to withstand high-PEEP ventilation. As another considerable factor, although we usually perform tracheostomy around 14 days after being intubated, we suspended performing this procedure due to minimize aerosolization for the COVID-19 patients. As the limitations of current report, since this is the single-center study and small preliminary report describing our treatment strategy and its short-term outcomes, and further multi-institutional evaluation will be needed.

We conclude that our systematic stepwise intensive care strategy for treating ARDS secondary to COVID-19 achieved permitted outcomes compared to the high mortality rate seen around the world including elsewhere in Japan. We have to follow up these patients continuously to assess their long-term outcomes.

Acknowledgements

All authors have no COI to declare regarding the present study.

Written informed consent for this report was obtained from patients and if not available from the patient, the consent was obtained from their family members.

We sincerely dedicate this paper to all essential health workers who have fought against COVID-19 not only directly but also secondarily in Osaka City University Hospital. The excellent results are due to the tremendous cooperation and teamwork of all of the involved staff such as in preventing nosocomial infections, redistributing staff, and temporarily limiting elective operations.

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Complications after Open Reduction and Internal Fixation of Olecranon Fractures: Elderly vs Young

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Abstract

Background

Although tension band wiring (TBW) is used commonly for simple olecranon fractures, we often encounter redisplacements in the elderly. We hypothesized that elderly patients have more complications after olecranon fracture operations than young patients. Therefore, we compared outcomes of these procedures including complications in young and elderly patients.

Methods

We retrospectively investigated outcomes including complications of 31 patients aged ≧65 years and 40<65 years who underwent olecranon fracture operations at two hospitals. Average follow-up was 10 months. Complications included redisplacement (fracture site displaced ≧2 mm), non-union and infection. We statistically compared the outcomes of TBW (simple TBW and ring pin) and locking plate between elderly and young patients.

Results

Redisplacement occurred in 21 elderly patients (67%), 2 of whom (6%) had huge displacements resulting in nonunion. The postoperative redisplacement rate using TBW in the elderly was significantly higher than that in young patients (71% vs 27%, $p<0.001$). The postoperative redisplacement rate using locking plate in the elderly was not significantly higher than in young patients (33% vs 10%, $p=0.07$). There was no statistically significant difference in redisplacement rate and distance among simple TBW, ring pin and locking plate. We confirmed no deep infections, but only superficial infection in one patient in each group.

Conclusions

Elderly patients had more complications after olecranon fractures, including redisplacement rate and distance, especially when TBW was used. However, there were no statistically significant differences in redisplacement rate and distance among the implants.

Key Words: Fracture: Olecranon; Complication; Elderly patient; Osteoporosis; Displacement

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Introduction

With an increasingly aging society, fracture fixation modalities for patients with osteoporotic bone are changing. Although tension band wiring (TBW) is used commonly for simple olecranon fractures, some reports recommend plate or suture anchor fixation for highly comminuted fractures in the elderly. Complications such as redisplacement, infection and non-union may lead the loss of function and some cases may relate in the mortalities of the elderly[1-4]. We report outcomes including complications of olecranon fractures in the elderly compared to those of young patients. We hypothesized that elderly patients have more complications after surgical operations of olecranon fractures than young patients.

Methods

We received institutional review board approval for this study. We used electronic medical charts to identify 96 patients who underwent surgery for olecranon fractures between January 2011 and December 2016 at our hospital and another related hospital. All charts were reviewed in 71 patients (37 men, 34 women). We divided the patients into two groups, Group O aged ≧65 years (31 patients) and Group Y aged <65 years (40 patients). Average age at surgery was 58 years (range, 15-95). Minimum follow-up period was 6 months postoperatively. We excluded patients who showed no range of motion (ROM) data at the final follow-up. The right and left sides were affected in 21 and 50 patients, respectively. Average follow-up period was 10 months (range, 6-17). According to the Mayo classification[5], one patient had Type Ⅰ, 27 Type ⅡA, 38 Type ⅡB, and five Type ⅢB fractures. All patients with Types Ⅰ and ⅡA fractures were treated with TBW. Types ⅡB and ⅢB fractures were treated with locking plate in 13 patients and TBW in 30 patients (Table 1). Simple TBW, ring pin (TBW with eyelet preventing wire backout), and three kinds of locking plates were used. Although we usually chose locking plates for highly comminuted fractures, the implants were chosen according to the operators' preference. We usually used splint for 1 or 2 weeks after surgery. Redisplacement was defined when the fracture site was displaced ≧2 mm postoperatively on a plain X-ray examination[6]. Redisplacement distance was defined as the gap between fracture fragments, and we calculated the average values of redisplacement cases.

We investigated complications including redisplacement rate and distance as primary outcomes. We statistically compared the outcomes of TBW and locking plate between groups O and Y. Furthermore, we statistically compared the outcomes of TBW only for simple fractures (Type Ⅰ and ⅡA). We also investigated the redisplacement rate and distance statistically for three different implants (TBW, ring pin, and locking plate). Secondary outcomes were active ROM of the elbow at final follow-up and other complications, such as non-union, implant irritation, reoperation and infection. Statistical analyses were performed with Fisher's exact test, Mann–Whitney U test and Kruskal-Wallis test. All statistical analyses were performed with EZR, which is for R. More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics. $P<0.05$ was considered statistically significant.

Results

Demographic data were not statistically significantly different between the groups. Follow-up was longer in group Y (Tables 1 and 2). Redisplacement rates in cases using TBW were 71% in group O and 27% in group Y ($p<0.001$). Redisplacement rates in cases using TBW for simple fracture were

Table 1. Mayo classification

	≧65 y	<65 y	Total
Type Ⅰ	0 (0%)	1 (2.5%)	1
Type Ⅱ A	15 (48.4%)	12 (30%)	27
Type Ⅱ B	14 (45.2%)	24 (60%)	38
Type Ⅲ B	2 (6.5%)	3 (7.5%)	5
			* p=0.384

TBW (simple TBW and TBW with eyelet)

	≧65 y	<65 y	Total
Type Ⅰ	0 (0%)	1 (3.3%)	1
Type Ⅱ A	15 (53.6%)	12 (40%)	27
Type Ⅱ B	12 (42.9%)	15 (50%)	27
Type Ⅲ B	1 (3.6%)	2 (6.7%)	3
			* p=0.618

Locking plate

	≧65 y	<65 y	Total
Type Ⅰ	0 (0%)	0 (0%)	0
Type Ⅱ A	0 (0%)	0 (0%)	0
Type Ⅱ B	2 (66.6%)	9 (90%)	11
Type Ⅲ B	1 (33.3%)	1 (10%)	2
			* p=0.423

* Fisher's exact test. TBW, tension band wiring.

Table 2. Demographic data, follow-up period, complications and ROM

		Group O	Group Y	p value
Sex	Male	19	15	* 0.058
	Female	12	25	
Affected side	Right	10	29	* 0.794
	Left	21	11	
Implant	TBW	14	16	* 0.252
	Ring pin	14	14	
	Plate	3	10	
Follow-up		8 M	10 M	** 0.02
Rediplacement rate		64%	23%	* <0.001
Rediplacement distance		3 mm	2 mm	** 0.16
ROM	flexion	140°	140°	** 0.285
	extension	8°	10°	** 0.04
non-union		2	0	
irritation		1	0	
reoperation		3	1	
infection		1	1	

* Fisher's exact test, ** Mann-Whitney U test. M, month; ROM, range of motion; and TBW, tension band wiring.

66% in group O and 23% in group Y (p=0.03). Redisplacement rate in cases using locking plate was not significantly different between group O and Y (Table 3).

Displacement occurred on an average of 1.9 weeks after surgery. Redisplacement distance in cases using TBW was 4.8 mm in group O and 3.3 mm in group Y (p=0.281), and redisplacement distance in cases using TBW for simple fracture was 5.1 mm in group O and 2 mm in group Y (p=0.019) (Table 3). Redisplacement rate and distance were not significantly different among TBW, ring pin, and locking plate (Table 4). Although ROMs of flexion were not significantly different between the groups, ROMs of extension in group O were significantly worse than those in group Y (Table 2).

Two patients in group O had huge displacements resulting in non-union without reoperation. Reoperation was not possible in one because of multiple general diseases, while the other refused reoperation. Redisplacement occurred in 2 cases of plate fixation and 28 cases of TBW. Reoperation was performed for three patients in group O and one in group Y. We confirmed no deep infections, but only superficial infection in one patient in each group (both recovered with use of oral antibacterial agents).

Two cases of complications after surgical operations are presented. Patient 1 is an 84-year-old woman sustained a Type ⅡA fracture fixed using TBW. Wire back-out from the bone fragment occurred at 1 month postoperatively. Reoperation was performed because of skin irritation. The wire back-out reocurred, but we delayed removal of the implant after bony union was confirmed. ROM at last follow-up was −15° extension and 110° flexion (Fig. 1). Patient 2 is an 86-year-old man sustained a Type ⅡB fracture fixed using a locking plate (VA-LCP® OLECRANON PLATE 2.7/3.5). Because of poor capturing of the proximal locking screw to the bone fragment, redisplacement occurred at 1 week

Table 3. Displacement rate and distance

		Group O	Group Y	p value
TBW (simple TBW and ring pin)				
Displacement	rate	71%	27%	*<0.001
	distance	3 mm	2 mm	**0.281
TBW for simple fracture (Type Ⅰ and ⅡA)				
Displacement	rate	66%	23%	*0.03
	distance	3.5 mm	2 mm	**0.019
Locking plate				
Displacement	rate	33%	10%	*0.073

*Fisher's exact test, **Mann-Whitney U test. TBW, tension band wiring.

Table 4. Redisplacement rate and distance by each implant

Displacement	Group	TBW	Ring pin	Plate	p value
Rate	O	9 (64%)	11 (79%)	1 (33%)	*0.29
	Y	5 (31%)	3 (21%)	1 (10%)	*0.51
Distance	O	4.0 mm	2.0 mm	20 mm	**0.09
	Y	2.0 mm	2.0 mm	2.0 mm	**0.33

*Fisher's exact test, **Kruskal-Wallis test. TBW, tension band wiring.

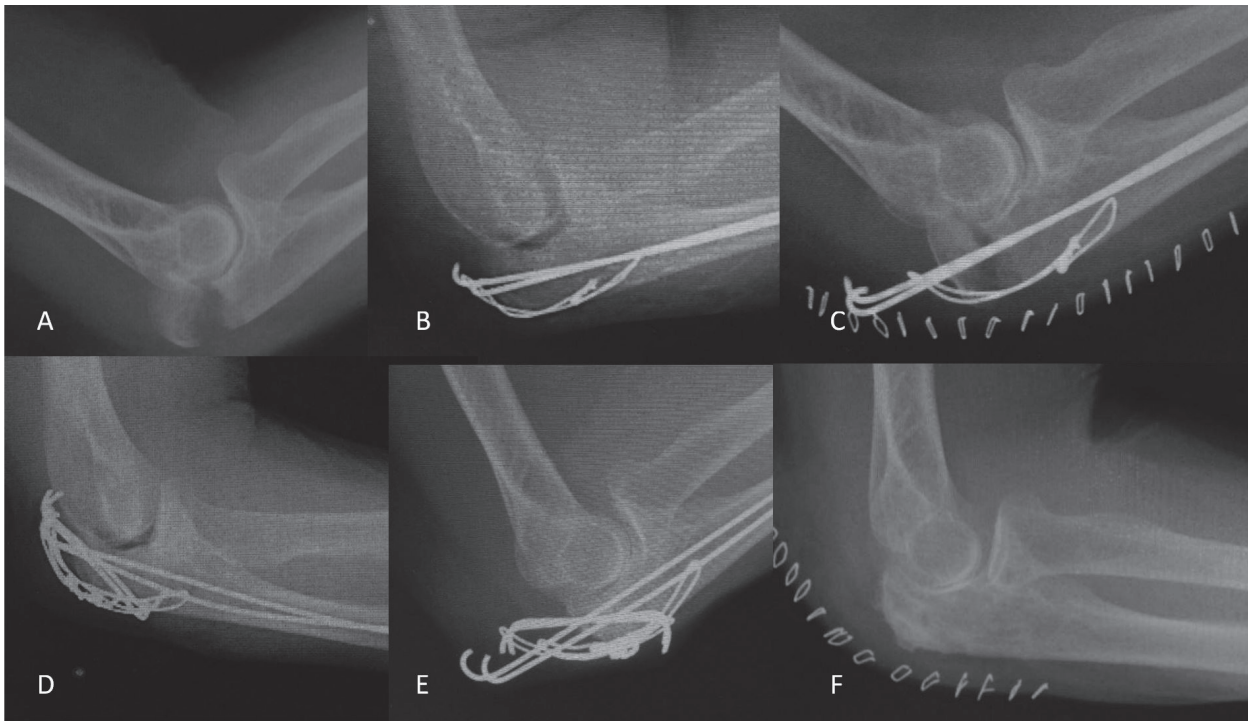

Figure 1. An 84-year-old elderly female with type Ⅱ A fracture. A, Preoperative X-ray. B, Immediate postoperative X-ray. C, One month postoperative X-ray. D, Immediate post-reoperation X-ray. E, Two weeks post-reoperation X-ray. F, Final follow-up X-ray.

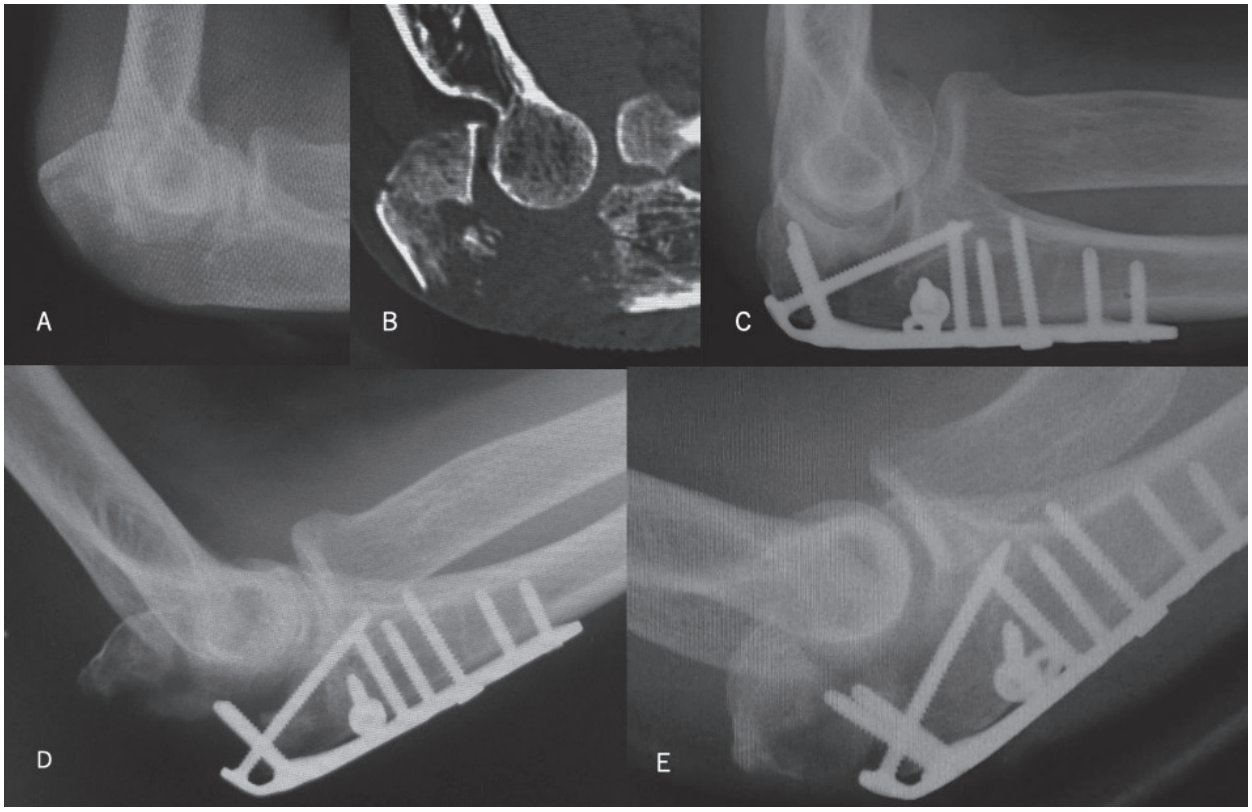

Figure 2. An 86-year-old elderly male with type Ⅱ B fracture. A and B, Preoperative X-ray and computed tomography. C, Immediately postoperative X-ray. D, One week postoperative X-ray. E, Final follow-up X-ray.

postoperatively. The patient refused reoperation, resulting in non-union. ROM at last follow-up was −15° extension and 145° flexion (Fig. 2).

Discussion

Olecranon fracture is not an osteoporotic fracture[7,8], but we often encounter failures after open reduction and internal fixation in the elderly with olecranon fractures. Several reports have evaluated various implants such as ring pins to prevent wire backout and nails and double plates to achieve rigid fixations. However, to our knowledge no reports compared the distance or rate of redisplacement between each implant. Which implant is best to fix osteoporotic bone has been controversial. Patients with redisplacement resulting in union recover very well, and patients with a huge redisplacement who subsequently underwent reoperation had severe contracture and worse recovery. Otherwise, patients with a huge redisplacement and resulted in non-union gained wide ROMs (Figs. 1 and 2). Whether to perform reoperation should be considered carefully.

According to our results, the redisplacement rate was higher in elderly than young patients. There was a statistically significant difference only in the rates of redisplacement in cases using TBW between in the elderly and young, but there were significant differences in both distance and rate of redisplacement in cases using TBW for simple fractures. And there were no significant differences in distance and rate of redisplacement using locking plate. Wilson et al reported that precontoured plates provide significantly greater compression than TBW in the treatment of transverse fractures of the olecranon[9]. Hume et al reported that plate fixation achieved good functional results more often than TBW in a prospective randomized study. Loss of reduction was more frequent with TBW (53%) than with plate fixation (5%)[10]. Recently, plates with multidirectional locking screws are available for comminuted olecranon fractures. We considered that the locking plate osteosynthesis is an effective and safe tool for comminuted olecranon fractures in the elderly[11-13]. However, we are concerned that surgery time may be longer and the occurrence of complications, such as infection, might be increased.

The main factor of redisplacement seemed to be our technical errors. There was a possibility of inadequate fracture fixations due to insufficient evaluation of preoperative fracture patterns. Some patients experienced immediate postoperative wire loosening. On the other hand, one patient with an ipsilateral trochanteric femoral fracture had redisplacement when she performed gait exercise of the lower extremity, although fracture fixation was strong enough. Jin et al reported that TBW using Kirschner wire with eyelets produced excellent clinical and radiographic outcomes[14]. However, no significant improvement in the post operative pain relief was observed. Similarly, in our results, there were no significant differences in redisplacement rate and distance between TBW and ring pin. Two non-union patients in our study gained wide ROM. Duckworth et al reported that nonoperative functional treatment of displaced olecranon fractures in the elderly (>70 years old) provided good results and a high rate of satisfaction[15]. Gallucci et al also reported similar results in the elderly (average age 76)[16]. Duckworth et al reported no significant difference between groups in a prospective randomized controlled trial comparing nonoperative and operative management for acute isolated displaced fractures of the olecranon in patients aged ≧75 years[17]. The postoperative rehabilitation protocol was free ROM exercise with a sling following 1 week immobilization with a cast or splint. For olecranon fractures in the elderly, in particular for severely comminuted fractures, nonoperative management might be a choice of treatment. Furthermore, operative treatment might not be chosen

in patients with comorbidities and when huge redisplacement occur, we must consider carefully whether to perform a reoperation.

This study has following limitations. At first, the sample size was small. Secondly, several operators chose different kinds of implants and method of fixations. There were many biases in statistical analyses because the fracture types were not unified.

In conclusion, the postoperative redisplacement rates of olecranon fractures using TBW in the elderly were significantly higher than those in young patients. There were no statistically significant differences in redisplacement rate and distance among three different implants.

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Optimal Surgery for Abdominal Intermediate-risk Neuroblastoma: Retrospective Study in a Single Institution

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Abstract

Background

The treatment outcome of intermediate-risk neuroblastoma has improved and it is an important issue to reduce the treatment complication. To identify the optimal surgery, we evaluate the surgical risk factors for abdominal intermediate-risk neuroblastoma treatment.

Methods

Twelve patients with abdominal intermediate-risk neuroblastoma, according to the risk stratification in the Children's Oncology Group, treated at our hospital between 1995 and 2016 were included. The patients were divided into two groups according to the presence (group A, n=5) or absence (group B, n=7) of surgical complications. Clinical features were compared between groups A and B.

Results

The median age at diagnosis was 7 (range 4-8 months) and 7 (0.1-23 months) months in groups A and B. Surgical complications were nephrectomies (n=2), renal atrophy (n=1), bowel obstruction (n=1), and ejaculation disorder (n=1). All tumors in group A and 29% (n=2) of tumors in group B had ≧95% resection. All patients had tumors with image-defined risk factors at diagnosis. Only one of tumors in group B changed to "image-defined risk factors not present" status after chemotherapy. All patients were alive without disease after a median follow-up of 175 months (44-263 months).

Conclusions

Resection of ≧95% could be a surgical risk factor in abdominal intermediate-risk neuroblastoma treatment. Due to the positive outcomes, less aggressive surgery minimizing surgical complications for abdominal intermediate-risk neuroblastoma is recommended even if residual tumors persist.

Key Words: Neuroblastoma; Pediatrics; Complications; Intermediate-risk; Surgery

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Introduction

Neuroblastoma, the most commonly occurring extracranial malignant solid tumor in children, is a heterogeneous tumor that exhibits various behaviors, including spontaneous regression and metastatic diseases with poor outcome. Neuroblastoma is classified into low-, intermediate-, or high-risk categories based on the clinical and biological features, with the risk category correlating with outcome. Identification of risk groups has allowed tailoring of therapy to improve outcomes and minimize the risk of deleterious consequences of therapy[1].

A recent large, prospective, multicenter trial by the Children's Oncology Group (COG) revealed that the rate of overall survival of patients with intermediate-risk tumors exceeded 90%, with a consequent reduction in the application of treatment[2]. On the other hand a relatively high surgical complication rate of 28% with four deaths was observed in their trial.

Iehara et al[3] retrospectively reviewed 20 patients with intermediate-risk neuroblastoma after 15 years of the median follow-up time. They concluded that the presence of a residual mass at the end of treatment did not influence the patients' prognoses. Although these results suggested that aggressive surgery is not necessary, optimal surgery for intermediate-risk neuroblastoma has not been clearly discussed previously.

A previous study showed the potential prognostic importance of clinical characteristics, including the primary tumor site. Patients with abdominal primaries have a less favorable prognosis than those with cervical, pelvic, and thoracic primaries[4]. Furthermore, Image-Defined Risk Factors (IDRFs) were separately defined according to the anatomical sites[5]. Therefore, to identify the optimal surgery for intermediate-risk neuroblastoma, we conducted a retrospective study to evaluate the surgical risk factors of abdominal intermediate-risk neuroblastoma treatment.

Methods

Of the 148 patients with neuroblastoma treated at our hospital between January 1995 and December 2016, 17 were classified as intermediate-risk neuroblastoma cases following the COG risk classification. Intermediate-risk neuroblastoma was defined as International Neuroblastoma Staging System (INSS)[6] stage 3 or 4 disease without *MYCN* amplification in an infant (<1 years), stage 3 disease with favorable histopathological features in a child (≧1 years), and stage 4S disease with a diploid tumor-cell DNA index, unfavorable histopathological features, or both[2]. We did not recruit in accordance with the current International Neuroblastoma Risk Group (INRG) risk classification[7] because no information of 11q LOH was available in patients treated prior to the publication of the INRG risk classification. Of these patients, 12 with abdominal neuroblastoma were selected. We divided the patients into two groups according to the presence (group A, n=5) or absence (group B, n =7) of surgical complications. We retrospectively evaluated the risk factors in the surgical treatment of abdominal intermediate-risk neuroblastoma. The study design was approved by the ethics review board of our institution (No. 1804002).

IDRFs were determined according to the Guidelines for imaging and staging of neuroblastic tumors[5]. Therefore, isolated contact with renal vessels was considered an IDRF-positive condition in this study. Surgical complications were defined as major complications of surgery that occurred during the intraoperative or postoperative period. With respect to nephrectomy, expanded resection was also allowed at that time, and it was not considered a complication. However, we classified planed nephrectomy as complications according to the current neuroblastoma treatment policy. The

Table 1. Patients' characteristics

	group A (N=5)	group B (N=7)
Sex, n (%)		
Male	4 (80)	4 (57)
INSS, n (%)		
3	4 (80)	6 (86)
4	1 (20)	1 (14)
4S	0 (0)	0 (0)
Intraspinal extension, n (%)	1 (20)	1 (14)
Primary therapy, n (%)		
Chemotherapy	4 (80)	6 (86)
Surgical resection	1 (20)	1 (14)
INPC, n (%)		
FH, NB	5 (100)	7 (100)
DNA ploidy, n (%)		
Hyperdiploidy	3 (60)	6 (86)
Diploidy	0 (0)	1 (14)
Unknown	2 (40)	0 (0)

INSS, International Neuroblastoma Staging System; INPC, International Neuroblastoma Pathology Classification; FH, Favorable histology; and NB, Neuroblastoma.

extent of resection was classified into the following three categories: resection of ≧95%, 50%-95%, and <50% of the tumor volume[8]. Two surgeons decided the extent of resection according to the preoperative and postoperative images and surgical records.

Age of onset, INSS stage, initial treatment, pathological findings [International Neuroblastoma Pathology Classification (INPC)], tumor biology (*MYCN* amplification, DNA diploidy), primary tumor location, tumor size, IDRFs, association with renal pedicles, extent of resection, and prognoses were compared retrospectively between the two groups.

Data were expressed as medians and ranges. To obtain pairwise comparisons of the data, the Fisher exact test and Student's t-tests was applied. A p value of 0.05 indicated statistical significance. All analyses were performed using R version 3.4.0 (R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/)[9].

Results

The patients' characteristics are shown in Table 1. Four patients (80%) in group A and six patients (86%) in group B had stage 3 tumors. Intraspinal extensions were present in one patient in both groups. Of the patients in groups A and B, 80% (n=4) and 86% (n=6) received chemotherapy as an initial treatment, respectively. None of the patients had *MYCN* amplified or an INPC unfavorable tumor in both groups.

The median age at diagnosis was 7 months (range: 4-8 months) in group A and 7 months (0.1-23 months) in group B (Table 2 and Table 3). The treatment protocols were not uniform. The drugs of chemotherapy were used in this study, cyclophosphamide (CPM), vincristine (VCR), pirarubicin (THP), cisplatin (CDDP), carboplatin (CBDCA), dacarbazine (DTIC) and etoposide (VP). The surgical

Table 2. Clinical features in group A

Case	Age at diagnosis (month)	Preoperative chemotherapy (cycle)	Chemotherapy after surgery (cycle)	Complications	Median follow-up period (month)
1	4	VCR+CPM (7)	NA	Nephrectomy	167
2	5	VCR+CPM+THP (2) VCR+CPM+THP+CDDP (2)	VCR+CPM+THP+CDDP (1)	Nephrectomy	177
3	8	NA	VCR+CPM+THP (5)	Bowel obstruction	172
4	7	VCR+CPM+THP (2)	VCR+CPM+THP (5)	Renal atrophy	205
5	7	VCR*CPM+THP (3) VCR+CPM+THP+CDDP (3)	VCR+CPM (5)	Retrograde ejaculation	263

VCR, vincristine; CPM, cyclophosphamide; THP, pirarubicin; CDDP, cisplatin; and NA, not applicable.

Table 3. Clinical features in group B

Case	Age at diagnosis (month)	Preoperative chemotherapy (cycle)	Chemotherapy after surgery (cycle)	Median follow-up period (month)
6	2	VCR+CPM (3)	NA	52
7	7	CBDCA+VP (1) CBDCA+CPM+THP (1)	VP+CPM (2) VP+CBDCA+THP (2) VP+CBDCA (1) CPM+THP (1)	44
8	7	VCR+CPM+THP (4)	VCR+CPM+THP (2)	104
9	23	VCR+CPM+THP+CDDP (5)	VCR+CPM+THP+CDDP (3) CPM+DTIC (1) CPM+THP+CDDP (1)	118
10	0.1	NA	VCR+CPM (18.5)	190
11	7	VCR+CPM+THP (2) VCR+CPM+THP+CDDP (9)	NA	215
12	7	VCR+CPM (3) VCR+CPM+THP (4)	VCR+CPM+THP (3)	208

VCR, vincristine; CPM, cyclophosphamide; CBDCA, carboplatin; VP, etoposide; THP, pirarubicin; CDDP, cisplatin; DTIC, dacarbazine; and NA, not applicable.

complications in group A were planed nephrectomies (n=2), renal atrophy (n=1), bowel obstruction (n =1), and ejaculation disorder (n=1). All the patients were alive without disease after a median follow-up of 175 months (44-263 months). Tumors' characteristics showed in Table 4. Group A had three adrenal tumors (60%), and group B had two (29%). Two retroperitoneal tumors were found in group A (40%); and five, in group B (71%). All the patients had tumors with IDRFs at diagnosis in both groups. Only one of tumors in group B changed from "IDRFs present" to "IDRFs not present" status after preoperative chemotherapy. Three tumors encased renal vessels and two tumors contacted with them in group A. Three tumors encased, three contacted, and one separated in group B. Only one tumor in group B changed from "contact" to "separate" status after preoperative chemotherapy.

The size of the primary tumor was 80 mm (45-110 mm) in group A and 55 mm (32-86 mm) in group B. The preoperative tumor size was 58.5 mm (30-103 mm) in group A and 40 mm (36-80 mm)

Table 4. Tumors' characteristics

	group A (N=5)	group B (N=7)	p-value
Primary tumor location, n (%)			0.56
Adrenal	3 (60)	2 (29)	
Retroperitoneal	2 (40)	5 (71)	
IDRFs at diagnosis, n (%)	5 (100)	7 (100)	1
Preoperative IDRFs, n (%)	5 (100)	6 (86)	1
Primary relationship with RP, n (%)			NA
Separate	0 (0)	1 (14)	
Contact	2 (40)	3 (43)	
Encase	3 (60)	3 (43)	
Preoperative relationship with RP, n (%)			NA
Separate	0 (0)	2 (29)	
Contact	2 (40)	2 (29)	
Encase	3 (60)	3 (43)	
Primary tumor size, mm (range)	80 (45-110)	55 (32-86)	0.13
Preoperative tumor size, mm (range)	58.5 (30-103)	40 (36-80)	0.43
Resection of ≧95%, n (%)	5 (100)	2 (29)	**0.028**

IDRFs, Image-Defined Risk Factors; RP, renal pedicles; and NA, not applicable.

in group B. No tumors were increased in size in group A, while three tumors were increased in size in group B during preoperative chemotherapy.

All the tumors were resected by at least 95% of the tumor volume in group A, including five complete resections, whereas two complete resections, five 50%-95% resections, and one nonsurgical treatment were performed in group B. Thus, all the tumors were resected ≧95% in group A, whereas 29% (n=2) of the tumors were resected ≧95% in group B. Significantly more tumors in group A than in group B were resected ≧95% (p=0.028).

Discussion

In this study, the risk factor in the surgical treatment of patients with abdominal intermediate-risk neuroblastoma could be tumor resection of ≧95%. As all the patients in this study were alive without disease, complete resection could be unnecessary in patients with abdominal intermediate-risk neuroblastoma. This finding is in accordance with some previous reports. Two large studies showed that the extent of resection was not associated with event-free and overall survival in unresectable neuroblastoma without *MYCN* amplification[10,11]. The presence of a residual mass at the end of treatment has been reported to have no influence on patient prognosis after a long-term follow-up in patients with intermediate-risk neuroblastoma[3,12]. These findings supported our opinions that conservative surgery that allows residual tumors to avoid complications was acceptable.

One patient (case 11) who did not undergo surgery for family wishes at the first treatment required additional surgery 8 years after the treatment in this study. Although the pathological finding of the biopsy sample at the time of initial diagnosis was neuroblastoma, it was changed to ganglioneuroma. This result suggests that the residual tumor may have had a differentiation tendency. Marachelian et al showed that the post-chemotherapy histopathology of intermediate-risk neuroblastoma was characterized by regression or maturation[13].

IDRFs have been propounded for predicting the surgical risks of localized neuroblastoma by the INRG task force. The report showed 94% of patients with INSS Stage 3 had IDRFs[14]. In this study, all patients in both groups had tumors with IDRFs at diagnosis. A study from Germany showed that the surgical complication rates were 26.6% and 14.5% (among 366 patients who underwent resection other than biopsy) in patients with localized neuroblastoma tumors identified as IDRF-present and IDRF-absent at diagnosis, respectively[15]. IDRFs at diagnosis were associated with higher rates of operative complications. To avoid surgical complications, a biopsy followed by neoadjuvant chemotherapy is recommended as the initial treatment in patients with IDRF-present tumors, rather than surgical resection. Moreover, due to the positive outcome in this study, conservative surgery to avoid complications is recommended even if residual tumors remain after surgery.

The European Unresectable Neuroblastoma study revealed that the unchanged IDRF pattern was observed in 50% of patients and the appearance of new IDRFs during chemotherapy in approximately 20% of patients[11]. A study from Japan reported that tumors should shrink to <20% of the volume at the time of diagnosis for negative IDRFs and that major surgical complications were observed even in the patients who had disappearance/numerical reduction of IDRFs[16]. In this study, IDRFs disappeared after chemotherapy in only one of patients in group B. Therefore, patients with intermediate-risk neuroblastoma whose tumors had IDRFs at diagnosis may have a potential risk for undergoing surgery even after neoadjuvant chemotherapy.

A previous study showed that the primary tumor size was associated with the risk of nephrectomy[17]. Contrary to expectations, surgical complications were not associated with the primary and preoperative tumor sizes in this study. None of the tumors in group A increased in size, whereas three tumors in group B increased in size.

In Guidelines for imaging and staging of neuroblastic tumors, isolated contact with renal vessels is considered an IDRF-positive condition[5]. On the other hand, only encasement of the renal pedicles is considered an IDRF-positive in Japan Neuroblastoma Study Group (JNBSG)[18]. The previous report showed if isolated contact with renal vessels was considered an IDRF-positive condition, the sensitivity increased but the specificity decreased for the predictor of the complication[18]. In this study, three patients with renal complications in group A had tumors encasing renal pedicles and the tumors were completely resected. In group B, three patients had tumors encasing renal vessels, but no tumors were resected completely. No renal complications were observed on contact in both groups. Therefore, complete resection could be unnecessary in patients with tumors encasing renal pedicles and isolated contact with renal vessels could not be surgical risk.

This study has the following limitations: The number of the patients was limited, and the treatment protocols were not uniform. To better investigate the risk factors in the surgical treatment of patients with intermediate-risk neuroblastoma, larger prospective studies with uniform therapeutic protocols should be designed.

In conclusion, aggressive resection of ≧95% of the tumor could be a surgical risk factor in the treatment of abdominal intermediate-risk neuroblastoma. As all the patients in this study were alive without disease, conservative surgery to avoid complications could be acceptable even if residual tumors persist.

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All authors have no COI to declare regarding the present study.

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Laparoscopic Percutaneous Extraperitoneal Closure for Inguinal Hernia in Young Adults: Assessment of Safety, Efficacy, and Reliability

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Abstract

Background

Inguinal hernias can occur in both children and adults. Indirect hernias in children, are primarily treated with simple high ligation of the hernia sac. However, no conclusive guidelines exist on age limits for the indication of this surgical approach. We investigated indications for laparoscopic percutaneous extraperitoneal closure (LPEC) in adults with indirect hernias.

Methods

This study was conducted at two centers from April 1, 2008 to March 31, 2019. The following indications were considered for LPEC: 1) indirect hernia without coexistence of direct or femoral hernias and a hernia orifice diameter ≦20 mm and 2) patients younger than 45 years of age without a history of abdominal surgery who could tolerate general anesthesia. LPEC was performed in 32 patients who met the criteria, and the following parameters were investigated: hernia orifice diameter, operative time, hospital stay, postoperative pain, surgical site infection (SSI), time to return to work or school, and recurrence.

Results

The median hernia orifice diameter was 8 mm, and the median operative times were 31.5 and 32 min for unilateral and bilateral hernias, respectively. The median hospital stay was short (3 days), and no patient required analgesics postoperatively. There were no SSIs, recurrence, or hernia onset on the opposite side during the median follow-up period of 1812 days.

Conclusions

LPEC should be considered a superior treatment for indirect hernias in individuals aged less than 45 years with a hernia orifice diameter ≦20 mm.

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Key Words: Inguinal hernia; Laparoscopic percutaneous extraperitoneal closure; High ligation; Young adults

Introduction

Inguinal hernias can occur in both children and adults. Indirect hernias originating in the patent processus vaginalis (PPV), the most common inguinal hernias in children, are primarily treated with simple high ligation of the hernia sac. However, no conclusive guidelines exist on age limits for the indication of this surgical approach. Although the European Hernia Society guidelines on the treatment of inguinal hernia in adult patients strongly recommend the use of a mesh for inguinal hernia in patients aged ≧18 years[1], the International Guidelines for Groin Hernia Management do not offer a unified opinion on whether mesh-based techniques are indicated in all patients, including those with small lateral hernias (European Hernia Society L1 and L2)[2]. In pediatric surgery, laparoscopic percutaneous extraperitoneal closure (LPEC) has been commonly performed in recent years to perform high ligation similar to that achieved using the Potts method under laparoscopy[3]. In the present study, we investigated the indications for LPEC in young adult patients with indirect hernias.

Methods

Patients

Considering LPEC might be indicated for adult indirect hernias sharing the same etiology as pediatric inguinal hernias, the following criteria were considered indications for LPEC in young adults: 1) indirect hernia without coexistence of direct or femoral hernias and a small hernia gate (hernia orifice diameter ≦20 mm), 2) adolescents and adults aged 15-45 years without a history of abdominal surgery, and 3) ability to tolerate general anesthesia.

From April 1, 2008 to March 31, 2019, 53 of 273 patients with indirect hernia met the inclusion criteria. Preoperative diagnosis was achieved by computed tomography or ultrasound. The two available hernia repair methods, transabdominal peritoneal repair (TAPP) and LPEC, were explained to the patients, and we performed LPEC in the patients who provided consent to undergo LPEC. The final decision for LPEC was reached based on intra-operative findings. Specifically, the hernia gates were evaluated under laparoscopy, and the indications for TAPP versus LPEC were evaluated. If the patient was determined not to fulfill the indications for LPEC, TAPP was planned to perform as the alternative approach. The present study included 32 patients who provided consent and underwent LPEC (Fig. 1).

The following parameters were evaluated in the present study: hernia orifice diameter, operative time, hospital stay, postoperative pain, surgical site infection (SSI), time to return to work or school, and recurrence. Prognosis was surveyed via telephone or mail.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of Tsukazaki Hospital (#181035) and Bioethics Committee of Izumiotsu Municipal Hospital (#R2-5). All procedures used in this study conformed to the tenets of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

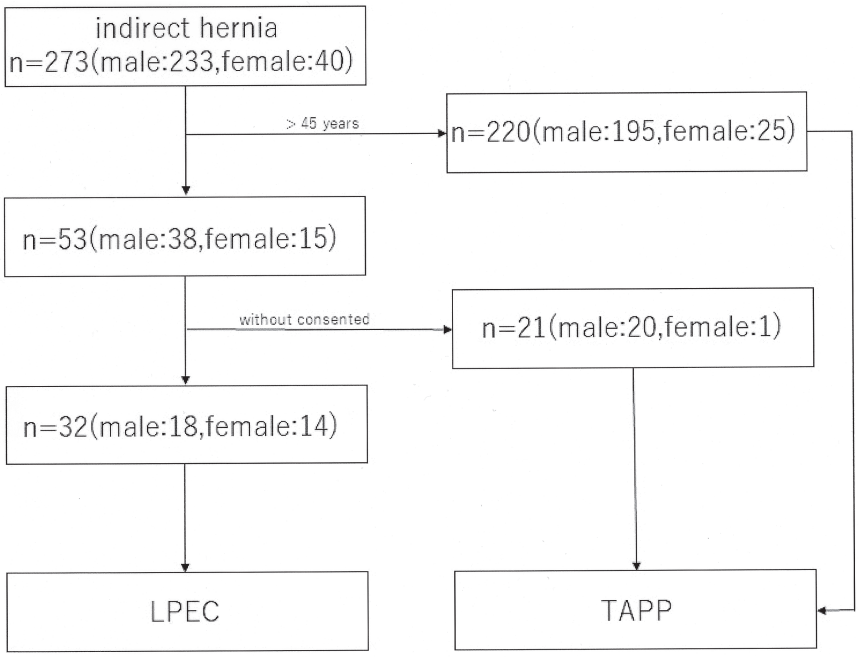

Figure 1. Study flowchart. From April 2008 to March 2019, 53 of a total of 273 patients with symptomatic indirect hernias met the study inclusion criteria. After details on transabdominal peritoneal repair (TAPP) and laparoscopic percutaneous extraperitoneal closure (LPEC) were provided, 32 patients provided consent and underwent LPEC.

LPEC

LPEC was performed following the method described by Takehara et al[4]. Briefly, a 3-mm laparoscope was placed through an umbilical incision and 3-mm grasping forceps were inserted in the right abdominal regions through an abdominal incision. A 19-gauge LPEC needle with a 2-0 Surgilon® suture (COVIDIEN, Tokyo, Japan) was used for ligation. The pneumoperitoneum was maintained at 10 mm Hg using a carbon dioxide insufflator. The LPEC needle with a wire loop to hold the 2-0 Surgilon® suture was inserted at the midpoint of the right or left inguinal line. Half of the circuit suturing was performed extraperitoneally, without involving or injuring the spermatic duct or gonadal vessels, and the peritoneum was punctured at the medial edge of the internal inguinal ring. The 2-0 Surgilon® was placed into the abdominal cavity, and circuit suturing of the medial side of the internal ring was performed extraperitoneally using the same technique. The LPEC needle was introduced into the abdominal cavity through the same puncture hole. After the suture was held in the wire loop inside the LPEC needle, the LPEC needle was removed from the abdomen. Next, the orifice of the hernia sac was closed extraperitoneally with complete circuit suturing around the internal inguinal ring using an LPEC needle. Of note, we performed the method by Takehara et al twice to create double ligation of the internal inguinal ring (double LPEC) to prevent recurrence due to loosened ligatures in all study patients (Fig 2). The circuit suturing was tied extracorporeally, and the internal inguinal ring was completely closed without skipping any areas.

The maximum diameter of the hernia orifice was measured using scale-marked sutures.

Results

Thirty-two patients, including 18 male (56%) and 14 female (44%) patients, who fulfilled the

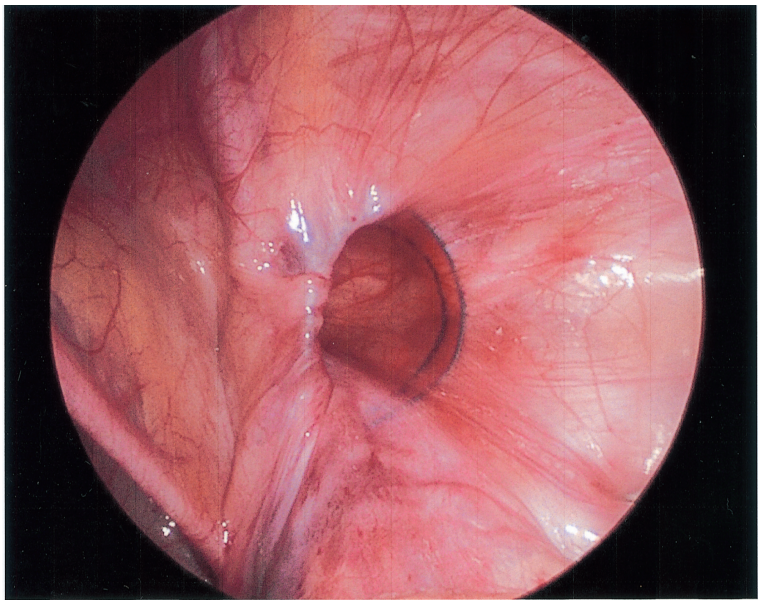

Figure 2. Double laparoscopic percutaneous extraperitoneal criteria (LPEC) in a young adult male patient. The orifice of hernia sac is closed extraperitoneally twice with complete circuit suturing around the internal inguinal ring using an LPEC needle.

Table 1. Clinical characteristics of the study patients

	Male	Female	Total
Number of patients	18	14	32
Age*	28.5 (20.75-33.5) [15-43]	28 (24-33) [16-40]	28 (23-33) [15-43]
Affected side			
Right	7	7	14
Left	6	2	8
Bilateral	5	5	10
BMI (kg/m^2)*	21.9 (19.4-25.5) [16-28.3]	19.4 (18.3-22.9) [18-24.4]	21.5 (18.7-23.7) [16-28.3]

*quartile range [range]. Abbreviations: BMI, body mass index.

criteria were included in the present study. The median age was 28 [15-43] years (28.5 [15-43] and 28 [16-40] years in male and female patients, respectively). There were 14, 8, and 10 patients with right-sided, left-sided, and bilateral hernias, respectively. The median body mass index was 21.5 [16-28.3] kg/m^2 (21.9 [16-28.3] and 19.4 [18-24.4] kg/m^2 in male and female patients, respectively). The American Society of Anesthesiologists physical status was class 1 for all patients. The study cohort included eight male smokers, whereas none of the female patients were smokers. None of the patients had a medical history or were on oral medications (Table 1).

The median hernia orifice diameter was 8 [2-20] mm. The median operative times for unilateral and bilateral hernias were 31.5 [20-51] and 32 [20-72] min, respectively, and the median hospital stay was 3 days. All wounds were small in all patients, and no patient required analgesics postoperatively or developed SSI (Fig. 3). The majority of the patients returned to school or work within three days after the operation (Table 2).

The median follow-up period was 1812 days, no patients developed recurrence or new hernia onset

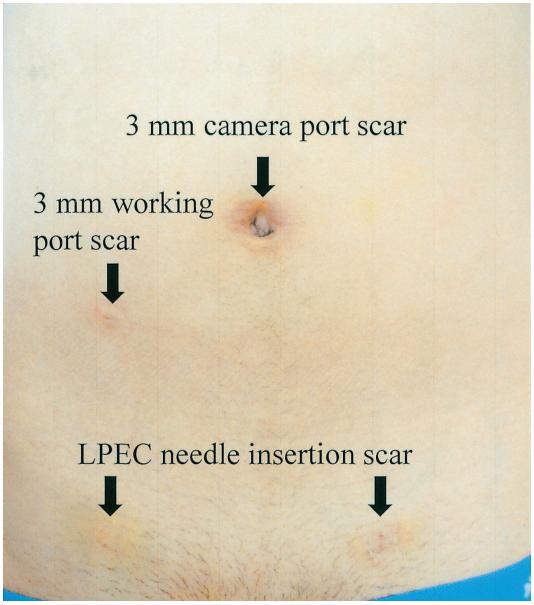

Figure 3. Surgical scars one week after bilateral surgery in a patient with bilateral patient indirect hernias to illustrate that the scars were very small in patients undergoing laparoscopic percutaneous extraperitoneal closure (LPEC).

Table 2. Surgical outcomes

	LPEC [n=32]	TAPP [n=241]
Median diameter of the hernial orifice (mm)*	8 (7-10) [2-20]	20 (15-28.8) [5-40]
Median duration of unilateral surgery (min)*	31.5 (23.8-38.5) [20-51]	91 (72-106) [49-129]
Median duration of bilateral surgery (min)*	32 (28.5-42) [20-72]	92.5 (72.3-111.8) [50-163]
Surgical site infection	0	6
Median hospital stay (days)	3	5
Recurrence	0	7
Discomfort in wound site	1 (3.2%)	NA
Follow-up period (days)*	1812 (1040-2386) [321-3965]	NA

*quartile range (range). Abbreviations: NA, Not applicable.

on the opposite side. One patient underwent two transvaginal births after LPEC, and one patient had two deliveries by caesarian section; however, to date, none of the patients experienced recurrence. There were no cases with seroma as a complication. Although one female patient experienced discomfort in the inguinal region three years postoperatively, she did not require analgesics and was able to perform daily activities of living.

Discussion

Indirect hernias originating in the PPV, the most common inguinal hernias in children, are treated by high ligation in which the hernia sac is ligated directly on the internal inguinal ring. However, the age limit for this surgical method remains inconclusive. We considered the possibility that simple high ligation can be used to treat external inguinal hernias in selected young adults. In the present study, no recurrence of hernia was observed in young adult patients who underwent LPEC for indirect hernias.

LPEC, a high-ligation method for pediatric hernia developed by Takehara et al in 1995[4], is a relatively new operative method that achieves simple high ligation that is as effective as conventional methods and has become a widely used method for the treatment of pediatric inguinal hernia. On the other hand, surgical techniques for adult inguinal hernia predominantly use a mesh, such as mesh plug; an anterior approach, TAPP, totally extraperitoneal repair (TEP); and laparoscopic posterior approaches.

Adolescent inguinal hernias are treated using high ligation or posterior wall suture repair and tension-free repair method using a mesh. The 2015 Inguinal Hernia Treatment Guidelines of the Japanese Hernia Society recommend a tension-free repair method using a mesh indiscriminately for young, middle-aged, and older adults alike. The European Hernia Society guidelines strongly recommend the use of a mesh, particularly in male patients ≧18 years of age to avoid higher recurrence rates[1]. The choice of method depends on the surgeon. However, adult indirect hernias caused by PPV in the absence of a weakened abdominal wall are considered to be curable with high ligation, and whether abdominal wall reinforcement with artificial materials should be indicated indiscreetly for all patients remains controversial[5]. The Nyhus classification, which determines the operative method preoperatively, indicates that type I hernia without internal inguinal ring's dilatation common in children and young adults can be treated with high ligation[6].

Hayakawa et al classify indirect hernia originating from an origin other than a PPV as de novo hernia[7]. De novo hernia, a direct type of indirect hernia caused by the surrounding fascial tissue pushing through a weakened hernia orifice, can be diagnosed based on whether the displaced peritoneum can be smoothly replaced back into the abdominal cavity[7]. However, we have never encountered this condition in young patients and we consider that LPEC is not indicated in these acquired hernias; thus, the decision can be easily made under laparoscopy.

Regarding the measurement of hernia orifice diameter, we often perform LPEC in pediatric patients with an inguinal hernia orifice diameter of 20 mm without recurrence; therefore, in the present study the LPEC indications for indirect hernias included a hernia orifice diameter ≦20 mm. We predict that the indication for LPEC might be extended to patients with larger hernia orifices based on the lack of recurrence in the present study.

We consider that the patient age is the most important indication for LPEC, because the definition of a young adult is ambiguous. In a study of 1983 inguinal hernia patients who were 18 years of age or older, Neumayer et al reported that patients' mean age ± SD were approximately 45 years to 71 years[8], indicating possible weakening of the transversal fascia around 45 years; therefore, the age cutoff was 45 years for LPEC in the present study.

The most important advantage of LPEC is that there is no need for insertion of foreign objects and it involves no risk of mesh infections. Additionally, the first surgery does not become an obstacle for repeat surgery in cases of recurrence because the inguinal canal is not opened during the first surgery. The operative time is short, and can be performed during a short hospital stay. The surgeries were performed the day after admission in all cases, and the patients were discharged on postoperative days 1-2 according to the patient's request. However, surgery can be performed on the day of admission and the patient can be discharged the following day, further shortening the hospital stay; therefore, LPEC provides an economic advantage. Moreover, the wound size was small, and no SSI occurred in the current study cohort. Selection of the operative method, LPEC or TAPP, is important, but incorrect indications are not made under laparoscopy because it enables the

observation of the hernia type.

According to the 14th Nationwide Survey of Endoscopic Surgery including Japanese endoscopic surgeons in Japan, the recurrence rates of TAPP, TEP, and mesh plug for adult patients with inguinal hernia were 1.9%, 1.6%, and 3.9%, respectively[9]. However, the recurrence rate was 0% in the present study. We performed double LPEC to avoid the loosening of ligatures, which might have prevented recurrence in the current cohort.

In this study, we did not compare LPEC with TAPP, because the patient's background was so different. Of course, we should consider the effect of the size of the hernial orifice diameters and patient's age, the operative time, hospital stays were significantly shorter in LPEC than in TAPP. We considered that LPEC was superior to TAPP, in safety and efficacy.

This study has several limitations. First, the sample size of 32 patients was small. However, although the exact rate is unknown, the incidence of inguinal hernia is substantially lower in young adults compared with middle-aged and elderly patients. Second, the median follow-up period was 1812 days, which was a relatively short period. Thus, follow-up should be conducted for a longer duration, and future investigations should include larger patient cohorts in multicenter studies.

Based on the current study results, we propose LPEC as an indication for indirect hernias without coexistence of direct or femoral hernias and a hernia orifice diameter ≦20 mm in adults younger than 45 years of age without a history of abdominal surgery who can tolerate general anesthesia. For these patients, LPEC can be considered a superior treatment option as it does not require the use of a mesh; LPEC is also associated with shorter operative time and hospital stay, reduced postoperative pain, no SSI or recurrence, earlier return to work or school, and lower medical costs. Furthermore, the relationships among patient age, hernia orifice size, and potential for treatment with simple high ligation should be assessed in future studies.

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All authors have no COI to declare regarding the present study.

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The Clinical Course of Patients with Influenza after Administration of Various Anti-influenza Drugs during the 2019-2020 Influenza Season in Osaka, Japan

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Abstract

Background

In Japan, four neuraminidase inhibitors (NAIs) and one cap-dependent endonuclease inhibitor, baloxavir marboxil (baloxavir), are currently available for treatment of influenza. We investigated prescription trends of each anti-influenza drug and the clinical course of patients with influenza who were treated with anti-influenza drugs, including baloxavir, during the 2019-2020 influenza season.

Methods

A multicenter observational study in Osaka was conducted with postcard questionnaires. Patients who were diagnosed with influenza responded to a postcard questionnaire containing questions about their background characteristic, and their body temperature. We analyzed the factors that were associated with early fever alleviation and biphasic fever, and compared the duration of fever among four anti-influenza drug groups excluding peramivir, because few patients were prescribed this drug.

Results

A total of 252 patients with influenza were enrolled and analyzed (97 patients aged <10 years, and 155 patients aged $\geqq 10$ years). Baloxavir was prescribed to three of the 97 patients aged <10 years (3.1%) and to 19 of the 155 patients aged $\geqq 10$ years (12.3%). The duration of fever in patients with influenza was not significantly different among the four groups that received oseltamivir, laninamivir, zanamivir, or baloxavir. We found no significant difference between the frequency of biphasic fever episodes and the choice of anti-influenza drugs.

Conclusions

Our study showed no significant association between baloxavir and early fever alleviation or the frequency of biphasic fever episodes. One cause may be that no statistically association was detected

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due to the decrease in the number of prescriptions of baloxavir.

Key Words: Influenza; Neuraminidase inhibitor; Baloxavir marboxil; Biphasic fever

Introduction

Influenza is an acute viral respiratory disease that is epidemic in the winter months. The seasonal epidemic of influenza is a major cause of morbidity and mortality globally, and the majority of deaths occur in the elderly. In Japan, about 10-15 million people are infected with influenza every year. Thousands of deaths occur each year due to influenza, and tens of thousands die during a pandemic[1].

Baloxavir marboxil (baloxavir) was newly released as a cap-dependent endonuclease inhibitor in March 2018 in Japan, and is now available in addition to four existing neuraminidase inhibitors (NAIs), oseltamivir, zanamivir, peramivir, and laninamivir. An international clinical trial showed that baloxavir has good therapeutic activity against influenza A and B virus infections[2,3]. A few clinical studies reported that the duration of fever in influenza patients treated with baloxavir is shorter than in those taking NAIs[4,5]. The number of baloxavir prescriptions increased explosively due to the convenience of the single oral dose and the effect; more than 5.2 million people were estimated to be prescribed baloxavir during the 2018-2019 influenza season[6]. We also reported that baloxavir was prescribed to about 40% of influenza patients[5].

On the other hand, in a clinical trial, the emergence of viruses with amino acid substitutions at position 38 of polymerase acidic protein, which reduces the susceptibility to baloxavir, occurs at a high rate, and sometimes in association with rebounds in viral titers and possibly prolongation of symptoms[2]. In October 2019, the Japanese Association for Infectious Disease and the Japan Pediatric Society suggested that doctors carefully consider the administration of baloxavir for children aged <12 years[7,8].

There are few reports which examine the clinical effects of baloxavir and compare with NAIs in clinical practice. Our objective was to investigate prescription trends of each anti-influenza drug and the clinical course of patients with influenza who were treated with anti-influenza drugs, including baloxavir, during the 2019-2020 influenza season.

Methods

Procedures

This multicenter observational study was conducted in 52 hospitals or clinics in Osaka prefecture, Japan. Physicians, pediatricians, and otorhinolaryngologists participated in this study. Patients with influenza who were diagnosed using an antigen detection kit and who were treated with an anti-influenza drug from December 1, 2019 through April 30, 2020 were enrolled. After obtaining oral informed consent from the patients or their guardians, clinicians completed the sections on age, sex, type of influenza (A or B), and the prescribed anti-influenza drug, and then handed the postcard questionnaire to the patients. Patients mailed the postcard to the Department of Respiratory Medicine, Osaka City University Graduate School of Medicine after they filled out the questionnaire.

The study protocol was approved by the Institutional Ethics Committee (Osaka City University Graduate School of Medicine, Approval No. 2019-035).

Questionnaire items

Patients recorded their peak body temperature before first visiting the hospital or clinic, and their

body temperature twice a day (morning and afternoon) for 4 days from first visit. They also completed the questionnaire regarding their vaccination status this year; underlying diseases; adverse events of anti-influenza drugs such as coughing, vomiting, diarrhea, abdominal pain, abnormal behavior, and headache; and the episode of biphasic fever.

Definition of the duration of fever, fever reduction and biphasic fever

We defined the duration of fever as the time from anti-influenza drugs administration until the fever was alleviated for more than one day with no relapse thereafter. Fever reduction was defined as a temperature below 37.5℃ in patients aged <10 years or below 37.0℃ in patients aged ≧10 years[9,10]. Biphasic fever was defined as developing a fever again after alleviation of the fever for more than 1 day[11,12].

Statistical analysis

Statistical analyses were performed with JMP, ver. 10 (SAS Institute, Inc., Cary, NC, USA). The Kruskal-Wallis test followed by the Steel-Dwass test for multiple comparisons were used to compare the duration of fever with each anti-influenza drug. We conducted univariate analysis followed by multivariate analysis with logistic regression models to examine the factors (sex, age, type of influenza virus, underlying disease, vaccination status, and type of anti-influenza drug) that were associated with the alleviation of fever in 2 days after treatment with anti-influenza drugs began. Independent variables with $p < 0.20$ in univariate analysis and those reported to be associated with early fever alleviation were included in the multivariate model[11,13]. The logistic regression model was used to determine the factors (sex, age, type of influenza, underlying diseases, vaccination status, and type of anti-influenza drug) influencing the episodes of biphasic fever, and no multiplicity adjustment was performed in the analyses. To evaluate the frequency of adverse events in each anti-influenza drug, a Chi-square test was used. Three patients were prescribed peramivir, and they were excluded from statistical analyses which compared the duration of fever, examined the factors that were associated with the early fever alleviation, or biphasic fever episodes, and evaluated the frequency of adverse events.

Results

Patient characteristics

A total of 900 postcards were handed to patients with positive results on the rapid diagnostic kits. The response rate was 28.9% (260/900). Eight patients were excluded from the analyses because of incomplete questionnaire data for age, sex, type of influenza, body temperatures, or prescribed anti-influenza drug (Fig. 1). Thus, a total of 252 patients were enrolled and analyzed: 97 patients aged <10 years (Type A, 80; Type B, 17), and 155 patients aged ≧10 years (Type A, 147; Type B, 8) (Table 1). The anti-influenza drugs prescribed for the patients aged <10 years were oseltamivir for 54, laninamivir for 24, zanamivir for 17, peramivir for 0, and baloxavir for 3, and those for the patients aged ≧10 years were oseltamivir for 41, laninamivir for 77, zanamivir for 15, peramivir for 3, and baloxavir for 19. Of all patients, 51 had underlying disease (Hypertension, 10; Hyperlipidemia, 2; Diabetes mellitus, 3; Bronchial asthma, 8; Allergy, 18; Other, 20). A total of 110 patients had received the influenza vaccine this year.

Factors related to early alleviation of fever

Multivariate analysis revealed that laninamivir was significantly associated with alleviation of fever in 2 days compared to oseltamivir (odds ratio, 1.91; 95% confidence interval: 1.05-3.54; $p=0.034$)

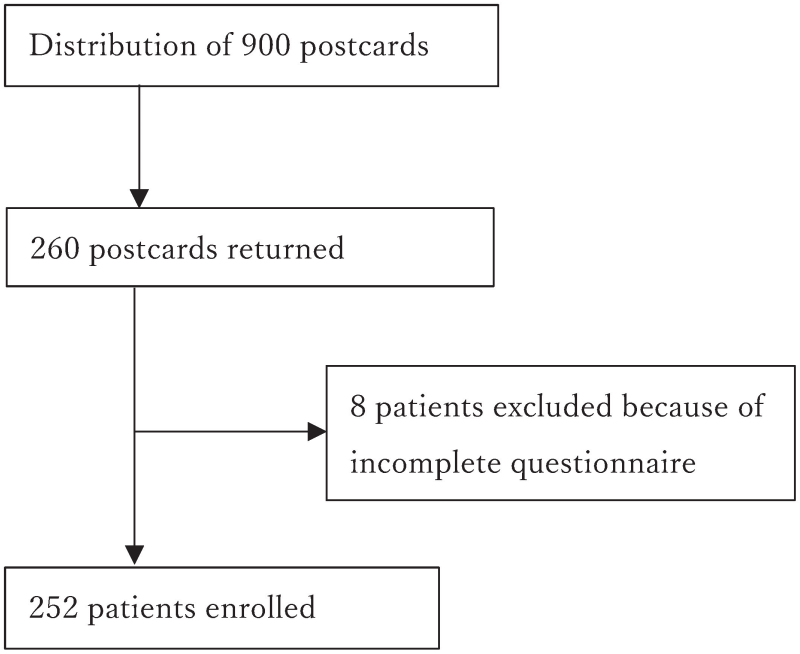

Figure 1. Flow of participants through the study. A total of 900 postcards were handed to patients with influenza. The number of postcards which were returned was 260. Eight patients were excluded from the analyses because of incomplete questionnaire data for age, sex, type of influenza, body temperatures, or prescribed anti-influenza drug. Thus, a total of 252 patients were enrolled and analyzed.

Table 1. Clinical characteristics of the study subjects

Characteristics		<10 years (n=97)	10 years≦ (n=155)	Total (n=252)
Age, Mean years±SD		6.17±2.46	31.6±20.4	21.8±20.3
Range	0-4 years	24	0	24 (9.5)
	5-9 years	73	0	73 (28.9)
	10-19 years	0	74	74 (29.4)
	20-39 years	0	14	14 (5.6)
	40-59 years	0	52	52 (20.6)
	60 years-	0	15	15 (6.0)
Gender, male/female	male	51	69	120 (47.6)
	female	46	86	132 (52.4)
Type of influenza virus	Type A	80	147	227 (90.1)
	Type B	17	8	25 (9.9)
Underlying diseases	Hypertension	0	10	10 (4.0)
	Hyperlipidemia	0	2	2 (0.7)
	Diabetes mellitus	0	3	3 (1.2)
	Bronchial asthma	2	6	8 (3.2)
	Allergy	3	15	18 (7.1)
Vaccinated this year	Yes/No/	46/48/3	64/85/6	110 (43.6) /133
	Unspecified			(52.8) /9 (3.6)
Anti-influenza drugs	Oseltamivir	53	41	94 (37.3)
	Laninamivir	24	77	101 (40.1)
	Zanamivir	17	15	32 (31.7)
	Peramivir	0	3	3 (3.0)
	Baloxavir	3	19	22 (21.8)

Data are number or proportion (%) of patients. Abbreviation: SD, standard deviation.

Table 2a. Factors influencing alleviation of fever in 2 days

Variable			Univariate analysis			Multivariate analysis		
		n/N (%)	O.R.	95% CI	p value	O.R.	95% CI	p value
Gender	Female	65/130 (50.0)	1	-	-			
	Male	72/119 (60.5)	1.53	0.93-2.54	0.096	1.58	0.94-2.65	0.08
<10 years		54/97 (55.7)	1	-	-			
≧10 years		83/152 (54.6)	0.96	0.58-1.60	0.87	0.80	0.45-1.41	0.44
Type of influenza virus	Type A	122/224 (54.5)	1	-	-			
	Type B	15/25 (60.0)	0.80	0.34-1.85	0.60	1.24	0.52-3.07	0.63
Underlying diseases	No	103/186 (55.4)	1	-	-			
	Yes	28/51 (54.9)	0.98	0.53-1.84	0.95			
Vaccinated this year	No	73/131 (55.6)	1	-	-			
	Yes	60/110 (54.5)	0.95	0.57-1.59	0.85			
Anti-influenza drug	Oseltamivir	45/94 (47.9)	1	-	-			
	Laninamivir	62/101 (61.4)	1.73	0.98-3.07	0.058	1.91	1.05-3.54	0.034
	Zanamivir	16/32 (50.0)	1.09	0.48-2.44	0.84	0.99	0.44-2.26	0.99
	Baloxavir	14/22 (63.6)	1.91	0.74-5.17	0.18	2.10	0.79-5.96	0.14

Abbreviation: O.R., odds ratio; and CI, confidence intervals.

(Table 2a).

Table 2b showed sub-group analysis for factors influencing alleviation of fever in 2 days by age group. Laninamivir was significantly associated with alleviation of fever in 2 days compared to oseltamivir in patients aged <10 years (odds ratio, 2.93; 95% confidence interval: 1.08-8.69; p=0.035). We also analyzed the factors influencing alleviation of fever in 2 days in patients with influenza A (n=227). No statistically significant association was found between alleviation of fever in 2 days and sex, age group, underlying disease, vaccination status, or choice of anti-influenza drugs in patient with influenza A.

Duration of fever after administration of the first dose of anti-influenza drug

The duration of fever in influenza patients was not significantly different among the four groups that received oseltamivir, laninamivir, zanamivir, or baloxavir (Fig. 2). The median durations of fever in influenza patients who received each anti-influenza drug was 2.0 to 2.5 days.

Episodes of biphasic fever

Biphasic fever occurred in 10 of 249 patients (4.0%). No statistically significant association was found between the frequencies of biphasic fever and sex, age group, type of influenza, underlying disease, vaccination status, or choice of anti-influenza drugs (Table 3).

Adverse events for each anti-influenza drug

The frequency of each adverse event after administration of the anti-influenza drug is shown in Table 4. There was no statistically significant difference in the frequency of all adverse events, such as coughing, diarrhea, vomiting, abdominal pain, headache, and abnormal behavior among the four groups that received oseltamivir, laninamivir, zanamivir, or baloxavir.

Discussion

In this study, the duration of fever was not significantly different among the four groups that

Table 2b. Sub-group analysis for factors influencing alleviation of fever in 2 days by age groups

Variable		<10 years			
		n/N (%)	O.R.	95% CI	p value
Gender	Female	21/45 (46.7)	1	-	-
	Male	30/49 (61.2)	1.80	0.80-4.14	0.16
Type of influenza virus	Type A	42/80 (52.5)	1	-	-
	Type B	9/14 (64.3)	1.63	0.52-5.70	0.41
Underlying diseases	No	46/83 (55.4)	1	-	-
	Yes	6/11 (54.6)	0.97	0.27-3.59	0.96
Vaccinated this year	No	25/48 (52.1)	1	-	-
	Yes	25/44 (56.8)	1.21	0.53-2.77	0.65
Anti-influenza drug	Oseltamivir	24/53 (45.3)	1	-	-
	Laninamivir	17/24 (70.8)	2.93	1.08-8.69	0.035
	Zanamivir	10/17 (58.8)	1.73	0.58-5.41	0.33
	Baloxavir	3/3 (100.0)	-	-	-

Variable		≧10 years			
		n/N (%)	O.R.	95% CI	p value
Gender	Female	43/84 (51.2)	1	-	-
	Male	40/68 (58.8)	1.58	0.94-2.65	0.35
Type of influenza virus	Type A	80/144 (55.6)	1	-	-
	Type B	3/8 (37.5)	1.24	0.52-3.07	0.32
Underlying diseases	No	57/103 (55.3)	1	-	-
	Yes	22/40 (55.0)	0.99	0.47-2.07	0.97
Vaccinated this year	No	48/83 (57.8)	1	-	-
	Yes	33/64 (51.6)	0.78	0.40-1.50	0.45
Anti-influenza drug	Oseltamivir	21/41 (51.2)	1	-	-
	Laninamivir	45/77 (58.4)	1.34	1.05-3.54	0.45
	Zanamivir	6/15 (40.0)	0.63	0.44-2.26	0.46
	Baloxavir	11/19 (57.9)	1.31	0.79-5.96	0.63

Abbreviation: O.R., odds ratio; and CI, confidence intervals.

received oseltamivir, laninamivir, zanamivir, or baloxavir, and the frequencies of biphasic fever episodes and each adverse event in influenza patients who were treated with baloxavir was similar to that in patients treated with other anti-influenza drugs. In addition, laninamivir significantly contributed to early fever alleviation compared to oseltamivir in patients aged <10 years. The number of patients with influenza who were prescribed baloxavir decreased compared to the previous season (8.7% vs 37.5%)[5].

In international clinical trials, the virus titer was significantly lower from the second day of administration in the baloxavir group than in the oseltamivir group[2]. Our recent report also showed that the baloxavir group had a significantly shorter duration of fever than the NAI group in those with influenza A in the 2018-2019 season[5]. However, a previous study reported the emergence of viruses with reduced susceptibility to baloxavir following baloxavir treatment, and these viruses were associated with transient rises in infectious virus titers, prolongation of virus detectability, initial

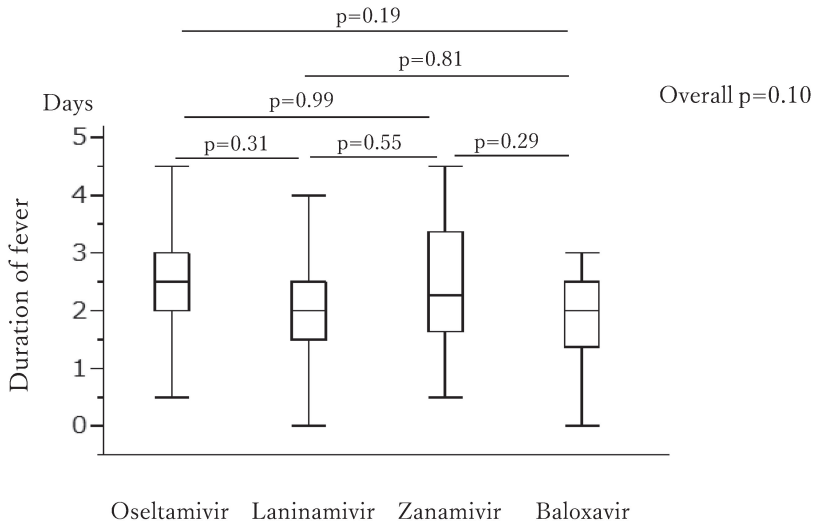

Figure 2. Comparison of the duration of fever in patients with influenza who received each anti-influenza drug. Data are the median days of fever in patients who received each anti-influenza drug; oseltamivir (median 2.5 days; interquartile range (IQR) 2.0-3.0), laninamivir (median 2.0 days; IQR 1.5-2.5), zanamivir (median 2.3 days; IQR 1.6-3.4), and baloxavir (median 2.0 days; IQR 1.4-2.5).

Table 3. Factors influencing episodes of biphasic fever according to age group, type of influenza, and anti-influenza drug

		n/N (%)	O.R.	95% CI	p value
Gender	Male	5/130	1	-	-
	Female	5/119	0.91	0.26-3.23	0.89
<10 years		4/99 (4.0)	1	-	-
≧10 years		6/155 (3.9)	0.94	0.26-3.73	0.92
Type of influenza virus	Type A	9/227 (4.0)	1	-	-
	Type B	1/25 (4.0)	1.00	0.05-5.72	0.99
Underlying diseases	No	7/186	1	-	-
	Yes	3/51	0.89	0.48-1.66	0.89
Vaccinated this year	No	3/131	1	-	-
	Yes	7/110	2.90	0.79-13.7	0.11
Anti-influenza drug	Oseltamivir	5/94 (5.3)	1	-	-
	Laninamivir	4/101 (4.0)	0.73	0.18-2.86	0.65
	Baloxavir	1/22 (4.5)	0.85	0.04-5.63	0.88

Abbreviation: O.R., odds ratio; and CI, and confidence intervals.

Table 4. Adverse events in each anti-influenza drug

	Oseltamivir (N=94)	Laninamivir (N=101)	Zanamivir (N=32)	Baloxavir (N=22)	p value
Coughing n (%)	32 (34.0)	39 (38.6)	18 (56.2)	6 (27.3)	0.10
Diarrhea n (%)	25 (26.6)	16 (15.8)	8 (25.0)	6 (27.3)	0.27
Vomiting n (%)	16 (17.0)	7 (6.9)	2 (6.3)	2 (9.1)	0.11
Abdominal pain n (%)	12 (12.77)	8 (7.92)	2 (6.25)	2 (9.1)	0.61
Headache n (%)	2 (2.1)	1 (1.0)	2 (6.3)	0 (0.0)	0.27
Abnormal behavior n (%)	3 (3.2)	2 (2.0)	0 (0.0)	0 (0.0)	0.62

delay in symptom alleviation, and uncommonly, with symptom rebound[2,3]. Our study showed no difference between the duration of fever or the frequency of biphasic fever episodes in the patients who received baloxavir and those in the patients who received oseltamivir, laninamivir, or zanamivir. Further studies will be needed to address the clinical effects of baloxavir, which contributed to shortening of the duration of fever or time to alleviation of symptoms, and the frequency of viruses with reduced susceptibility to baloxavir and their effects on clinical outcomes.

We have shown no difference between the frequency of adverse events after administration of the anti-influenza drug. Abdominal symptoms such as vomiting, diarrhea, and abdominal pain in patients who were treated with oseltamivir were previously reported as adverse events and bronchospasm after inhalation of laninamivir or zanamivir were also reported as adverse events[9,14,15]. However, it is difficult to accurately evaluate abdominal symptoms, coughing, and others as adverse events of anti-influenza drugs because they also occur with the symptoms of influenza. The frequency of adverse events after administration of baloxavir was similar to that of other influenza drugs. Because baloxavir is still a new drug, further studies on adverse events of baloxavir are needed in the future.

We have shown that laninamivir significantly contributed to early fever alleviation compared to oseltamivir in patients aged <10 years. We also found that all patients aged ≦4 years were prescribed laninamivir with a nebulizer. Laninamivir is not sold overseas, because the time to alleviation of symptoms in patients treated with laninamivir was not significantly different from that in patients who received a placebo in a phase Ⅱ trial, although the drug is effective in reducing the virus[16]. However, in Japan, some previous reports have shown that laninamivir has a similar efficacy and safety as oseltamivir for the treatment of influenza[10,17,18]. Because laninamivir is a single-dose inhalation drug that has an advantage over oseltamivir for medication adherence especially in children who frequently refuse to take an oral drug, it may be significantly associated with early fever reduction in patients aged <10 years. Nebulizers were used for inhaling laninamivir beginning in October 2019 in addition to a dry powder inhaler. We consider that nebulized administration of laninamivir can be widely prescribed to infants and elderly patients who may have difficulty using a dry powder inhaler.

The number of patients who were prescribed baloxavir was significantly reduced in our survey of the 2019-2020 season compared to the 2018-2019 season[5], similar to national trends in Japan[19]. We consider that one cause of the decrease in the number of prescriptions of baloxavir is the suggestions from the Japanese Association for Infectious Diseases and the Japan Pediatric Society based on some reports of the emergence of viruses with reduced susceptibility to baloxavir in children and their human-to-human transmission[7,8,20,21]. The decrease in the number of prescriptions of baloxavir may have affected the results in our study. The frequency and odds ratio of alleviation of fever in 2 days in patients who were prescribed baloxavir was higher than those in patients who were prescribed laninamivir, however no significant difference could be detected due to the small number of prescriptions of baloxavir.

Some limitations of this study should be recognized. First, the response rate of the postcard questionnaires was not high. Therefore, the sample may not be representative of all patients with influenza. The proportion of our patients who were in their 20's and 30's was lower than that in the data from the Ministry of Health, Labour and Welfare (MHLW) (5.5% vs 16.1%). However, the proportion of patients aged 5-9 years and 10-14 years was higher than those in the MHLW data

(53.2% vs 38.7%). The proportions of the other age groups in our subjects were similar to those in the MHLW data[22]. We suggest that the working populations who were in their 20's and 30's may not return many postcards because they didn't have enough time to answer and mail the postcard questionnaire. Second, the answers including body temperature were self-reported data, and the reliability of the answer is a limitation. Third, the use of antipyretics was not considered, and the duration of fever may shorter than the actual one. Based on the above limitations, we should consider adding or modifying questionnaire items and other questionnaire methods such as an online survey for the further development of the study in the future. Fourth, this study was an observational study, not a randomized controlled study. The selection of the anti-influenza drug was at the discretion of each physician, introducing invisible selection bias. Making an accurate comparison of the effects of each anti-influenza drug may be difficult, because their prescription numbers were different. Fifth, we could not confirm the influenza subtype in this study. For the 2019-2020 season, the National Institute of Infectious Disease reported that more than 90% of the influenza subtype was type A (H1N1 pdm09), which almost constituted an epidemic[23].

In conclusion, our study showed no significant association between baloxavir and early fever alleviation or the frequency of biphasic fever episodes that have been reported in the previous study. One cause may be that no statistically association was detected due to the decrease in the number of prescriptions of baloxavir. Further studies will need to address the clinical effects of baloxavir, which contributes to the shortening of the duration of fever or the time to alleviation of symptoms, and the association between baloxavir and biphasic fever episodes. Because epidemic influenza virus subtypes change from season to season, annual influenza surveys are also important for investigating the appropriate use and efficacy of anti-influenza drugs.

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All authors have no COI to declare regarding the present study.

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