論文の内容の要旨

論文題目 Site specificity of acute disuse muscle atrophy in critically ill patients and construction of early rehabilitation programs targeting lower-limb muscles in intensive care units

(ICU 入室患者の廃用性筋萎縮の部位別特異性と下肢筋群に重点をおいた急性期リハビリテーションの構築)

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Objective

The aim of this study was to evaluate the degree of skeletal muscle atrophy and to elucidate the region of skeletal muscle that would be susceptible to disuse muscle atrophy in critically ill patients who were on bed rest because of severity of their disease or postoperative condition during their 6-day ICU stay (Chapter 1). Considering the results of Chapter 1, I constructed a feasible early rehabilitation program to prevent disuse muscle atrophy (Chapter 2). Furthermore, I examined the efficacy of the early rehabilitation program in Chapter 3.

Chapter 1: Site specificity of acute disuse muscle atrophy in critically ill patients

Introduction

The effect of short-term bed rest on the degree of disuse muscle atrophy in critically ill patients, who often present with high inflammatory response as well as hemodynamic and respiratory instabilities, has not been fully elucidated in previous studies. The aim of the study in Chapter 1 was to compare the degree of skeletal muscle atrophy between ADL-independent and ADL-dependent patients before the ICU admission, and clarify the region of skeletal muscle that was susceptible to disuse muscle atrophy in critically ill patients on bed rest due to the severity of their disease or postoperative condition during their 6-day ICU stay.

Materials and Methods

Setting: This observational study was conducted in ICU of Keio University Hospital, which is a teaching hospital that includes 1044 beds, from October 2012 to October 2013. This study was approved by the hospital's ethics committee before any participants were enrolled (approval number of the hospital's ethics committee: 20130181), and informed consent was obtained from participants or their authorized representatives according to the code of ethics when needed.

Patients: Patients over 20 years old and who were expected to stay in ICU for over 6 days and required bed rest as the initial rest level at ICU admission were eligible for this study. The exclusion criteria were as follows: patients who had received either upper-limb or lower-limb amputation, patients with refractory shock after large numbers of transfusions and high-dose catecholamine therapy, deep-vein thrombosis, either upper-limb or lower-limb burns, and also limb-bone fractures. Obese patients, with a body mass index (BMI) of over 35 (morbid obesity), who had more adipose tissue at the peripheral sites, such as the upper and lower limbs, were also excluded to eliminate the effects of the fat layer. Subjects were divided into 2 groups depending on the ADL level before ICU admission: ADL-independent group and ADL-dependent group. The ADL dependency level before ICU admission was classified for either group on the basis of the diagnosis procedure combination (DPC). The demographic information and baseline characteristics of the subjects, such as age, sex, BMI, sequential organ failure assessment (SOFA) score, blood chemical analysis data, and ICU primary admission diagnosis, were also recoded.

Outcome: The primary outcome of this study was the degree of skeletal muscle atrophy in the upper and lower limbs measured by the chronological change of muscle thickness in the critically ill patients in ICU. For the evaluation of muscle thickness, I measured the limb circumference using the same soft tape. The measurement sites were selected on the basis of previous studies regarding anthropometric measurements. There were 5 sites: the midpoint of the upper limb between the acromion and olecranon for the biceps brachii evaluation, the maximum point of the lower leg for the triceps surae evaluation, and 3 different points of 5 cm, 10 cm, and 15 cm above the superior pole of the patella for the quadriceps femoris evaluation. Limb circumferences were measured to the nearest 5 mm. The measurements were taken at the day of ICU admission, and at 72 hours (hrs), and 144 hrs after ICU admission. Subjects were maintained in the supine position with each limb being at extension position during the measurement of the circumference, and respective measurement points were marked by red marker for the initial measurement to avoid inter-measurement errors. Inter-class and intra-class correlation coefficients (ICC) were calculated to evaluate the anthropometrical artificial error (ICC (1, 1) = 0.997, ICC (2, 1) = 0.996). To exclude the effect of fluid therapy on the limb circumference, I also recorded the daily fluid balance for each day.

Statistics: Demographic data and fluid balance were compared with Student *t*-test or chi-square test between the ADL-independent group and the ADL-dependent group, and presented as mean ± standard deviation (SD). The length of limb circumference was described as the percentage compared with the value at ICU admission, and results were presented as median (interquartile range). The change of limb circumference during the ICU stay at each site and the difference in the limb circumference change at 72 and 144 hrs after ICU admission among the 5 different sites were compared with 1-way analysis of variance (ANOVA) followed by a *post hoc* analysis. All statistical analyses were performed with IBM SPSS Statistics, version 22 (SPSS, Inc., Chicago, IL). A p value of <0.05 was considered as statistically significant.

Results

After eliminating participants on the basis of exclusion criteria, forty-one patients were enrolled in this study during the study period, including 31 patients in the ADL-independent group and 10 patients in the ADL-dependent group. Except for age, there were no significant differences in the demographic information and baseline characteristics between the ADL-independent group and the ADL-dependent group.

In the ADL-dependent group, at 72 hrs after ICU admission, the limb circumferences were not significantly decreased compared with the baseline except in the left thigh at 15 cm above the patella. However, limb circumferences at all sites were decreased significantly at 144 hrs after ICU admission compared with the baseline. On the other hand, the limb circumferences at all sites except for the left upper limb decreased significantly at 72 hrs after admission in the ADL-independent group, and limb circumferences at all sites were all decreased significantly compared with the baseline at 144 hrs after admission.

There were no significant differences in the change of limb circumference among all 5 sites at 72 and 144 hrs after ICU admission in the ADL-dependent group. Whereas, in the ADL-independent group, the change of limb circumference at the 4 different lower-limb sites was larger than that in the upper limb in both the right and left sides at 72 and 144 hrs after ICU admission. The change at the site 15 cm above the superior pole of patella was particularly noticeable. The fluid balance during the first 72 hrs and the next 72 hrs after ICU admission in the ADL-independent group was +1260 mL and −74 mL, respectively. The fluid balance of the ADL-dependent group was +2511 mL and +479 mL, respectively. There were no significant differences in the chronological changes in the fluid balance between the ADL-independent group and the ADL-dependent group. To eliminate the bias caused by fluid balance, I classified the patients in the ADL-independent group into 3 groups according to the fluid balance 144 hrs after ICU admission, and compared the limb circumferences between these 3 groups. There were no significant differences in the change of limb circumferences between the 3 groups.

Because there was a significant difference in age in the demographic information between the ADL-independent group and the ADL-dependent group, I examined whether aging affected the progress of muscle atrophy by classifying the patients of the ADL-independent group into 4 groups by age, and comparing the limb circumferences between these 4 groups. There were no significant differences in the change of limb circumferences between the 4 groups.

Discussion

The major finding of this study was that the acute muscle atrophy progressed during only 6 days in ICU, and advanced faster in the ADL-independent patients than in the ADL-dependent patients. Furthermore, the degree of muscle atrophy was more severe in the lower limbs, which are used as antigravity muscles for maintaining sitting and standing positions, than in the upper limbs in the ADL-independent group during a short-term ICU stay. It has been reported that age-related sarcopenia progressed greater in lower-limb muscles in the elderly. Another studies demonstrated that in healthy people, the muscle atrophy caused by prolonged bed rest for 5–17 weeks was more severe in the lower-limb muscles than in the upper-limb muscles. However, there have been few studies, which compared the degree of muscle atrophy between the upper and lower limbs during this relatively short period in critically ill patients. In this study, I focused on the acute disuse muscle atrophy during the acute stage of critically ill patients admitted to ICU who often presented with both hemodynamic and respiratory instabilities, a high inflammatory response, and malnutrition; I also demonstrated that muscle atrophy progressed more in the lower-limb muscles than in the upper limb muscles, which was consistent with sarcopenia associated with aging in elderly patients. Furthermore, compared with the state before ICU admission, the muscle atrophy progressed greater and faster during the short period of 6 days in the ADL-independent patients. These results strongly emphasized that a rehabilitation program to prevent acute muscle atrophy targeting the lower-limb muscles should be initiated as early as possible after ICU admission, especially for the ADL-independent patients.

In this observational study, the disuse muscle atrophy in critically ill patients developed rapidly, especially in the lower limbs in the ADL-independent patients before ICU admission. This result emphasized the necessity of the intensive early rehabilitation program focusing on the lower-limb muscles to prevent muscle atrophy, which could affect the prognosis of critically ill patients.

Chapter 2: Construction and introduction of ARH program in a clinical field

Introduction

In Chapter 1, I elucidated the site specificity of the acute muscle atrophy, which progressed predominantly in the lower limbs during only 6 days in ICU, especially in the ADL-independent patients. The quadriceps femoris and triceps surae muscles, which are the major components of the lower-limb muscles, have a strong relationship with the patient's activities in their daily life, such as sitting and standing. The weakness of these muscles is associated with the decrement of the ADL performance. Furthermore, these muscles have the very important role of muscle pump to assist venous return and to stabilize hemodynamics. This function is needed to support ICU patients implement the stepwise mobilization safely and effectively. For that reason, I found that early rehabilitation should focus on the lower-limb muscles (the quadriceps femoris and triceps surae muscles as the targeted muscles) in the acute stage of critical illness in ICU.

Patients admitted to ICU are usually critically ill with systemic instability. These critically ill patients receive medical treatment and life support systems, such as mechanical ventilation, as a first priority. Because the increase of oxygen consumption caused by the initiation of rehabilitation in acute phase might impose the risk of deterioration in the cardiopulmonary or respiratory condition of critically ill patients, early initiation of the rehabilitation program is usually difficult to perform during this acute stage. However, a recent study has shown the safeness and feasibility of early rehabilitation. In these studies, only Morris *et al* showed the contents of a mobility protocol and described the effectiveness of the protocol on the patients with acute respiratory failure. However, none of them emphasized the importance of the physical therapies focused on the lower-limb muscles in the acute stage of critically ill patients in ICU, nor described the details regarding the introduction, assessment, step-up/step-down of the rehabilitation level, discontinuation criteria, and contraindications.

Thus, I modified the mobility protocol reported by Morris *et al*, and developed an acute rehabilitation (ARH) program, which described the detailed daily rehabilitation plan to optimize the contents of rehabilitation. This ARH program included many steps to effectively prompt rehabilitation according to the patient condition, regarding the introduction, frequent assessment, step-up/step-down of the rehabilitation level, discontinuation criteria, and contraindications. This ARH program also included intensive lower-limb intervention to prevent acute disuse lower-limb muscle atrophy that had been elucidated in the previous chapter. In this chapter, I have introduced the detailed process and contents of the ARH program that I established, and described the purpose and the background of the development of the ARH program, including the selection of the countermeasures for the lower-limb muscle atrophy, on the basis of systematic reviews.

Search strategy and selection of the countermeasure

In the previous studies, there have been several countermeasures to prevent lower-limb muscle atrophy, which can be performed during the period of bed rest. I searched the database PubMed (Issue 21st Feb 2015) to identify these studies, which reported the efficacy of countermeasures to prevent lower-limb muscle atrophy, written in English and published between 1995 and 2014. The search terms included these keywords; "muscle atrophy," either "bed rest" or "critically ill," and either with or without "lower limb." There were 228 studies identified. I then screened the titles and the abstracts to exclude studies, which had no relevance to any intervention to prevent lower-limb muscle atrophy. There were 28 studies after the screening. Then, I excluded the studies with countermeasures to prevent lower-limb muscle atrophy that were performed out of bed and with nutrition countermeasure because they were impracticable for an ICU. Furthermore, I excluded the studies which were not intensive interventions for lower-limb muscles because the lower-limb muscles were the targeted muscles for intervention. Finally, there were 19 studies with 4 types of countermeasures to prevent lower-limb muscle atrophy: passive stretching (n = 1), electric muscle stimulation (EMS) (n = 5), resistive vibration exercise (n = 5), and resistance exercises (n = 8). All these studies have shown the efficacy of the countermeasures to prevent lower-limb muscle atrophy. Because the subjects in this study were critically ill patients in ICU, who were bedridden because of hemodynamic or respiratory instabilities and were likely to have less exercise tolerance, I determined that the passive stretch could be the primary choice. However, even though it has been reported that the passive stretch prevented the progress of muscle atrophy in critically ill patients, the exact mechanism of its effect was not completely understood. For that reason, I excluded this method. The previous studies demonstrated that EMS, which is a noninvasive method to induce the muscle contraction directly without a patient's effort, can prevent muscle atrophy. The effect of muscle contraction by EMS is equivalent to that of the patient's voluntary muscle contraction by the resistance exercise when it is performed at the same intensity. However, EMS was not available in the ICU of the Keio University Hospital. The previous studies had demonstrated the efficacy of the resistive vibration as well as EMS. However, I excluded the resistive vibration exercise for the same reason as EMS. It was not available in the ICU of the Keio University Hospital. Considering the feasibility and the adoptability of the each countermeasure to the clinical field, I decided to adapt these resistance exercises for lower-limb muscle atrophy. There were several types of resistance exercises in the previous studies, which were divided into 2 categories. One is the resistance exercise, which uses special machines, such as the flywheel and calf press machine, and the others that can be performed without special machines. I finally decided to adapt the lower-limb resistance exercises that do not use the special machine at every level of the ARH program to prevent lower-limb muscle atrophy, because the special machines for resistance exercises were not available in the ICU of the Keio University Hospital; the conscious patients could perform the resistance exercises spontaneously with the limited level of range of motion in the bed without special machines.

According to the search strategy and the selection of the countermeasure based on the systemic reviews, I constructed an ARH program as the early rehabilitation program targeting lower-limb muscle atrophy; this program is likely to be practicable and adaptable to ICU patients in acute stage of a critical illness, and introduced it in a clinical filed.

Chapter 3: The efficacy of ARH program

Introduction

ARH program constructed in Chapter 2 was introduced into ICU practice. Then, I evaluated the efficacy of the ARH program. In order to evaluate the efficacy of the ARH program, a randomized control trial needed to be performed because of the high reliability of the study. However, because it was the first time for the initiation of the ARH program in ICU and it was uncertain whether this ARH program could work, an observational study was conducted to evaluate of the efficacy of the program as a preliminary study. The data before the initiation of ARH program described in Chapter 1 was used as the control, because the study setting was almost exactly the same except for the ARH intervention. The evaluation of muscle atrophy was performed in the same way as in Chapter 1.

Materials and Methods

Setting: The observational study was conducted in ICU of the Keio University Hospital, which is a teaching hospital that includes 1044 beds, from October 2012 to September 2014. This study was approved by the hospital's ethics committee before any participants were enrolled (approval number of hospital's ethics committee: 20130181), and informed consent was obtained from participants or their authorized representatives according to the code of ethics when needed.
Patients: Patients over 20 years old and who were expected to stay in ICU for more than 6 days and required bed rest as the initial rest level at ICU admission were eligible for this study. The exclusion criteria were as follows: patients who received either upper-limb or lower-limb amputations, patients with refractory shock after a significant amount of transfusions and high-dose catecholamine therapy, deep-vein thrombosis, either upper-limb or lower-limb burns, and limb-bone fractures. Obese patients with a BMI over 35 (morbid obesity), who had more adipose tissue at peripheral sites, such as the upper and lower limbs, were also excluded to eliminate the effects of the fat layer.

Subjects consisted of 2 groups: the control and intervention groups. Thirty-one ADL-independent patients from before the ARH program introduction that were enrolled in Chapter 1 were treated as the control group. Another 31 ADL-independent patients after the ARH program introduction in November 2013 were treated as the ARH intervention group.
Outcome: The primary outcome of this study was the degree of skeletal muscle atrophy in the upper and lower limbs measured by the chronological change of muscle thickness in the critically-ill patients in ICU in the same way as in the study from Chapter 1.
Statistics: Demographic data and fluid balance were compared with Student *t*-test or chi-square test between the control and intervention groups when appropriate, and presented as mean ± SD. The length of limb circumference was described as the percentage compared with the value at ICU admission, and results were presented as the median (interquartile range). The chronological change of the respective limb circumferences between the control and intervention groups during ICU stay were compared with ANOVA repeated measures. All statistical analyses were performed with IBM SPSS Statistics version 22 (SPSS, Inc., Chicago, IL). A p value of <0.05 was considered as statistically significant.

Results

Sixty-two patients were enrolled in this study during the study period, including 31 patients in the control group and 31 patients in the intervention group. There were no significant differences in the demographic information and baseline characteristics between the control and intervention groups. There were no significant differences in fluid balance during the first 72 hrs and the next 72 hrs after ICU admission between the control and intervention groups. The reduction of the limb circumference at the 4 different lower-limb sites in the intervention group was smaller than these in the control group in both right and left sides during the 144 hrs of ICU admission, while that of the upper limbs were not different significantly between the control and intervention groups.

Discussion

This study demonstrated that ARH program initiated soon after ICU admission could prevent acute disuse muscle atrophy in critically ill patients, especially in the lower limbs. The results of this study suggested that it should be mandatory to initiate an ARH program as early as possible. Furthermore, this rehabilitation program may be expected to shorten the hospital stay and help critically ill patients recover to their prior ADL level faster, which should be clarified in the future study. Although the efficacy of the ARH program in critically ill patients was shown in this study, there were various diagnoses of the critically ill patients, and the sample size was small. Therefore, in order to increase the reliability, a large, multicenter, randomized controlled trial will be warranted to evaluate the efficacy of this program, in which not only the muscle atrophy but the length of hospital stay and the ADL levels after discharge should be evaluated. I have to work so that the ARH program in the acute phase of critically illness becomes widespread in the field of ICU.

Conclusion

In conclusion, I evaluated the chronological changes in the acute disuse muscle atrophy of ICU patients using the anthropometric method, and found that the disuse muscle atrophy developed rapidly, specifically in the lower limbs of the ADL-independent patients after 6 days in ICU. These results strongly emphasized that the rehabilitation program to prevent acute muscle atrophy that targeted the lower-limb muscles should be initiated as early as possible after ICU admission, especially for the ADL-independent patients.

I then constructed an ARH program from the viewpoint of ICU nurses which consisted of a feasible daily rehabilitation plan, including lower-limb resistance exercises to prevent lower-limb muscle atrophy, and introduced it to the clinical field, as described in Chapter 2. As shown in the study of Chapter 3, the reduction of the lower-limb circumference in the intervention group was significantly smaller than that in the control group after the ARH intervention. These results suggested that it may be necessary to initiate an ARH program as early as possible. Furthermore, this rehabilitation program may shorten the hospital stay and help critically ill patients recover to their prior ADL level faster, which should be elucidated in the future study.