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Muscle strength and mortality while on a liver transplant waiting list

Força muscular e mortalidade na lista de espera de transplante de fígado

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Abstract

Objective: To evaluate respiratory muscle strength and hand strength in patients on a liver transplant waiting list and to associate these with mortality. **Methods:** one hundred and thirty-two patients who underwent routine physical therapy evaluation while waiting for liver transplantation were studied retrospectively. Respiratory muscle strength was assessed by measuring the maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP), and upper-limb strength was evaluated by dynamometry. The patients were divided into two groups: group A, consisting of 51 patients (14 females, 50.1±12.3 years) who died while on the waiting list; and group B, consisting of 81 patients (31 females, 45.0±3.8 years) who survived until the time of liver transplant. Student's t test was used with a 5% significance level. **Results:** The mean MIP values for groups A and B were 65.7±28.0 and 77.5±33.8mmHg (p=0.04), respectively, and the mean MEP values were 72.9±32.9 and 84.4±33.1mmHg (p=0.07), respectively. The mean values for left-hand strength in groups A and B were 18.5±8.1 and 21.5±10.5kgf (p=0.08), and the mean values for right-hand strength were 20.2±9.7 and 23.5±12.5kgf (p=0.10), respectively. **Conclusions:** MIP was lower in the patients who died while waiting for liver transplantation. In the same group, it was observed that the MEP values and right and left-hand strength were numerically lower, although they did not reach statistically significant differences.

Key words: liver transplantation; respiratory muscles; mortality; hand strength; physical therapy.

Resumo

Objetivo: Avaliar a força de músculos respiratórios e de mão em pacientes na lista de espera para o transplante de fígado e associá-los a mortalidade. **Materiais e métodos:** Foram estudados retrospectivamente 132 pacientes submetidos à avaliação fisioterapêutica de rotina e que esperavam o transplante de fígado. A força dos músculos ventilatórios foi avaliada por meio das pressões inspiratória e expiratória máximas e a força do membro superior por meio de dinamometria. Os pacientes foram divididos em dois grupos: grupo A, com 51 pacientes (14 mulheres, 50,1±12,3 anos) que morreram enquanto estavam na lista de espera e grupo B, com 81 pacientes (31 mulheres, 45,0±3,8 anos) que sobreviveram até o transplante de fígado. Foi utilizado o teste de *t* de *Student* com nível de significância de 5%. **Resultados:** Os valores médios da pressão inspiratória máxima (PImax) dos grupos A e B foram 65,7±28,0 e 77,5±33,8mmHg (p=0,04), respectivamente, e as pressões expiratórias máximas foram 72,9±32,9 e 84,4±33,1mmHg (p=0,07), respectivamente. Os valores médios da força da mão esquerda dos grupos A e B foram 18,5±8,1 e 21,5±10,5kgf (p=0,08), respectivamente, e da força da mão direita foram 20,2±9,7 e 23,5±12,5kgf (p=0,10), respectivamente. **Conclusões:** A PImax é menor nos pacientes que morreram enquanto aguardavam o transplante. No mesmo grupo, foi observado que a pressão expiratória máxima e a força da mão direita e esquerda foram menores, apesar de não apresentarem diferenças estatisticamente significante.

Palavras-chave: transplante de fígado; músculos respiratórios; mortalidade; força da mão; fisioterapia.

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Introduction

The natural history of patients suffering from hepatic cirrhosis is often complicated by the accumulation of extravascular liquid, gastrointestinal bleeding, changes in renal function, infections, coagulation disturbances and a large spectrum of neuropsychiatric disorders. About 50 to 60% of patients suffering from hepatic cirrhosis develop ascites due to renal difficulties in manipulating sodium and water, and this generates a prognosis reserved for patients which leads to a survival of 50% in two years[1]. The protein-caloric malnutrition has been described as an existing condition among all patients with hepatic cirrhosis since the liver plays an essential role in metabolism. Another important disturbance is the loss of muscle and bone mass and all of these factors can negatively influence both morbidity and mortality[1-4].

Patients with hepatic cirrhosis from different etiologies demonstrate malnourishment and vulnerability to infections, which consequently weakens their musclular and respiratory functions. They may also show ascites and pleural effusions, due to low levels of albumin and poor protein intake. Because of alimentary restrictions and hepatic metabolism inefficiencies, muscle mass may also be impaired[1]. Respiratory muscular strength can be decreased; nevertheless, it doesn't interfere with removal of mechanical ventilation, despite chirurgic interferences, pain and surgical incisions[5].

The high levels of intra-abdominal pressure affect adjacent organ and tissue function, which leads to increases in the intra-thoracic pressure that compresses the lungs, and impair the ventilation/perfusion[6] relationship. Some authors observed that the bulky and tense ascites alter the respiratory mechanics and decrease chest complacency[1]. The major disturbance occurs in the pulmonary volumes and for the functional residual capacity, which improves after paracentesis, however, without significant improvements in oxygenation[7].

Liver transplantation represents a great therapeutic advance to chronic liver diseases, but previously, it was only possible to treat the complications. Once the disease reached a certain stage, it resulted in death. The possibilities of replacing an inefficient liver allowed the changing, for the first time, of the natural history of these diseases, and offered a real perspective of long-term and quality possibilities of survival. Nevertheless, liver transplants have resulted in certain managerial difficulties, which both affect both the physicians and patients. Consequently, the number of candidates has increased faster than the performed transplants, which are limited by an insufficient supply of grafts. This disproportion between candidates and the supply of graft leads to high mortality rates while on the waiting list for transplants[8].

Patients with liver disease were classified with the Child-Turcotte-Pugh (CTP) score which used five criteria, two of them clinical and three from laboratory studies. Recently, another classification is being used now for the same purpose in Brazil. The severity of the patients disease is quantitatively assessed by the Model for End-stage Liver Disease (MELD), which measures the mortality risk of serious liver diseases from different etiologies and that serves for the evaluation the severity of the disease[9]. It would be important that the transplant was done at an early stage, before the manifestations of the disease, which negatively affect the prognosis. There are many studies that consider the prognosis, nutritional status, nutritional therapies, pre-transplantation and survival rates, but due to the organ shortage, this only generates endless discussion.

It has been reported that models to estimate the risks of mortality in transplants do not exist and that there are no norms to assess performance in various centers[10]. There are many ways to evaluate nutritional status, through protein-caloric intake, assessment of body composition, muscle strength, both from respiratory muscles and from upper and lower limbs, and also through lung volume and capacity[2-6]. As the disease becomes more severe, a greater number of the cirrhotic patients show decreases in trophism and in muscular strength, and thus a complete evaluation is required. Thus, the objective of this study was to evaluate the ventilatory muscle power and hand muscles' strength in patients on the waiting list for liver transplants and to associate them to mortality.

Materials and methods

The protocol for evaluation of the patients was approved by the Ethics Commission for Analysis of Research Projects (nº 094/04). Two hundred and four patients from the waiting list for liver transplants were submitted to the same physical therapy evaluation routines and they were in a stable condition while performing all pre-operative surgery evaluations. Seventy-two subjects were excluded for lack of information in their patient records. The patients were split in two groups: group A was composed of 51 patients (37 men and 14 women), with an average age of 50.1±12.3 years, who died while on the waiting list; and group B was made up of 81 patients (50 men and 31 women) with an average age of 45.0±3.8 years, who survived until the liver transplantation.

Laboratory tests of bilirubin, urea, creatinine, albumen, were collected during the evaluation as well, data on body weight, height and the body mass index (BMI). The power of the respiratory muscles was evaluated using a vacuum manometer measuring device (model MV150, Imebraz®, Brazil),

Table 1. Demographic and clinical characteristics of the patients.

	Group A	Group B	p	Reference
Sex (M/F)	37/14	50/31		
Age (years)	50.1±12.3	45±3.8		
BMI (Kg/m^2)	22	24		
Urea (mg/dl)	49.7±39.8	38.6±24.3	0.469	10 a 50
Creatinine (mg/dl)	1.21±0.6	1.09±0.5	0.453	0.2 a 0.7
Total bilirrubin (mg/100ml)	5.92±7.3	5.11±7.6	0.510	até 1.2
Albumin (g/100ml)	3.23±0.40	4.22±4.4	0.469	3.5 a 5.5

Group A=who died while on the waiting list; group B=who survived up to the liver transplants; (BMI)=body mass index.

Table 2. Strength of the hand and respiratory muscles.

Variables	Group A	Group B	p
Left hand strength	18.5±8.1	21.5±10.5	0.08
Right hand strength	20.2±9.7	23.5±12.5	0.10
Maximum inspiratory pressure	65.7±28.0	77.5±33.8	0.04*
Maximum expiratory pressure	72.9±32.9	84.4±33.1	0.07

Group A=who died while on the waiting list; group B=who survived up to the liver transplants.

using the Black and Hyatt technique[11]. The maximum inspiratory pressure (MIP) was measured from the residual volume (RV) and the maximum expiratory pressure (MEP) from the total lung capacity (TLC). Three measurements were taken, but only the highest value was retained. The strength of the muscles of the hand was measured with the subjects seated, with a Filizola®, Brazil, dynamometer brand, which was adjusted to their stature. Their feet were kept on the floor, with the knee and hip flexion of 90°. The shoulders remained adducted and the elbow was positioned at a 90° angle of flexion with the forearm in a neutral position, without consideration of the dominant limb. In order to control muscle fatigue, a one-minute interval was permitted between measurements[12,13]. The muscle strength was compared with the Student's t-test with a level of significance of 5%. This considered the percentage of the actual and predicted values of the respiratory muscles and manual strength, expressed in percentages, with a comparative effect[14].

Results

Patients were divided into two groups: group A, of those who died while on the waiting list and group B, of those who survived until the liver transplantation. The ages of groups A and B were 50.1±12.3 and 45.0±3.8 years, respectively. The mean values of the BMI from group A and B were 22 and 24kg/m^2, respectively. Other data, such as bilirubin, urea, creatinine and albumin that characterized the gravity of the state of the groups, did not show any statistical differences (Table 1).

The maximal respiratory pressures (MIP and MEP) of groups A and B are illustrated in Table 2. The regression equations for calculating the maximal respiratory pressures by age, according to the sex were used as predicted values.

The left hand strength (LH) of group A and B were 18.5±8.1 and 21.5±10.5kg (p=0.08), respectively. The right hand (RH) strength of group A and B were 20.2±9.7 and 23.5±12.5kg (p=0.10), respectively. LH strength was 41.8 and 42.9% lower than the predicted values for group A and B, respectively. RH strength was 43.4 and 44.5% lower than the predicted values for group A and B, respectively, and all are shown in Table 2.

Discussion

Due to the shortage of organs from donors with encephalic death, surgeons and professionals who work with organ allocation are constantly worried about the number of patients on the waiting list, the general state of the receiver, the transplant results and, mainly, in the determination of who would be the best receiver and which one would provide the best results. Liver transplantation is an efficient therapy and is highly accepted for children with liver diseases. Innovations such as reduced grafts, has increased the source of supplied organs both for children and for adults, thus significantly decreasing the mortality during pre-transplantation. Survival after transplantation improved and survival rates of 70 to 90% are the norm. After transplantation, children have rapid nutrition recovery and the muscular strength increases. This is shown through their motor development and by improvements in general health[15].

Laboratory tests for urea, creatinine, bilrubine and albumin were collected from the patients' records, and made it impossible to classify them by any score of gravity of the liver, because there was no collection of prothrombin time (PT), nor any description of encephalopathy, upper gastrintestinal bleeding and the necessary parameters to classify them by CTP. In both groups there were patients who showed ascites, however, this was not quantified by imaging exam methods, making it impossible to do correlation analyses in this study.

Patients who died while on the waiting list were older, which was an aggravating factor, although the differences were small and not significant. Despite the severity of the disease, muscle mass consumption and a protein restricted diet, these patients demonstrated a normal BMI.

Liver transplantation is recommended when the expected survival rate is lower than or equal to 90%. It is well established that patients who show a score equal or greater than 7 at the CPT, evolve with a varicous bleeding which is hard to control, accentuated muscle mass loss, refractory itching, hepathic encephalitis, intense fatigue, frequent acute cholangitis or spontaneous bacterial peritonitis, and meet the international criteria of indications for transplants. Recently, another classification is being used, where the receivers' state of health is quantitatively evaluated, by the MELD index, which measures the risk of mortality from hepatic diseases of different etiologies and that permits the ranking of the severity of the disease. Its calculation is based on a mathematical formula in which are placed the values for serum bilirubin, PT and serum creatinine. The score index ranges from 1 to 40, where the higher values match with the higher risks[9]. This index is now being used in Brazil and the waiting list for transplants is no longer chronological, but is determined by the gravity of the disease.

In this study, from the correlations between the MELD index at the pre-operative surgery period with the transplant results, it was concluded that the subgroup with the lower MELD score had a mortality rate of 15% during the first six months and that, among those with a higher MELD, the rate was of 26%. It was demonstrated that the mortality rate doubles for every increase of 15 points on the MELD scale. By means of the obtained equation, it is estimated that, in the patients with MELD equal or higher than 40, the mortality after transplantation exceeds 50%[9].

These patients are usually quite debilitated, due to the disease, but there are other complicating factors, such as their nutritional status and a poor protein diet. This association of factors causes metabolic disturbances and produces some consequences such as the impairment of all muscles, especially the thoracic and diaphragmatic ones. In addition, the chest mobility, which sometimes will be impaired by ascites, generates an increase in intra-abdominal pressure and higher respiratory work, because of increases in the positive pressure at the termination of expiration[16].

The patients, during the liver pre-transplantation period, are shown to be atrophic, with muscle weakness, which generates physical de-conditioning, expressed through a reduction in their aerobic capacity, muscle strength and resistance. The decreases in physical capacity of the liver pre-transplantation patient affects the performance on the activities of daily living and, consequently, their quality of life[2,5,17].

Malnutrition is common in patients with chronic liver disease waiting for the liver transplants and it has been correlated to morbidity and mortality rates associated with the transplantation[18]. However, this prevalence depends on the disease etiology and on the type of nutritional evaluation used[4]. Although many studies use classical parameters of nutritional evaluation, like anthropometric measurements and plasmatic protein determination, but these malnutrition indicators in patients with advanced liver disease, cannot always be used in an isolated manner[2,4,5].

It is known that hepatic cirrhosis may change the majority of these parameters, what leads some authors to suggest a more detailed nutritional evaluation for this kind of patient[4]**.** In this study, although the mean values of BMI were normal, the calculation was not indicated, since this method was not able to distinguish fat from water located in the abdomen and the measurements were overestimated. An efficient and low cost evaluation would be the analysis of skin folds to determine the nutritional status.

The waiting period for transplants contributes to the development of morbid conditions, which originated from the worsening of the hepatic disease, malnutrition, hypermetabolism and physical inactivity, which would interfere with the prognosis[18]. However, few studies have investigated the physical capacity and the functional performance levels while waiting for the liver transplants or during the post-operatory period[19,20].

While on the waiting list, patients develop many episodes of secondary infections, like bacterial peritonitis, urinary infections and pneumonia, what can cause severe infectious conditions of high mortality[21]. In these patients, the laboratory analysis showed the degree of severity of the hepatic disease. These values demonstrated that both groups were in seriously poor conditions, and although there were no statistical differences, group B showed lower mean values, what predisposed them to a lower level of mortality.

Protein-caloric malnutrition may be measured through the body mass depletion in patients during the terminal stage of the disease. Another study correlated BMI, anthropometric measurements, dynamometry, laboratory tests and

body compositions, as measured by X-rays and verified that dynamometry is a sensitive and specific marker to indicate muscle mass depletion[22].

The measurement of hand grip strength characterizes the nutritional state of patients. Hand grip strength values lower than 85% of normal predicted values, lead to possible post-operative complications[22]. For another author, manual hand strength depends on sex and age, but would not be correlated with height[17]. In this work, hand grip strength of cirrhotic patients has proven to be very low when compared to the predicted value by age[12]. Hand grip strength of the left hand was 41.8 and 42.9% and of right hand was 43.4 and 44.5% lower than predicted values of group A and B, respectively.

In another study, by analyzing the quality of life, the knee extensors muscle dynamometry, hand grip strength and the aerobic threshold, there was found a reduced functional status dependent only on the CPT classification, but not for the etiology[23].

However, not all authors reported the same results. For some authors, hand dynamometry and the anthropometric measurements are fast and cheap tests to detect poor nutrition, but are not useful for pre-operative surgery selection, as a predictor of post-operative surgery morbidity[24]. The incidence of protein-caloric malnutrition in adult hospitalized patients may reach 30 to 50% and may influence clinical results. Another work performed a detailed evaluation, including anthropometric measurements, hand strength and measurements of MIP and MEP, at admission and discharge, and concluded that hand strength and BMI are good predictors of nutritional status declines, but the respiratory muscle strength were not correlated[25].

In the present study, respiratory muscle strength was lower than the predicted values according to weight and age. MIP from group A and B were 58.6 and 62.5% lower, respectively. MEP from group A and B were 58.7 and 65.9% lower, respectively. In spite of these low values, it has already been shown that this is not predictive of failure in the recovery from post-operative liver transplants[26]. It is believed that patients with hepatic cirrosis and ascites have a mechanical disadvantage of the diaphragm muscles, which may interfere with the length-tension of the muscles and, consequently, on respiratory muscle strength, however, there are still very few articles in the literature.

It was shown that the variables, MIP and MEP demonstrated modifications during the period of ten days after surgery and only the MIP and the minute volume returned to their initial values[27]. In the comparative study between conventional cholecystectomy (CC) and cholecystectomy by laparoscopy (CL), the MIP was analyzed in both procedures, and there was observed a significant reduction in MIP over the first 24 hours in CC and a tendency of returning to the basal values after 72 hours. In CL, there was found a mean reduction of 30% in MIP, however, this returned to its basal values in the first 24 hours after surgery[28].

The classification of severity has been used to give priority to patients waiting for transplantations in some countries. In the present study, by analyzing the patients with hepatic cirrhosis, it was concluded that the MELD elevation was a significant predictor of mortality at six and 12 months and that the presence of complications had a similar profile as well[29]. This study confirmed the experience of many surgeons, that patients with more severe disease will develop more complications, both during the pre, during and post-operative surgery periods, with longer lengths of hospital stay, higher costs with antibiotics and other medicines, besides the high risks associated with the surgery. Considering the organ shortage, the number of patients on the list, what would be the best criterion to select the receivers and not ignore ethical principles?

For some authors, muscle mass consumption, associated with inactivity, generates a decrease in the muscle strength[30]. Cirrhotic patients in an advanced stage also show reductions in muscle strength and physical inactivity, both by ascites, that hamper their dynamism, and by their insertion into society, due to frequent infections and hospitalizations. All these factors, in association, produce a worse quality of life, which will improve only with liver transplantation.

Conclusions

It can be concluded that the maximal inspiratory pressure was significantly lower in patients who died while waiting for the transplantations. In the same group, it was observed that the maximal expiratory pressure and right hand strength were lower, although not statistically significant. The maximal inspiratory pressure can be considered to be a predictor of mortality.

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