

Evaluation of respiratory conditions in early phase of hematopoietic stem cell transplantation

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Objective: To investigate the effectiveness of respiratory physiotherapy based on clinical evidence and analyze the improvement in respiratory parameters.

Methods: A prospective study was carried out in the Bone Marrow Transplant Unit of the Universidade Estadual de Campinas (UNICAMP). Two different previously established respiratory physiotherapy protocols were applied from days D-1 to D+7 that aimed to improve airway clearance, pulmonary re-expansion and the strengthening of respiratory muscles. Group A were subjected to diaphragmatic proprioceptive stimulation, breathing exercises, incentive spirometry with Respirom[®], inspiratory muscle training with the Threshold[®] Inspiratory Muscle Training device, bronchial hygienization with Shaker[®] and cough stimulation. Group B performed a protocol that only used incentive spirometry. The parameters analyzed were: tidal volume, minute volume, maximal inspiratory pressure, maximal expiratory pressure, oxygen saturation, heart rate and respiratory frequency.

Results: Sixty-seven patients submitted to myeloablative hematopoietic stem cell transplantation were included in this study. Among these, thirty-nine were evaluated and randomized in the two groups. There were significant differences between the groups for tidal volume at D+2 (p -value = 0.007) and maximal inspiratory pressure (p -value = 0.03), maximal expiratory pressure (p -value = 0.03) and tidal volume (p -value = 0.004) at D+7.

Conclusion: On comparing Group A with Group B, the authors concluded that the protocol of respiratory physiotherapy applied in this study resulted in an improvement in ventilation and in respiratory muscle strength of patients submitted to hematopoietic stem cell transplantation.

Keywords: Breathing exercises; Hematopoietic stem cell transplantation; Physical therapy; Respiratory function tests

Introduction

Hematopoietic stem cell transplantation (HSCT) is a treatment with a high curative potential that may benefit a great number of patients with hematological, oncological, immunologic and hereditary diseases⁽¹⁾. In contrast, there are significant risks of chronic and acute complications due to conditioning regimens and immunosuppression, toxicity, infections, graft versus host disease (GVHD) and inactivity including being bedridden^(2,3).

Pulmonary complications may occur in 40-70% of patients submitted to HSCT and are associated to significant morbidity and mortality^(1,4). Wah et al.⁽⁴⁾ estimate that about 30% of affected patients die from this type of complication.

HSCT requires restrictions in activities and sometimes patients become bedridden, sedentary and/or prostrated. This state leads to loss of overall and respiratory muscular strength. In addition, reduction in ventilation results in pulmonary volume loss, reduction of diaphragmatic excursion and retention of secretion in the upper and lower airways⁽⁵⁾. Moreover, conditioning regimens may lead to lung and respiratory dysfunction due to toxicities^(6,7). Respiratory physiotherapy (RP), as prevention or treatment of respiratory complications, includes an arsenal of therapies for patients submitted to HSCT.

The benefits of physical exercise on the physical performance and muscular strength of patients submitted to HSCT are well documented^(3,8). However, as far as we know, there is no evidence of the efficacy of RP in this population.

The aim of the current study was to investigate the impact of RP performed in the immediate post-transplant period by analyzing the effect of this intervention on patients submitted to myeloablative HSCT.

Methods

This is a pilot, randomized prospective study carried out in the Bone Marrow Transplant Unit of the Universidade Estadual de Campinas (UNICAMP). The study was submitted and approved by the Ethics Committee of the Institution. All patients agreed to participate and signed informed consent forms.

Conflict-of-interest disclosure:
The authors declare no competing financial interest

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The inclusion criteria comprised patients submitted to myeloablative HSCT with ages ranging from 18 to 60 years and normal lung function according to spirometry. The exclusion criteria were non-myeloablative HSCT, refusal to participate, recent lung infection, fever at the time of evaluation, hemodynamic instability any time in the study, Glasgow coma scale under 13 and severe mucositis (grade IV or grade II-III associated to pain).

Sixty-seven patients were included in the study but only 39 (58%) participated in all of the trial. The reasons for exclusion for 28 (42%) patients were that 15 had mucositis grade 4 or grades 2-3 associated to pain, six had strong abdominal pain that did not allow the exercises, four had pulmonary complications, one patient suffered an early death and two patients withdrew informed consent.

The trial included three respiratory assessments at different times; the first on D-1 before any intervention (baseline evaluation), the second on D+2 and the last on D+7, both after respiratory exercises.

These evaluations included tidal volume (TV) measured using an Oxigel 953 ventilometer, minute volume (MV) calculated by TV multiplied by respiratory frequency in one minute ($MV = TV \times f$), oxygen saturation (SaO_2) and heart rate (HR) measured by a pulse oximeter (Onyx-Nonin 9500); muscular strength using the parameters of maximal inspiratory (MIP) and maximal expiratory pressures (MEP) in cmH_2O measured by a GERAR® manovacuometer. The MIP was measured from residual volume and MEP was measured from total pulmonary capacity. Measurements with a nose clip were performed in the seated position three times at one minute intervals; the highest value was considered for analysis.

After the first evaluation, patients were randomized in two groups (A and B) and respiratory exercises were initiated in the presence of a physical therapist. Group A (n = 20) performed the following protocol:

- *Diaphragmatic breathing*: patient was required to inhale deeply through the nose, directing the air flow toward the epigastric region and exhale calmly through the mouth. Three series of ten repetitions were performed once a day.
- *Fractional Inspiration*: patient was required to perform short and calm nasal inspirations combined with short periods of apnea, (three short breaths before reaching maximum inspiration). Three series of ten repetitions were performed once a day⁽⁹⁾.
- *Standard ventilation with short expirations*: consisting of intermittent cycles of inspiration with small expirations. The patient inhaled deeply and then exhaled a small quantity of air (phase 1), inhaled and exhaled again a small amount of air (phase 2), inhaled one last time and exhaled completely to a level of expiratory rest. Two series of five repetitions were performed in each session.
- *Exercises using incentive spirometry*: Three series of ten repetitions were performed with a Respirom® device. This device is an incentive inspiratory unit for pulmonary re-expansion using a load during the inspiratory phase of a patient's spontaneous breathing. The unit used in this study has three plastic chambers; inside each there is a

small, colored ball that is free to move up and down. As the patient inspires deeply, these balls rise successively due to the negative pressure at the upper end of the chambers, thus visually encouraging the patient to breath deeply^(10,11).

- *Muscle strengthening with a Threshold® Inspiratory Muscle Training device*: the load for each patient was established at 40% of the MIP. Three series of 15 repetitions were performed per day (mornings, evenings and night sessions). The inspiration pressure performed by patients is independent of air flow and respiratory frequency with these exercises strengthening and improving the muscles^(12,13).
- *Shaker® exercises*: the patient was required to inhale normally through the nose and exhale through a Shaker® device. Three series of fifteen repetitions was performed with one minute rests between series.
- *Spontaneous cough*: patients were required to cough after the Shaker® exercises to improve the removal of bronchial secretions.

Group B performed standard exercises of three series with ten repetitions using the Respirom® incentive spirometry device.

Both groups performed all exercises in the seated position from D-1 to D+7 with data being compared between groups at days D-1, D+2 and D+7.

Statistical analysis

Statistical analysis was conducted using SPSS 15.0. Descriptive statistics were made through univariate summaries. All comparisons were based on the intention-to-treat principle. Randomization was by the simplest manner by a manual draw before beginning the exercises. The Mann-Whitney test was used to compare groups. A p-value < 0.05 was considered significant.

Results

Patients' characteristics are presented in Table 1. The groups were well balanced and statistically comparable. Group A had ten male (50%) and ten female (50%) patients whereas Group B had ten male (53%) and nine female (47%) patients. The median ages were 36 (20-56) and 42 (23-54) years old for Groups A and B, respectively. Patients in Group A were submitted to 11 (55%) allogeneic and nine (45%) autologous HSCT whereas those in Group B underwent ten (53%) allogeneic and nine (47%) autologous HSCT.

At the time of HSCT seven patients in Group A had acute myeloid leukemia (35%), six had non-Hodgkin lymphoma (30%), three had chronic myeloid leukemia (15%), two had severe aplastic anemia (10%), one had multiple myeloma (5%) and one had myelodysplasia (5%). Six patients in Group B had acute myeloid leukemia (31%), one had non-Hodgkin lymphoma (6%), two had chronic myeloid leukemia (10%), six had multiple myeloma (31%), one had myelodysplasia (6%), two had Hodgkin's lymphoma (10%) and one had paroxysmal nocturnal hemoglobinuria (6%). On D+2, 95% of patients in both groups presented grade 0 mucositis. On D+7, 45% of patients presented grade 1 mucositis in Group A and 47% patients of Group B did not present any mucositis.

Table 1 - Characteristics of the patients

Variable	Group A Study (n = 20)	Group B Control (n = 19)
Gender: male - n (%)	10 (50)	10 (53)
Median age (range) years	36 (20-56)	42 (23-54)
Type of transplant - n (%)		
Allogeneic	11 (55)	10 (53)
Autologous	9 (45)	9 (47)
Disease at HSCT - n (%)		
acute myeloid leukemia	7 (35)	6 (31)
Non-Hodgkin Lymphoma	6 (30)	1 (6)
chronic myeloid leukemia	3 (15)	2 (10)
severe aplastic anemia	2 (10)	-
multiple myeloma	1 (5)	6 (31)
myelodysplastic syndrome	1 (5)	1 (6)
Hodgkin's lymphoma	-	2 (10)
Paroxysmal nocturnal hemoglobinuria	-	1 (6)
Mucositis D+2 - n (%)		
Grade 0	19 (95)	18 (95)
Grade 1	1 (5)	1 (5)
Mucositis D+7 - n (%)		
Grade 0	5 (25)	9 (47)
Grade 1	9 (45)	4 (21)
Grade 2	4 (20)	4 (21)
Grade 3	2 (10)	2 (11)

Results of variables for both groups at D-1 are presented in Table 2. Table 3 shows results at D+2; there was a significant difference only for TV (p-value = 0.007). Results at D+7 are presented in Table 4. TV (p-value = 0.004), MIP (p-value = 0.03) and MEP (p-value = 0.03) were statistically significant between groups. All results were favorable to Group A.

Discussion

Conditioning regimens and resulting adverse events induce patients to stay in their rooms and sometimes even to become bedridden. Among the many possible consequences of this are losses of muscle mass, muscle strength and decreases in the range of movements that will impair the skeletal muscle system. Moreover, decreasing in TV, MV, loss of respiratory muscle strength contribute to impaired physical performance^(3,5,14,15).

Physical therapy aims to prevent and treat complications after HSCT by specific exercises and may contribute to the success of this procedure and to the patients' full recovery, their reintegration in society and return to daily life and occupational activities.

There are many studies that show the benefits of physical exercise in patients submitted to HSCT, demonstrating the increase in muscle strength⁽⁸⁾, physical performance^(3,16) and improvement of symptoms such as fatigue⁽¹⁷⁾, but the influence of respiratory exercises on respiratory function and ventilation is still unknown.

Table 2 - Analysis of measurements of study and control groups on day D-1

	TV Mean (range) mL	MV Mean (range) mL	MIP Mean (range) cmH ₂ O	MEP Mean (range) cmH ₂ O	HR Mean (range) bpm	f Mean (range) breaths per minute	SpO₂ Mean (range) (%)
Study (Group A)	700 (408-1161)	14.5 (8.17-27.84)	-95 (-120 to -40)	97 (24-120)	90 (75-108)	21 (15-24)*	98 (96-99)
Control (Group B)	666 (396-852)	15.06 (7.92-20.23)	-90 (-120 to -46)	88 (36-120)	90 (64-120)	23 (20-26)*	97 (96-99)
p-value	0.88	0.38	0.44	0.51	0.96	0.02*	0.35

TV = Tidal Volume; MV = Minute Volume; MIP = Maximal Inspiratory Pressure; MEP = Maximal Expiratory Pressure; HR = Heart Rate; f = Respiratory Frequency; bpm = Beats per minute; SpO₂ = Oxygen Saturation *Although statistically significant, the range is normal for both groups

Table 3 - Analysis of measures of the study and control groups on day D+2

	TV Mean (range) mL	MV Mean (range) mL	MIP Mean (range) cmH ₂ O	MEP Mean (range) cmH ₂ O	HR Mean (range) bpm	f Mean (range) breaths per minute	SpO₂ Mean (range) (%)
Study (Group A)	806 (553-1140)	16.5 (11.64-23.59)	-95 (-120 to -48)	99 (20-120)	92 (65-109)	21 (16-24)	98 (96-100)
Control (Group B)	648 (331-829)	13.98 (6.60-19.82)	-89 (-120 to -50)	90 (28-120)	90 (63-120)	21 (16-28)	97 (95-99)
p-value	0.007	0.11	0.47	0.44	0.53	0.55	0.79

TV = Tidal Volume; MV = Minute Volume; MIP = Maximal Inspiratory Pressure; MEP = Maximal Expiratory Pressure; HR = Heart Rate; f = Respiratory Frequency; bpm = Beats per minute; SpO₂ = Oxygen Saturation

Table 4 - Analysis of measures of study and control groups on day D+7

	TV Mean (range) mL	MV Mean (range) mL	MIP Mean (range) cmH ₂ O	MEP Mean (range) cmH ₂ O	HR Mean (range) bpm	f Mean (range) breaths per minute	SpO₂ Mean (range) (%)
Study (Group A)	740 (592-981)	16.3 (11.3-23.6)	-98 (-120 to -48)	99 (32-120)	93 (72-120)	22 (18-28)	97 (95-100)
Control (Group B)	633 (440-809)	14.3 (8.8-19.4)	-82 (-120 to -48)	79 (26-120)	96 (76-115)	22 (18-26)	97 (95-98)
p-value	0.004	0.11	0.035	0.033	0.38	0.46	0.9

TV = Tidal Volume; MV = Minute Volume; MIP = Maximal Inspiratory Pressure; MEP = Maximal Expiratory Pressure; HR = Heart Rate; f = Respiratory Frequency; bpm = Beats per minute; SpO₂ = Oxygen Saturation

Baseline parameters were statistically similar for all variables of both groups, as was expected. On D+2, TV increased significantly in Group A and remained high until the last evaluation (D+7). Exercises were effective not only by preventing loss of pulmonary ventilation capacity but also increasing values with significant gains being recorded for specific parameters.

All exercises for pulmonary re-expansion such as diaphragmatic breathing, fractional inspiration, standard ventilation with short expirations and exercises using incentive spirometry aim to increase ventilation and may be responsible for these results.

The MIP had increased by D+7 for Group A while for the control group it had decreased. Suesada et al.⁽¹⁸⁾ observed that the MIP decreases significantly within only five days of hospitalization in short-term inpatients who are not submitted to respiratory exercises. Other studies report that after only 12 hours of mechanical ventilation, patients present ventilation-related diaphragm dysfunction associated to a decrease in contractile fiber units due to disuse⁽¹⁹⁻²¹⁾.

Nevertheless Sprague et al.⁽²²⁾ observed that for patients on mechanical ventilation, there were increases in MIP in patients on inspiratory training with a 50% MIP load that assisted weaning from ventilation (median time of 17 days). These findings support our results and reiterate the benefits of this intervention. Downey et al.⁽²³⁾ applied the same exercises with a similar methodology to seven healthy subjects, but the results were only favorable after two weeks of regular training; this suggests that muscle training is more beneficial in the short term in non-conditioned or non-healthy subjects.

MEP was also statistically higher at D+7 for Group A. Once again the protocol was not only effective in obtaining gain, but also in avoiding reductions in the conditions of expiratory muscles. The composition of MIP and MEP characterize the movement capacity of air beyond the subject's limits of deep breathing. The improvement of inspiratory and expiratory muscles also mediated the increase of TV. Although no specific training of expiratory muscles was included in this protocol, improvements were achieved by improved chest mechanics.

Weakness of expiratory muscles may cause powerless coughing, inefficiency in gas exchanges and the accumulation of secretions⁽²⁴⁾; this contributes to complications such as atelectasis and pneumonia. This concept reinforces the idea that this function is relevant in pulmonary rehabilitation.

The etiology of this clinical condition comprises many aspects of treatment and disease. Studies performed by Link et al.⁽²⁵⁾, Prince et al.⁽²⁶⁾, Ghalie et al.⁽²⁷⁾ and Crawford et al.⁽²⁸⁾ demonstrated that impairment in respiratory function depend on the type and intensity of the conditioning regimen. According to White et al.⁽²⁹⁾ and Kovalski et al.⁽³⁰⁾ many patients submitted to HSCT present overall muscle weakness including the respiratory muscles, so pulmonary rehabilitation could be helpful not only in prevention but also in treating dysfunction and other complications in this population.

Comparing the groups, our results suggest that a training program using a respiratory physiotherapy protocol applied regularly may help to improve respiratory muscle force and increase TV.

Despite the good results, further studies should be performed to confirm these findings with a larger sample to identify the real indication of this conduct and to show the benefits of applying this type of intervention as a regular program for HSCT patients.

We suggest the usefulness of this experimental strategy; this procedure proved to be feasible and cheap and may be applicable in most HSCT units.

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