A RANDOMIZED CONTROL TRIAL OF BENEFITS OF INTRAHOPSITAL EXERCISE ON POST-TRANSPLANTATION DECONDITIONING IN THE PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANT POPULATION

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Abstract

Deconditioning is a common adverse effect of short and long-term immobilization. For months pediatric hematopoietic stem cell transplant patients can be quarantined while hospitalized, much of which time is spent immobilized putting these patients at a higher risk for loss of muscle strength, functionality, endurance, and quality of life. Studies have shown that exercise as an effective countermeasure to deconditioning in stem cell transplant patients. However, research is lacking in pediatric HSCT due to the complications associated with treatment. This study was conducted to determine if there is a correlation between intrahopsital exercise and improved functionality, endurance, strength, and quality of life. In addition, this randomized control study looked at the merit and feasibility of adding an exercise routine into treatment plans. We have currently recruited 23 of our target 40 patients, 12 in the control arm and 11 in the intervention arm, ages 8-17 at Phoenix Children's Hospital. Each participant received baseline measured by an OT or a PT for functionality using (WeeFIM), muscle strength using manual muscle testing (MMT), endurance using the 6-minute walk test, and quality of life using the NIH PROMIS measures. Measurements were taken again at discharge and 6-weeks post-discharge. During hospital admittance the intervention group performed exercise routines 3-times weekly while the control group were encouraged to spend time out of bed. Patients recruited were receiving their first HSCT and did not have any post-HSCT complications such as severe infection or GVHD. Data and results are limited due to the timepoint of the study and the limited number of recruited patients affecting the power of the study. No statistically significant difference is noted between the two arms in functional status, muscle strength, or endurance. There appears to be an increase in quality of life patients in the interventional arm compared to the control arm. Simple analysis has shown that compliance with time out of bed decreases across both groups the further away from transplant. Currently the study is midway, and data is limited to make any conclusions but shows promise.

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Introduction/Significance

Pediatric stem cell transplant patients can be hospitalized for months, quarantined in a clean room. Much of this time is spent immobilized in bed. It's stated that 83% of time is spent in bed during a hospital stay [1]. Transplant involves administration of chemotherapy or irradiation based conditioning regimen, followed by infusion of hematopoietic stem cells. In addition to drug induced toxicities, infections and acute graft versus host disease, reduced physical performance and functioning contributes to the early morbidity and mortality (2-4] Multiple studies have shown that muscles, tendons, ligaments, and joints begin to contract and limit mobility after only 2-3 weeks of immobilization [5]. During treatment pediatric patients can develop dependency for ambulation and transferring due to these effects [6]. Difficulty with ambulation due to persistent muscle weakness and fatigue is one of the most common complaints of bed rested patients [7]. There is significant reduction in physical activity leading to loss of strength and performance and this can be severely debilitating.

Mobilization and exercise have been studied as a counter measure to these issues. Studies show that functional mobility (walking, standing or sitting up with or without assistance) improves fatigue, pain, delirium, DVT, depression, anxiety, and decreased hospital stay duration [1]. During the acute phase of a bone marrow transplant rehabilitation exercise was shown in one study to help improve outcomes associated with BMT. Rehabilitation correlated with improved quality of life (Qol) measures, decreased fatigue, and an increased resolution of pancytopenia [6]. Studies conducted by San Juan et al. showed that intra-hospital exercise training could improve outcomes as well. However, the exercise program was for survivors after treatment [8-9]. There is clear evidence on the benefit of exercise and mobilization for patients at risk for deconditioning due to bed rest [10-17].

Despite growing numbers of publications describing the effects of these exercise modalities in adult HSCT patients, only limited attention has been paid to this effective supportive therapy in children. Only four publications describe the effectiveness of exercise training in pediatric HSCT[18-20]. San Juan et al. showed beneficial effects on functional performance, muscle strength, and Qol scores in a study of children (aged 8–16) undergoing a supervised exercise

program that included resistance and aerobic exercises for 3 weeks after HSCT [19]. In another study, the moderate intensity exercise program implemented to children undergoing allogeneic HSCT for 3 weeks during hospitalization showed positive effects on body mass and body mass index (BMI), and no negative effect on immune cell recovery [20]. It was found that a structured physical activity program has positive effects on Qol and fatigue scores in children undergoing peripheral blood stem cell transplantation. The need for general acceptance of physical activity during hospitalization has been shown in this study. [20]

This study will implement an exercise program that is personalized to hematopoietic stem cell transplant recipients designed to prevent a decline in function/independence. We will accomplish this by conducting a randomized controlled trial (RCT) that will examine the effect of an 8-12 week personalized exercise program compared to standard care following hematopoietic stem cell transplantation. Data from this study should increase our understanding of the effect of exercise in this population on QoL, functional ability, endurance, muscle strength, and fatigue.

Research Methods and Materials

Methods: Patient Selection- Potential patients will be screened for inclusion and exclusion criteria as they present to the Phoenix Children's Hospital Center for Cancer and Blood Disorders clinic. Parental or guardian informed consent and child assent, if applicable, will be obtained upon admittance and previous to any study related procedures or measurements being performed.

Study Design:

Forty total patients, ages 5-18, will be recruited and divided randomly into two separate arms over an expectant two-year period using block randomization. Their demographic data, BMI, Lansky performance, medical and transplant variables will be collected at baseline. Outcome variables will be assessed at three stages by the same physiotherapist: at baseline (before HSCT procedure), at discharge and 6 weeks after discharge. There is no formal rehabilitation program for our pediatric patients during transplant. Both arms will be educated and encouraged to be out bed for about four hours daily. In addition, the treatment arm will receive a supervised exercise regimen administered by a Physical Therapist. All patients in the study will receive a Fitbit upon hospital admittance to track measured steps, continuous HR, active minutes, and monitor exercise. Variables in each arm will be measured using the 6-minute walk test, WeeFIM, Manual muscle testing, and the NIH PROMIS measures.

Table 1. Study Criteria for Recruitment	
Inclusion Criteria 1) All auto and allogenic transplants 2) Males or females age 4 to 18 years 3) Girls ≥ 11 years of age must have a negative urine/serum pregnancy test 4) Parental/guardian permission (informed consent) and child assent	Exclusion Criteria 1) Previous Stem Cell Transplant in the last 6 months 2) Subjects with any preexisting need for gait assistance such as crutches, wheelchair, braces, or walker

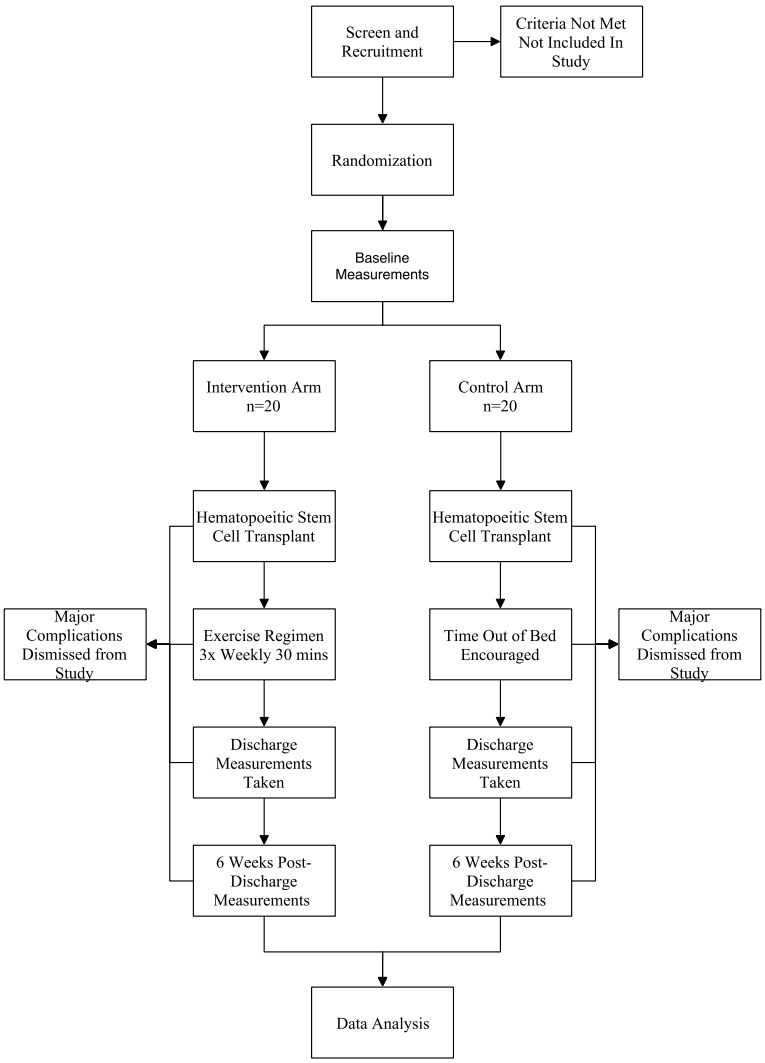

Figure 1. Study Timeline Flowchart

PROMIS Measures: Patient Reported Outcomes Measurement Information System (PROMIS®) is a tool funded in 2007 by the National Institute of Health (NIH) to evaluate the health of adults or children in physical, mental, and social categories [21]. Each category is further divided into domains. The testing can be administered via short forms or Computer Adaptive Tests (CATs). The pediatric assessments can be either self-reported (ages 8-17) or parent proxy-reported (ages 5-17 or according to need) [22]. This allows for measurement of health related quality of life. Scoring is done using T-scores with 50 as the mean and a standard deviation of 10. These PROMIS measures have been shown to be reliable and precise. [23] Specifically, in pediatric cancer patients, it has been shown that not only is it feasible to administer and complete, but it is valid. The short forms have also been shown previously to have a reliability of 0.85 or greater over 2-4 standard deviations. [24]. We will use the already composed collection of short forms from multiple domains called Profile 49 v2.0. This contains short forms from 8 domains: anxiety, depressive symptoms, pain interference, fatigue, physical function-mobility, peer relationships, and pain intensity. [25-30]

6MWT: The 6MWT is commonly used in measuring exercise capacity and endurance. It has been proven validated, safe and reliable. It has also been shown to be useful in cancer patients [31-33]. Normative distance values have also been produced for pediatrics in multiple studies [32, 34). According to the American Thoracic Society (ATS) they recommend performing the test in a straight, 30 m (100-ft) hallway. However, lengths as short as 15 m and as long as 50 m were shown to have no significant effect on the results [35-36]. The patient is to sit still for 10 minutes in a chair before starting the 6MWT. Their vitals and the Borg scale ratings for fatigue and dyspnea should be observed. Cones or markers are place every 3m and at the turnaround points. These are used for measuring the distance when the patient stops at the end of 6 minutes. When the patient reaches the starting line and turns to continue the administrator makes a clear check mark to keep track and encourage the participant. However, during the test the administrator is not allowed to vocally motivate the patient. They are allowed, however, to speak in an even tone when sharing the time combined with standard phrases of encouragement. The total distance walked is called the 6 Minute Walking Distance (6MWD) and

is rounded to the nearest meter. ATS provides a standard form for sue during the 6MWT [31, 35-36].

WeeFIM: The WeeFIM is a widely used and reliable tool used in pediatric studies to measure functionality. It consists of normative value sets. It contains 18 different functional items divided across three domains: self-care, mobility, and cognition. Each area is rated from 1-7 using observation or interview with 7 being the highest functional level. It is recommended for patients between 6 months and 7 years and between age 6 and 21 who have functional limitations expected of a 7-year-old. [37-39]

MMT: MMT has widely been known to be useful, valid, and reliable in measuring muscle strength [40]. Muscle strength is measured against gravity and also against manual resistance. Each muscle group is tested and rated from 0 with no palpable muscle contraction to 5 or holding position against maximal resistance [40].

Table 2. MMT Grading

Manual Muscle Test Score	Title	Percentile Value	Descriptive Explanation
5	Normal(N)	100%	Holds test position against maximal resistance
4	Good(G)	80%	Holds test position against moderate resistance
3	Fair (F)	50%	Holds test position against gravity
2	Poor(P)	20%	Able to move through full ROM gravity eliminated
1	Trace(T)	5%	No visible movement; palpable or observable tendon prominence/flicker contraction
0	0	0%	No palpable or observable muscle contraction

Exercise Intervention

This structured exercise program consists of strengthening, endurance, stretching and relaxation exercises tailored according to age and their ability to perform activities throughout their hospitalization. This exercise program will be done three times a week for 30-45mins supervised by the same physiotherapist throughout hospitalization and will be self-administered every weekend. A printed-out home exercise program with the appropriate resistance will be provided to family upon discharge, with instructions on how often to complete throughout the week. The family and patient will also be provided a weekly sheet to check off the days they completed strengthening and endurance exercises.

Age 4-6 years

The goal of the exercise regimen is to target lower extremity, core and upper extremity strengthening as well as activity tolerance. With supervision by the PT, the patient will ambulate throughout their room, and complete the following throughout play: squat, single leg stance, climb onto couch, half kneel to stand, quadruped and tall kneeling.

Age 7-21 years

There will be two components of the exercise program completed by the patients in this age group. The first component will be strengthening exercises that will be completed in bed or on a mat while sitting or standing. Multiple levels of strengthening exercises will be available, so that the exercise program can be tailored to each patient and to their ability to perform activities throughout their hospitalization. The strengthening exercises included will focus on core, hip musculature, and upper extremity strengthening; including exercises in quadruped and prone positioning, as well as supine, sitting and standing. Thera-Band will be used to increase resistance as needed for any exercise. The second component will be endurance activities. Since the patients will be confined to their room for most of their hospitalization this will include ambulation within the room, recumbent or pedal exerciser and step ups.

Results

Demographics

Current recruitment for our study shows a fairly even demographic split for ages and sex between the two groups. Of our current 23 patients recruited, the average age is 12 for the control group and 15 for the intervention group. The Interquartile range is listed for each group is listed in table 1 below. The sex and their ratio are also listed in table 3. There is also an appropriate spit between non-malignant and malignant diagnosis for each arm; there is a 50% split in each diagnosis among the control arm while the intervention arm had 36.4% non-malignant diagnosis and 63.6% malignant diagnosis in the intervention arm. The majority of transplants in each group were allogeneic.

Table 3. Demographics of recruited patients.

Variables	Overall N=23	Control N=12	Intervention N=11
Age, Years (median, IQR)	14 (7, 16)	12 (7, 15.5)	15 (10, 17)
Sex (male, %)	10 (43.5)	6 (50.0)	4 (36.4)
(Female, %)	13 (56.5)	6(50.0)	7 (63.6)
Diagnosis (%)			
Non-Malignant	10 (43.5)	6 (50.0)	4 (36.4)
Malignant	13 (56.5)	6 (50.0)	7 (63.6)
Type of Transplant			
Autologous	3	1	2
Allogeneic	20	11	9

Functionality

Functionality was measured using the standardized WeeFIM measurements. The results from these measurements are limited at the study midpoint and any statistically significant difference is challenging to measure at this point of the study. Graph 1 shows the difference between the two group's means and their changes over the three time points. The intervention arm shows a decrease at discharge but an increase back to slightly above the starting mean at post-6 week discharge. The control group shows a gradual increase over the entire study with the greatest increase coming between discharge and post-6 weeks discharge.

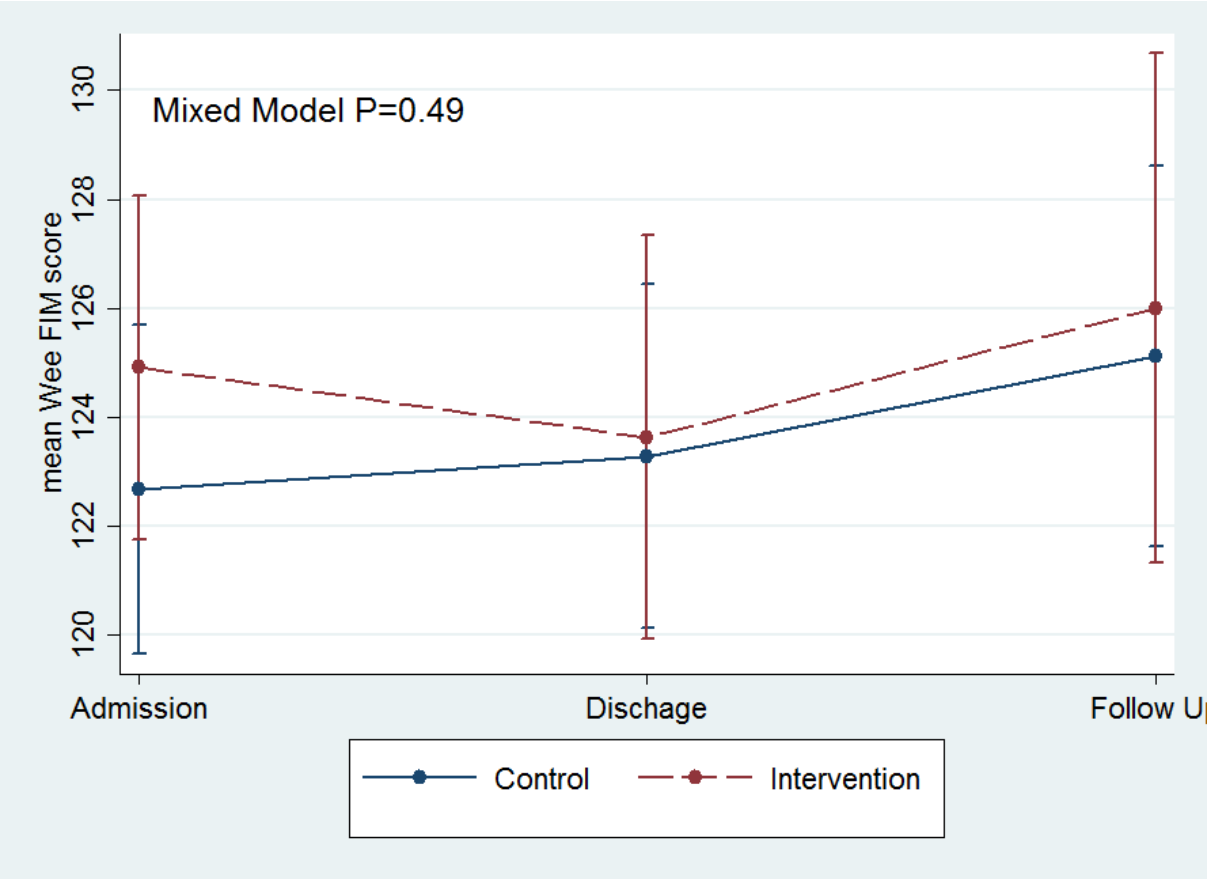

Figure 2. WeeFIM Mean (95% CI) stratified by Intervention vs Control, ascertained by the Linear Mixed Effects Model controlling for time, age and gender.

Endurance

Graph 2 illustrates the change in the 6-min walk test means over the study time period for both groups. The control group started with a better baseline than the intervention arm and showed an increase between admit and discharge. It then leveled off between discharge and post-6 week discharge follow-up. The intervention showed only a minimal, yet gradual, increase in 6MWT means over the study period.

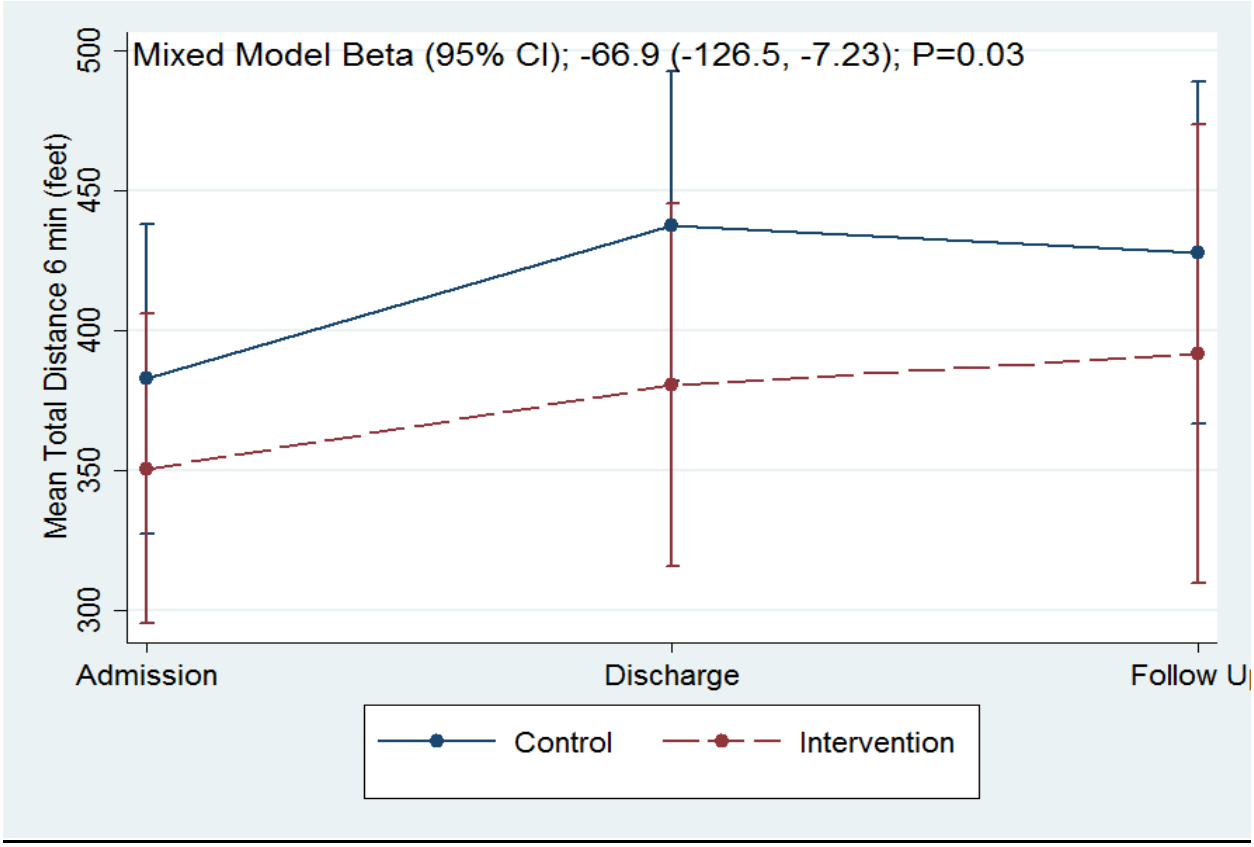

Figure 3. 6MWT distance Mean (95% CI) stratified by Intervention vs Control, ascertained by the Linear Mixed Effects Model controlling for time, age and gender.

Muscle Strength

Manual Muscle Testing did not show any major statistically significant differences between the two arms. Only two muscle groups tested approach a statistically significant difference: left knee extension had a p-value of 0.08 while right ankle plantarflexion had a p-value of 0.09. Table 4 below illustrates the change in aggregate means between the groups. Both research arms illustrated a change over the study period.

Table 4. Change in aggregate MMT means in both groups				
Questions	Baseline N=23	Discharge N=19	6 Week Follow-up N=14	P-value
	Mean (SD)	Mean (SD)	Mean (SD)	
L Knee Extension	4.72 (0.55)	4.84 (0.37)	4.92 (0.27)	0.08
R Ankle plantarflexion	4.66 (0.73)	4.31 (1.06)	4.57 (0.85)	0.09

A Mixed linear model comparing the intervention arm to the control arm showed deceased strength for the intervention arm. Statistically significant values were seen in the right hip flexion, left hip abduction, left knee flexion, right knee extension, and left knee extension. Left elbow flexion, left hip extension, and right knee flexion each approached a statistically significant decrease.

Table 5. Mixed Linear Model of MMT between intervention arm to control		
Muscle Group	Beta (95% CI)	P-value
L Elbow Flexion	-0.24 (-0.53, 0.04)	0.09
R Hip flexion	-0.37 (-0.69, -0.05)	0.02
L Hip abduction	-0.44 (-0.86, -0.03)	0.04
L Hip Extension	-0.52 (-1.12, 0.09)	0.09
R Knee Flexion	-0.26 (-0.55, 0.03)	0.08
L Knee Flexion	-0.43 (-0.85, -0.02)	0.04
R Knee Extension	-0.47 (-0.82, -0.12)	0.009
L Knee Extension	-0.45 (-0.76, -0.13)	0.005

Quality of Life

Table 6 above illustrates the aggregate means of both means for the PROMIS measure decreased over the study timeline. The categories *I felt nervous, I felt worried, I got scared really easy, and I felt weak* each showed a statistically significant decrease over the time period. The other above listed categories approached statistical significance.

Table 6. Change in Aggregate PROMIS Measure Means in Both Groups				
Questions	Baseline N=23	Discharge N=19	6 Week Follow-up N=14	P-value
	Mean (SD)	Mean (SD)	Mean (SD)	
I felt nervous	2.58 (0.79)	2.00 (1.15)	1.20 (0.45)	0.001
I felt worried	2.33 (1.07)	2.25 (1.50)	1.20 (0.45)	0.007
I got scared really easy	1.67 (0.78)	1.25 (0.50)	1.0 (0.0)	0.04
I was too tired to do sports or exercise	2.00 (0.95)	1.33 (0.58)	1.75 (0.96)	0.08
I felt weak	2.17 (1.03)	2.00 (1.15)	1.20 (0.45)	0.01
I had trouble finishing things because I was too tired	2.08 (0.79)	2.75 (0.50)	1.40 (0.55)	0.05
I had trouble starting things because I was too tired	1.75 (0.87)	2.00 (1.15)	1.40 (0.55)	0.07

Compliance

Compliance was also studied and showed a decrease in compliance with recording and spending time out of bed. The further out from transplant the less likely patients were likely to maintain their compliance with recording time out of bed, which is illustrated by Graph 3 below. There was a 50% decrease in compliance from week 1 to week 6 of hospitalization.

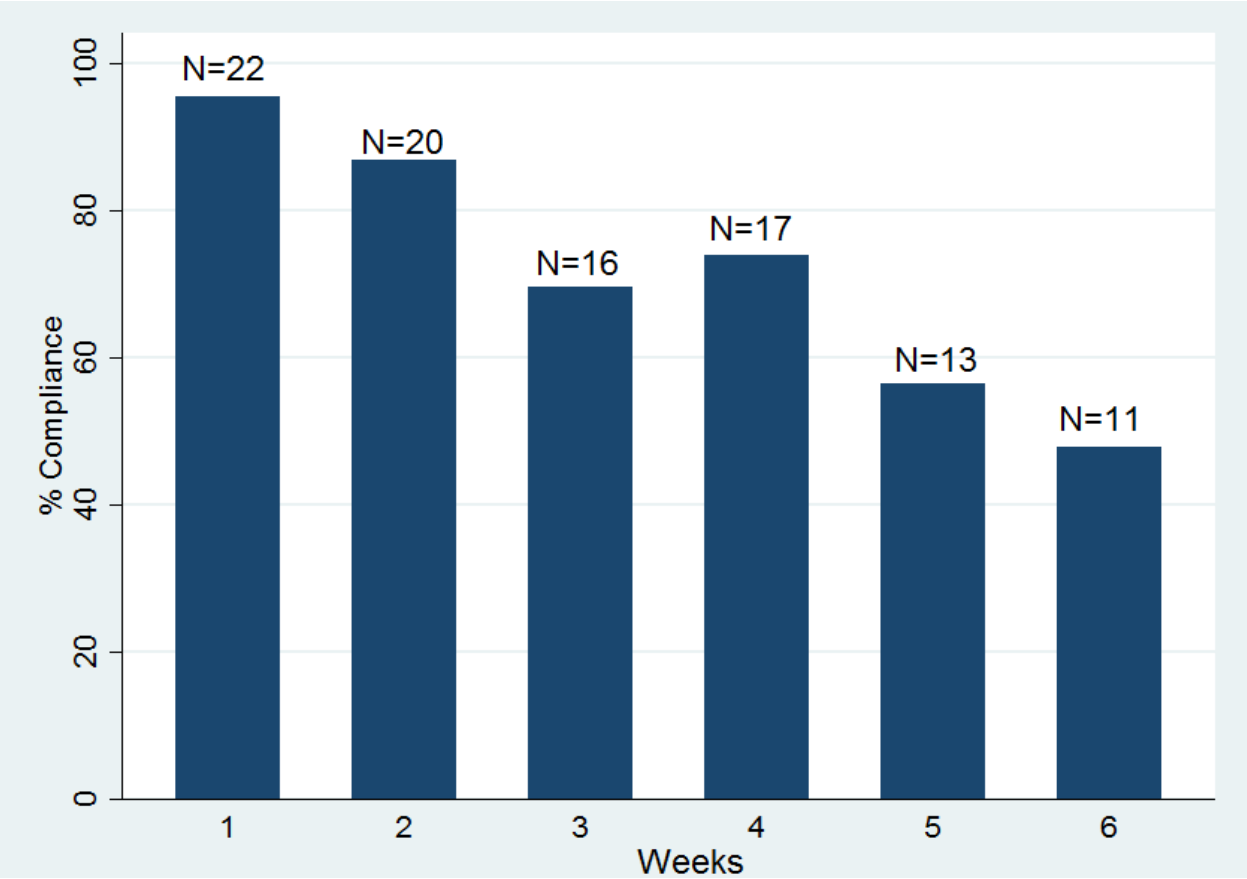

Figure 4. Compliance Percent Overall Compliance of Time Out of Bed**.**

Discussion

The current pilot study is only half way through its projected trajectory of 40 patients. Having only recruited 23 patients makes it challenging to draw conclusions based on the small number recruited and small sample size. However, even though changes are noted between the two arms, no real statistically significant difference has been seen between the intervention and control arms in functionality, endurance, and strength at this stage of the study. There is an increase in both function and endurance in both arms while there seems to be a decrease in strength in both groups. There appears to be better quality of life in patients in the interventional arm compared to the control arm. Compliance with getting out of bed gradually decreases the longer they stay in the hospital which makes is not surprising.

The data is slowly taking shape and appears promising once more subjects are recruited. With a larger sample size, a better comparison between the two groups will be possible; it will be possible to directly compare both groups rather then look at their aggregate means. The study is still ongoing and will estimated to be complete by September of 2019.

Future Directions

This study has proven as a good first step in the direction of decreasing deconditioning in pediatric stem cell transplant patients. However, this study was limited by time and by the number of patients recruited. At this point the project is only half-way completed and will end with a total of 40 patients. It serves as a pilot study which will need further exploration to fully determine exercise's role the transplant process. A large-scale, multi-facility study would be ideal to better distinguish the promising effects this study touches on.

Conclusions

Due to the expected mid-study limited sample size it unlikely that any conclusions can be drawn. However, it can be concluded that the data being collected is promising and that the pilot study holds promise. It can also be concluded that the methodology of the study appears to be effective and no adjustments to the study need to be made at this point. It could be assumed from the data that compliance decreases with time but still data is limited making a conclusion about compliance not possible. The study needs to be continued and finished to show any true conclusions. Even then a larger study might need to be conducted to truly get a better understanding of the possible benefits and treatment altering effects that exercise can have on pediatric stem cell transplant patients.

References

1. Kalisch, B.J., Lee, S., & Dabney, B.W. (2013). Outcomes of inpatient mobilization: a literature review. Journal of Clinical Nursing, 13, 1-16. doi: 10.1111/jocn.12315

2. de Souza CV, Miranda ECM, Garcia C, Aranha FJP, de Souza CA, Vigorito AC. Functional evaluation indicates physical losses after hematopoietic stem cell transplantation. *Rev Bras Hematol Hemoter*. 2012;34(5):345-351. doi:10.5581/1516-8484.20120090.

3. Kovalszki A, Schumaker GL, Klein A, Terrin N, White AC. Reduced respiratory and skeletal muscle strength in survivors of sibling or unrelated donor hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2008;41(11):965-969. doi:10.1038/bmt.2008.15.

4. Hacker ED, Ferrans C, Verlen E, et al. Fatigue and Physical Activity in Patients Undergoing Hematopoietic Stem Cell Transplant. *Oncol Nurs Forum*. 2006;33(3):614-624. doi:10.1188/06.ONF.614-624.

5. Dammeyer, J., Dickinson, S., Packard, D., & Rickleman, C. Building a protocol guide to mobility in the ICU. Critical Care Nursing Quarterly. 36(1), 37-49. doi: 10.1097/CNQ.0b013e3182750acd

6. Gillis, T. A., Donovan, E. S. (2001). Rehabilitation following bone marrow transplantation. Cancer, 92(4), 998-1007.

7. Brower, Roy G. (2009). Consequences of bed rest. Critical Care Medicine, 37(10), S422-S428. doi: 10.1097/CCM.obo13e3181b6e30a

8. San Juan AF, Fleck SJ, Chamorro-Viña C, et al. Early-phase adaptations to intrahospital training in strength and functional mobility of children with leukemia. *J strength Cond Res*. 2007;21(1):173-177. doi:10.1519/R-19175.1.

9. San Juan A, Chamorro-Viña C, Moral S, et al. Benefits of Intrahospital Exercise Training after Pediatric Bone Marrow Transplantation. *Int J Sports Med*. 2008;29(5):439-446. doi:10.1055/s-2007-965571.

10. Baumann FT, Zopf EM, Nykamp E, et al. Physical activity for patients undergoing an allogeneic hematopoietic stem cell transplantation: benefits of a moderate exercise intervention. *Eur J Haematol*. 2011;87(2):148-156. doi:10.1111/j.1600-0609.2011.01640.x.

11. Furzer BJ, Ackland TR, Wallman KE, et al. A randomised controlled trial comparing the effects of a 12-week supervised exercise versus usual care on outcomes in haematological cancer patients. *Support Care Cancer*. 2016;24(4):1697-1707. doi:10.1007/s00520-015-2955-7.

12. Jarden M, Hovgaard D, Boesen E, Quist M, Adamsen L. Pilot study of a multimodal intervention: mixed-type exercise and psychoeducation in patients undergoing allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2007;40(8):793-800. doi:10.1038/sj.bmt.1705807.

13. Knols RH, de Bruin ED, Uebelhart D, et al. Effects of an outpatient physical exercise program on hematopoietic stem-cell transplantation recipients: a randomized clinical trial. *Bone Marrow Transplant*. 2011;46(9):1245-1255. doi:10.1038/bmt.2010.288.

14. Wiskemann J, Dreger P, Schwerdtfeger R, et al. Effects of a partly self-administered exercise program before, during, and after allogeneic stem cell transplantation. *Blood*. 2011;117(9):2604-2613. doi:10.1182/blood-2010-09-306308.

15. Wiskemann J, Kuehl R, Dreger P, et al. Efficacy of exercise training in SCT patients-who benefits most? *Bone Marrow Transplant*. 2014;49(3):443-448. doi:10.1038/bmt.2013.194.

16. Wiskemann J, Huber G. Physical exercise as adjuvant therapy for patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2008;41(4):321-329. doi:10.1038/sj.bmt.1705917.

17. Wolin KY, Ruiz JR, Tuchman H, Lucia A. Exercise in adult and pediatric hematological cancer survivors: an intervention review. *Leukemia*. 2010;24(6):1113-1120. doi:10.1038/leu.2010.54.

18. Chamorro-Viña C, Guilcher GMT, Khan FM, et al. EXERCISE in pediatric autologous stem cell transplant patients: a randomized controlled trial protocol. BMC Cancer. 2012; 12:401. doi:10.1186/1471-2407-12-401.

19. Yildiz Kabak V, Duger T, Uckan Cetinkaya D. Investigation of the Effects of an Exercise Program on Physical Functions and Activities of Daily Life in Pediatric Hematopoietic Stem Cell Transplantation. *Pediatr Blood Cancer*. 2016;63(9):1643-1648. doi:10.1002/pbc.26038.

20. Marchese VG, Chiarello LA, Lange BJ. Effects of physical therapy intervention for children with acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2004;42(2):127-133. doi:10.1002/pbc.10481.

21. Ader, D. N. (2007). Developing the patient-reported outcomes measurement information system (PROMIS). *Medical Care, 45*(Suppl 1), S1–S2.

22. Irwin DE, Gross HE, Stucky BD, et al. Development of six PROMIS pediatrics proxy-report item banks. *Health Qual Life Outcomes*. 2012;10:22. doi:10.1186/1477-7525-10-22.

23. Cella D, Yount S, Rothrock N, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS). *Med Care*. 2007;45(Suppl 1):S3-S11. doi:10.1097/01.mlr.0000258615.42478.55.

24. Hinds PS, Nuss SL, Ruccione KS, et al. PROMIS pediatric measures in pediatric oncology: Valid and clinically feasible indicators of patient-reported outcomes. *Pediatr Blood Cancer*. 2013;60(3):402-408. doi:10.1002/pbc.24233.

25. Irwin DE, Stucky B, Langer MM, et al. An item response analysis of the pediatric PROMIS anxiety and depressive symptoms scales. *Qual Life Res*. 2010;19(4):595-607. doi:10.1007/s11136-010-9619-3.

26. Amtmann D, Cook KF, Jensen MP, et al. Development of a PROMIS item bank to measure pain interference. *Pain*. 2010;150(1):173-182. doi:10.1016/j.pain.2010.04.025.

27. Lai J-S, Stucky BD, Thissen D, et al. Development and psychometric properties of the PROMIS® pediatric fatigue item banks. *Qual Life Res*. 2013;22(9):2417-2427. doi:10.1007/s11136-013-0357-1.

28. Rose M, Bjorner JB, Gandek B, Bruce B, Fries JF, Ware JE. The PROMIS Physical Function item bank was calibrated to a standardized metric and shown to improve measurement efficiency. *J Clin Epidemiol*. 2014;67(5):516-526. doi:10.1016/j.jclinepi.2013.10.024.

29. Dewalt DA, Thissen D, Stucky BD, et al. PROMIS Pediatric Peer Relationships Scale: development of a peer relationships item bank as part of social health measurement. *Health Psychol*. 2013;32(10):1093-1103. doi:10.1037/a0032670.

30. Jacobson CJ, Kashikar-Zuck S, Farrell J, et al. Qualitative Evaluation of Pediatric Pain Behavior, Quality, and Intensity Item Candidates and the PROMIS Pain Domain Framework in Children With Chronic Pain. *J Pain*. 2015;16(12):1243-1255. doi:10.1016/j.jpain.2015.08.007.

31. Hooke MC, Garwick AW, Neglia JP. Assessment of Physical Performance Using the 6-Minute Walk Test in Children Receiving Treatment for Cancer. *Cancer Nurs*. 2013;36(5):E9-E16. doi:10.1097/NCC.0b013e31829f5510.

32. Li AM, Yin J, Yu CCW, et al. The six-minute walk test in healthy children: reliability and validity. *Eur Respir J*. 2005;25(6).

33. Schmidt K, Vogt L, Thiel C, Jäger E, Banzer W. Validity of the Six-Minute Walk Test in Cancer Patients. *Int J Sports Med*. 2013;34(7):631-636. doi:10.1055/s-0032-1323746.

34. Geiger R, Strasak A, Treml B, et al. Six-Minute Walk Test in Children and Adolescents. *J Pediatr*. 2007;150(4):395-399.e2. doi:10.1016/j.jpeds.2006.12.052.

35. ATS Statement. *Am J Respir Crit Care Med*. 2002;166(1):111-117. doi:10.1164/ajrccm.166.1.at1102.

36. Salzman SH. The 6-Min Walk Test: Clinical and Research Role, Technique, Coding, and Reimbursement. *Chest*. 2009;135(5):1345-1352. doi:10.1378/chest.07-1682

37. Grilli L, Feldman DE, Majnemer A, Couture M, Azoulay L, Swaine B. Associations between a functional independence measure (WeeFIM) and the pediatric quality of life inventory (PedsQL4.0) in young children with physical disabilities. Qual Life Res. 2006;15(6):1023-1031. doi:10.1007/s11136-006-0041-9.

38. Ottenbacher KJ, Msall ME, Lyon N, Duffy LC, Granger C V, Braun S. Measuring developmental and functional status in children with disabilities. Dev Med Child Neurol. 2007;41(3):186-194. doi:10.1111/j.1469-8749.1999.tb00578.x.

39. Wong V, Wong S, Chan K, Wong W. Functional Independence Measure (WeeFIM) for Chinese Children: Hong Kong Cohort. Pediatrics. 2002;109(2):e36-e36. doi:10.1542/peds.109.2.e36.

40. Fan E, Ciesla ND, Truong AD, Bhoopathi V, Zeger SL, Needham DM. Inter-rater reliability of manual muscle strength testing in ICU survivors and simulated patients. Intensive Care Med. 2010;36(6):1038-1043. doi:10.1007/s00134-010-1796-6.