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Safety and Feasibility of Rehabilitation Interventions in Children Undergoing Hematopoietic Stem Cell Transplant with Thrombocytopenia

Katarzyna Ibanez, MD¹, Noel Espiritu, PT, DPT¹, Regine L. Souverain, PT, DPT, C/NDT, PCS¹, Laura Stimler, OTD, OTR/L, BCP, C/NDT², Lauren Ward, PT, MSPT, PCS¹, Elyn R. Riedel, MA³, Rachel Lehrman, CCRP⁴, Farid Boulad, MD⁴, and Michael Dean Stubblefield, M.D.⁵

¹Department of Neurology, Rehabilitation Medicine Service, Memorial Sloan Kettering Cancer Center, New York, NY 10065

²Auerbach School of Occupational Therapy, Spalding University, Louisville, KY 40203

³Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY 10065

⁴Department of Pediatrics, Bone Marrow Transplant Service, Memorial Sloan Kettering Cancer Center, New York, NY 10174

⁵National Medical Director for Cancer Rehabilitation, Select Medical, Kessler Institute for Rehabilitation, West Orange, NJ 07302

Abstract

Objective: To analyze the relationship between platelet counts, the intensities of physical therapies (PT) and occupational therapies (OT) services received, and the frequency of bleeding complications in children undergoing hematopoietic stem cell transplants (HSCT) during a period of severe thrombocytopenia.

Design: Retrospective review study

Setting: Tertiary care hospital

Participants: Children (age <18) hospitalized for HSCT in 2010 and 2011 who received PT and OT services while markedly thrombocytopenic (platelets < 50K/mcL).

Corresponding author: Katarzyna Ibanez, M.D., Assistant Attending Physiatrist, Department of Neurology, Rehabilitation Medicine Service, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065, Phone #: 646-888-1930, Fax #: 646-888-1910, ibanezk@mskcc.org.

Author Conflict of Interest:

We certify that no party having a direct interest in the results of the research supporting this article has or will confer a benefit on us or on any organization with which we are associated AND, if applicable, we certify that all financial and material support for this research (eg, NIH or NHS grants) and work are clearly identified in the title page of the manuscript.

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Interventions: None

Main Outcome Measures: Intensities of PT and OT interventions, the patients' platelet counts on specific therapy days and any bleeding events (minor or major) that occurred during or briefly following rehabilitation interventions.

Results: Sixty-two patients (accounting for sixty-three HSCTs) met the criteria for analysis. Fifty-six of these patients (fifty-seven HSCTs) underwent PT and/or OT while markedly thrombocytopenic. There was no correlation between the platelet count and the intensity of rehabilitation interventions. There were no major bleeding events. There was no association between minor bleeding and intensities of PT or OT interventions and no association between minor bleeding events and platelet counts. Only 5 minor bleeding events occurred during or following moderate or intensive therapy out of 346 PT and OT sessions (1.5%).

Conclusion: The results of our study suggest that bleeding complications during or following mobilization and supervised exercise during PT and OT in children with severe thrombocytopenia undergoing HSCT are minor and relatively rare. These are encouraging results for both patients and rehabilitation specialists treating this population who is at high risk for developing immobility related complications.

Keywords

hematopoietic stem cell transplantation; rehabilitation; pediatric; thrombocytopenia

Hematopoietic stem cell transplantation (HSCT) is an established treatment modality for patients with malignant and non-malignant hematologic and immunologic disorders. Autologous HSCT involves the infusion of the individual's own hematopoietic progenitor cells with the goal of restoring hematopoiesis following ablative chemotherapy. Allogeneic HSCT involves the infusion of a related or unrelated donor's progenitor cells with the goal of creating a new and competent immunohematopoietic system potentially also resulting in a therapeutic graft-versus-malignancy or graft-versus-autoimmune disease response. Allogeneic HSCT is preceded by a conditioning regimen, which may be fully ablative to the bone marrow (high-dose regimen) or non-myeloablative (reduced-intensity conditioning). Conditioning therapy includes chemotherapy +/- total body irradiation (TBI).

Since the first successful allogeneic transplantation in 1968¹ remarkable advances occurred in histocompatibility testing, control of graft-versus-host disease (GVHD), and supportive care which resulted in significantly improved outcomes following HSCT. In 2013, 8,338 individuals underwent allogeneic bone marrow transplant in the United States.² Over 2,000 patients ages 20 years were registered with The Center for International Blood and Marrow Transplant Research (CIBMTR) as recipients of allogeneic bone marrow transplants in 2012.³ Many of these pediatric patients will be long-term survivors. Their expected long-term disease survival depends on the indication for transplant as well as the stage of the disease. The estimated one year survival rate after a first allogeneic HSCT performed between years 2010 and 2012 in a pediatric recipient was 71.6%.⁴

Despite improved survival following HSCT, children continue to experience physical and psychosocial sequelae related to the hospitalization, toxicities and complications of the

treatment and immobility.^{5–14} Children undergoing HSCT require prolonged protective isolation given their vulnerability to infections and many of them are very sedentary while hospitalized and confined to their room. Prolonged immobility negatively affects multiple organ systems, including musculoskeletal,^{15–17} cardiovascular,^{17,18} respiratory,^{17,19} integumentary¹⁷ and endocrine systems.¹⁹ Complete bed rest may result in a 1% to 1.5% decline of muscle strength per day.²⁰ Commonly reported physical symptoms during cancer treatment include fatigue, muscle weakness, pain, poor sleep,²¹ limited endurance as well as deficits in functional mobility and activities of daily living (ADLs). Physical performance, strength, fitness, cardiovascular and respiratory capacity tend to be affected and may be ameliorated by structured and early rehabilitation efforts.^{21–24} The goals of PT for these children include improving or maintaining functional mobility, strength and muscle bulk, joint range of motion, coordination, endurance as well as gait and balance training. The goals of OT as identified by the child, his or her family and the treating therapist are to improve the child's participation in meaningful occupations including ADLs, fine motor skills, visual-perception, cognition, and psychosocial well-being. Treatment approaches include neuromotor, sensory, acquisition of developmental milestones, biomechanical, cognitive-psychosocial, and visual-perceptual. The benefits of rehabilitation interventions in adult HSCT patients are well established.^{21,23,25–32} The evidence for similar benefits in the pediatric population is growing.^{33–36}

Historically, rehabilitation interventions in children admitted for HSCT are limited. Medical and rehabilitation providers as well as patients and families voiced concern that physical activity and mobilization may cause bleeding in these profoundly thrombocytopenic patients requiring platelet transfusions. Some of these patients may also develop veno-occlusive disease (VOD) following HSCT and require treatment with an antithrombotic agent defibrotide, which places them at an even higher risk for bleeding. Exercise is presumed to increase the risk for cerebral, intramuscular and joint hemorrhage in profoundly thrombocytopenic patients.^{37,38} There are no well established evidence-based guidelines specific to the pediatric population regarding safety of mobilization and activity recommendations with respect to platelet counts. Common recommendations frequently used as PT and OT practice guidelines for physical activity in thrombocytopenic patients are listed in Table 1.^{39–43} These guidelines are broad and if applied strictly to our unique group of patients they would prevent children undergoing HSCT from benefiting from rehabilitation interventions. Our physical and occupational therapists successfully mobilize patients with severe thrombocytopenia. Exercise intensity is guided primarily by the patient's overall medical status and his/her activity tolerance unless otherwise specified by the medical team.

This retrospective study evaluates a cohort of children who underwent allogeneic HSCT at Memorial Sloan Kettering Cancer Center in 2010 and 2011. The primary goal of this study is to assess whether there is a relationship between the platelet count, the intensities of rehabilitation therapies received, and the frequencies of bleeding complications related to activity in these patients. Based on our clinical experience we did not expect to find an association between platelet count and bleeding complications. We did not know whether or not we would find a correlation between platelet count and intensities of therapies. Rehabilitation interventions were deemed safe if children experienced no major bleeding

events attributed to PT or OT. We would conclude that rehabilitation therapies were feasible if children were able to participate in therapies while profoundly thrombocytopenic.

Methods

Our application for an exemption from An Institutional Review Board/Privacy Board to study existing data was approved. The study was performed in compliance with the Health Insurance Portability and Accountability Act. Pediatric patients (ages 18 and under) who underwent allogeneic HSCTs in 2010 and 2011 were identified using a pediatric database. All patients meeting the above criteria and who underwent PT or OT during their hospitalizations were included in the study. We did not apply any additional exclusion criteria.

All data was collected retrospectively from clinical and laboratory data pertinent to inpatient admissions for HSCT. Clinical notes reviewed included PT and OT documentation when patients' platelets were $\leq 50\text{K}/\text{mL}$, medical and nursing progress notes within 24 hours of PT or OT interventions and discharge summaries. Data collected included the patient's age, sex, indication for HSCT, hospitalization dates, platelet count, number of days during hospitalization when platelets were less than or equal to $50\text{K}/\text{mL}$, the number and intensity of PT and OT sessions provided during the severely thrombocytopenic period (defined as platelets $\leq 50\text{K}/\text{mL}$), the number of attempted, withheld and completed PT and OT sessions, any reported "side effects" of rehabilitation interventions with a special emphasis on bleeding complications, as well as the number of patients on defibrotide at some point during admission. Patients with prior history of thrombosis, on unfractionated or low molecular weight heparin, were taken off their anticoagulant when thrombocytopenic with platelets $\leq 50\text{K}/\text{mL}$ and therefore did not constitute an issue for this study.

For the purpose of our analysis, a patient "declined" a PT or OT session when he/she or his/her family deferred therapy treatment even though there was no medical contraindication to therapy and the patient was available and in the room at the time the therapy was offered. If the patient was unavailable or the medical team did not clear the patient for participation in therapy, the session was classified as "withheld". It was noted if a patient received a platelet transfusion between the time his/her platelet count was obtained and an initiation of PT or OT session. Rehabilitation interventions were classified as very light, light, moderate and intensive based on pre-determined criteria agreed upon by the study team based on our collective experience (Table 2).

Data was reviewed by three senior physical therapists, one senior occupational therapist and one physiatrist. Each person was assigned specific medical records to review. When the intensity of therapy provided was unclear, the entire group reviewed the documentation and agreed upon the selected category. Documented musculoskeletal complaints were noted if they were possibly related to or exacerbated by rehabilitation interventions. All bleeding events within 24 hours of PT or OT were reviewed and recorded as possibly related to rehabilitation interventions unless there was a strong alternative explanation to account for bleeding (i. e. BK virus related hematuria, etc.).

The correlation between PT or OT intensity and platelet count was examined by calculating the Spearman Rank Correlation Coefficient and corresponding 95% confidence interval. The associations between bleeding complications and intensities of therapies, and between bleeding complications and platelet counts, were examined using a logit model with generalized estimating equations in order to account for correlations within patients. Odds ratios (OR), 95% confidence intervals and p-values from the models are reported. All computations were performed using SAS version 9.4 (SAS Institute, Cary, NC). Of note, the terms “association” and “correlation” have different statistical meanings. “Association” is a general term used to represent the investigation of the relationship between variables, while the term “correlation” is specifically used to refer to the correlation coefficient between two continuous (or ordinal) variables.

Results

Sixty-two patients met the criteria for this review and analysis. They accounted for 63 admissions for HSCTs in 2010 and 2011. Patient characteristics are listed in Table 3. Median age at the time of admission was 8 years. Thirty-five patients were males. Reasons for HSCT included malignancies (N=47) and non-malignant hematologic or immunologic disorders (N=16). Median duration of admission was 41 days. Patients' platelet counts were 50K/mcL for a period of days ranging from 3 to 93 (median 23 days). Eight patients were on defibrotide at some point during their HSCT admission. Fifty-six patients in 57 admissions underwent PT and OT interventions while their platelets were 50K/mcL. Tables 4 and 5 summarize the number and intensities of PT and OT sessions in relationship to the platelet count, and group them into separate categories based on whether or not the patient received a platelet transfusion between the time the blood work was obtained and the therapy session took place.

PT/OT sessions were attempted 652 times in our group of patients. There were 346 completed sessions (53%), 149 declined sessions (23%) and 157 withheld sessions (24%). Patients ages 0–5 (16 patients) underwent a total of 87 PT/OT sessions (Table 4), while patients ages 6–18 (47 patients) underwent a total of 259 PT/OT sessions (Table 5) with an average of 5–6 sessions per patient. Therapy sessions were attempted and completed on 36% and 18% of the days when platelet count was 50K/mcL, respectively. There was no correlation between intensity of the intervention and platelet count in either the 0–5 age group (correlation coefficient: -0.01 , 95% CI: -0.22 – 0.20) or the 6–18 age group (correlation coefficient: 0.01 , 95% CI: -0.12 – 0.13). No major bleeding complications related to therapy interventions occurred. Five episodes of minor bleeding were noted out of 346 total sessions (1.5%, 95% CI: 0.2% – 2.7%) (Table 6). None of those patients were on defibrotide. One patient (14-year-old male) developed small emesis with “bloody streaks” 90 minutes following a PT session. His platelet count was 11 K/mcL, he received a platelet transfusion in the interim, and underwent PT intervention that was moderate in intensity. Another patient (10-year-old male) experienced two episodes of epistaxis when his platelet counts were 34 K/mcL and 48 K/mcL. He also received platelet transfusions prior to therapies and participated in intensive PT and OT sessions, respectively. The last patient (14-year-old female) incurred two episodes of epistaxis associated with PT sessions when her platelets were 33 K/mcL and 36 K/mcL. She received a platelet transfusion prior to PT and

engaged in an intensive type of therapy. None of the minor bleeding complications occurred in patients in the 0–5 age group. The rate of bleeding complications in patients in the 6–18 age group is 1.9% (95% CI: 0.3%–3.6%) as illustrated in Table 6. We did not find a statistically significant association between minor bleeding complications and platelet count in the 6–18 age group (OR: 1.2 per 10 unit increase, 95% CI: 0.4–3.5, $p=0.67$) (Table 7). We also did not find statistically significant association between minor bleeding complications and intensity of the intervention (OR: 4.0 per increase in intensity, 95% CI: 0.7–21.6, $p=0.11$); however, all of the five minor bleeding complications occurred in patients receiving moderate or intensive therapy (Table 8).

Musculoskeletal complaints attributed to or exacerbated by PT or OT sessions and reported by patients during or following therapies included delayed onset muscle soreness (1), hip pain (1), knee pain (2), and leg/foot pain (1). Other symptoms concomitant with, and possibly exacerbated by therapies, included hypertension (1), nausea (2), dyspnea (1), tachycardia (5) and tachypnea (1), all of which were transient and did not necessitate any additional medical intervention.

Discussion

Studies show that in patients with thrombocytopenia without additional risk factors or active bleeding the risk of hemorrhage was independent of platelet count.⁴⁴ In patients with acute lymphoblastic leukemia, hemorrhage was rare with platelets $>20\text{K}/\text{mcL}$ and no intracranial hemorrhage occurred in those with platelets $>10\text{K}/\text{mcL}$.⁴⁵ Studies documented the safety of physical exercise in adult patients with critical thrombocytopenia undergoing intensive chemotherapy.³⁸ In our study, PT and OT interventions in pediatric patients admitted for HSCT are safe and feasible. There was no correlation between platelet counts and intensities of therapy interventions. This finding is likely related to the fact that intensities of rehabilitation interventions in our patient population are primarily guided by the child's overall medical status and symptoms as opposed to an isolated platelet count.

There were no major bleeding complications and only five minor bleeding complications. Although we did not find statistically significant associations of either platelet count or therapy intensity on minor bleeding complications, we did not have enough power to adequately detect differences in bleeding complication rates with only five bleeding events. The five minor bleeding events all occurred in patients receiving moderate or intensive therapy. However, the overall low rate of minor bleeding complications (1.5%) suggests that PT and OT are safe interventions in this patient population. Safety of PT and OT interventions cannot be extrapolated to a non-supervised exercise program as the therapist adjusted and personalized each patient's program based on the child's functional needs and medical status while ensuring no falls or injuries occur during therapy.

Study Limitations

One of the limitations of our study given its retrospective nature was our inability to account for the patient's exact platelet count at the time that therapies were provided. Most patients had their blood work drawn the night prior or early morning and based on the lab result and clinical status platelet transfusion might have been ordered that morning. There is no reliable

way to predict or calculate an actual platelet count at the time a PT or OT session occurred or to predict the individual patient's response to a platelet transfusion. The platelet counts recorded in our study likely overestimated the actual platelet count at the time the therapy session took place. We realize that the platelet count is not the only variable affecting bleeding. Individual factors, platelet function, superimposed medical problems including infection, fever and coagulopathy, as well as medications can all influence the bleeding risks. However, it is the platelet count that routinely drives the decisions of clinicians as to whether to hold or proceed with therapy and the intensity of therapy provided. Also, patients with acutely developing medical problems, such as fever or infection are likely to be on a temporary medical "hold" from rehabilitation interventions until those conditions are addressed. We also realize that the platelet count may not be the only variable affecting the intensity of rehabilitation interventions. Patients may only be able to participate in a light intensity of therapy due to multiple factors, including motivation, fatigue, pain, nausea, symptomatic anemia, limited endurance or dizziness. The purpose of our study was to assess if the platelet count was associated with an increased risk of bleeding during mobilization with PT or OT.

Another limitation of this retrospective review is our inability to adequately assess external validity of our findings. We did not collect information regarding duration and quality of sessions, so we can't make conclusions as to how our therapy sessions compare to therapy elsewhere. We made an interesting observation that pediatric patients are not able to participate in therapy about 50% of the time when they are approached. Twenty three percent of the time therapies were deferred, while 24% of the time sessions were withheld due to either a change in the child's medical status or his/her unavailability. Further breakdown of the reasons for the patient's inability to participate in therapies would be helpful when assessing practitioners' expectations, feasibility and types of interventions needed to increase overall participation in therapies. The reason for this relatively high percentage of missed therapy sessions may be explained by the fact that patients who are transplant recipients can be ill with complications such as poor nutrition, weight loss, fatigue, nausea rendering any activity difficult to sustain. Physical and occupational therapists need to make frequent attempts to see these patients in order to ensure that they receive adequate intensity of very much needed rehabilitation services. This may affect therapists' productivity and necessitate adding additional therapy staff to meet these children's rehabilitation needs.

Conclusions

This retrospective study supports our hypothesis that supervised exercise is safe and feasible in pediatric patients undergoing HSCT with thrombocytopenia. Early rehabilitation interventions are very much needed in this patient population in order to prevent or ameliorate the consequences of immobility leading to weakness and functional decline and many other adverse effects of immobility. The outcomes of our study are encouraging and hopefully will increase the acceptance of rehabilitation interventions during hospitalization for HSCT. The results of our study need to be validated in a larger prospective trial.

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Abbreviations:

PT	physical therapy
OT	occupational therapy
HSCT	hematopoietic stem cell transplant
TBI	total body irradiation
GVHD	graft-versus-host disease
CIBMTR	Center for International Blood and Marrow Transplant Research
ADLs	activities of daily living
VOD	veno-occlusive disease
AROM	active range of motion
AAROM	active assisted range of motion
OOB	out of bed
MMT	manual muscle testing

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Table 1:

Activity recommendations with respect to platelet count

Platelet Count (K/mcL)	Source: Ref. 39 & 40	Source: Ref. 41 & 43	Source: Ref. 42
<10		No therapeutic exercise. Hold therapy	
<20	With permission from primary oncology service: ambulation, self-care with assistance, minimal or cautious exercise/activity, essential ADLs only		Light program of active exercise in extenuating circumstances
10–20		Therapeutic exercise Bike without resistance	
>20		Therapeutic exercise Bike with or without resistance	
20–30	Self-care activities, functional mobility, light exercise (passive or active)		Exercise with care Avoid heavy resistance work and activities that traumatize the joints
30			Moderately vigorous exercise
30–50	Moderate active exercise/ROM, light weights (1–2lbs; no heavy resistance/isokinetics); ambulation, aquatic therapy, stationary bike		
>50		Resistive AROM permitted	
50–150	Progressive resistance, swimming, bicycling		
150–450	Unrestricted normal activity		

Table 2:

Classification of intensity of PT/OT interventions

Age Range	Very light	Light	Moderate	Intensive
0–5 years	<ul style="list-style-type: none"> • AROM/AAROM • Essential ADLs (in bed) <ul style="list-style-type: none"> ◦ sitting edge of bed ◦ self feeding ◦ grooming ◦ dressing • Bed mobility <ul style="list-style-type: none"> ◦ Transfer supine to sit in/edge of bed ◦ rolling • Therapeutic activity in bed • Seated fine motor play • Reaching activities seated 	<ul style="list-style-type: none"> • Transfers/transitions <ul style="list-style-type: none"> ◦ quadruped, ◦ prone prop, ◦ pull to stand etc • Limited ambulation (in room) • PROM • ADLs (standing edge of bed) • Static balance on even and stable surfaces (mat, floor) • Fine motor play in standing at stable support surface 	<ul style="list-style-type: none"> • Dynamic balance/coordination on uneven or unstable surfaces (physioball, bosu ball, wedge, balance/foam disc) • Reaching outside base of support on uneven/unstable surface • Endurance • OOB ADLs (in bathroom or away from sitting surface) 	<ul style="list-style-type: none"> • Stretching/elongation • Climbing: negotiation over uneven surfaces (multiple changes in position) • Percussion • Vibration • Pulmonary toileting • Strengthening • Progressive resistive exercises • Jumping • Propelling on scooter
6–18	<ul style="list-style-type: none"> • AROM/AAROM • Essential ADLs (sitting edge of bed/in bed/chair) <ul style="list-style-type: none"> ◦ grooming, ◦ dressing, ◦ bathing, ◦ feeding, etc • Bed mobility (rolling, supine to sit edge of bed) • Therapeutic activity in bed 	<ul style="list-style-type: none"> • Transfers • Limited ambulation (in room) • PROM • ADLs (standing edge of bed) • Static balance on even and stable surfaces (mat, floor) 	<ul style="list-style-type: none"> • MMT • Dynamic balance/coordination (uneven surfaces) • Endurance • Unlimited ambulation (out of room) • OOB ADLs (in bathroom or away from sitting surface) • Restorator (NO resistance) 	<ul style="list-style-type: none"> • Stretching/elongation • Strengthening • Progressive resistive exercises • Jumping, obstacle course, climbing • Restorator (WITH resistance) • Percussion • Vibration • Pulmonary toileting

Abbreviations: AROM - active range of motion; AAROM -active assisted range of motion; ADLs - activities of daily living; OOB -out of bed; MMT -manual muscle testing

Table 3:

Patient characteristics

Patient and Admission Characteristics	n=63
Age (years)	
0–1	3 (5%)
1–5	13 (21%)
6–18	47 (75%)
Median	8
Range	(0.1–18)
Sex	
Male	35 (56%)
Female	28 (44%)
Diagnosis	
Leukemia (ALL - pre-B, T cell, AML)	42 (67%)
MDS	4 (6%)
NHL	1 (2%)
Non-malignant heme conditions	16 (25%)
Duration of admission (days)	
Median	41
Range	20–159
Duration of plt<50k (days)	
Median	23
Range	3–93

Intensities of PT/OT interventions and platelet counts (+/- interim transfusions) in patients ages 0–5 years

Table 4:

Age 0–5						
Platelet Count/Transfused	OT/PT				Total	
	Very Light	Light	Moderate	Intensive		
0–10	0	3 (75%)	1 (25%)	0	4	
Yes	0	3	1	0	4	
No	0	0	0	0	0	
11–20	3 (21%)	7 (50%)	1 (7%)	3 (21%)	14	
Yes	3	6	1	3	13	
No	0	1	0	0	1	
21–30	1 (3%)	20 (59%)	11 (32%)	2 (6%)	34	
Yes	0	1	3	0	4	
No	1	19	8	2	30	
31–50	3 (9%)	23 (66%)	5 (14%)	4 (11%)	35	
Yes	0	2	0	0	2	
No	3	21	5	4	33	
Total	7	53	18	9	87	

Intensities of PT/OT interventions and platelet counts (+/-) in patients ages 6–18

Table 5:

Age 6 +		OT/PT				Total
Platelet Count/Transfused	Very Light	Light	Moderate	Intensive		
0–10	1 (14%)	0	1 (14%)	5 (71%)	7	
Yes	1	0	1	5	7	
No	0	0	0	0	0	
11–20	2 (5%)	8 (20%)	13 (33%)	17 (42%)	40	
Yes	1	6	11	15	33	
No	1	2	2	2	7	
21–30	4 (7%)	20 (34%)	10 (17%)	24 (41%)	58	
Yes	2	8	3	5	18	
No	2	12	7	19	40	
31–50	5 (3%)	39 (25%)	44 (29%)	66 (43%)	154	
Yes	3	12	10	25	50	
No	2	27	34	41	104	
Total	12	67	68	112	259	

Table 6:

Bleeding complications

	N	Freq	Bleeding Event Rate (95% CI)
PT/OT sessions in all patients	346	5	1.5% (0.2%–2.7%)
PT/OT sessions in patients 0–5 years	87	0	0%
PT/OT sessions in patients 6–18 years	259	5	1.9% (0.3%–3.6%)

Associations between platelet counts and bleeding complications in patients ages 6–18.

Table 7:

Platelets	No bleeding complications	Bleeding complications
0–10	7 (100%)	0
11–20	39 (97%)	1 (3%)
21–30	57 (100%)	0
31–50	150 (97%)	4 (3%)

Note: There were no bleeding complications in patients <=5 years
Odds ratio: 1.2 (per 10 unit increase in platelets), 95% CI: 0.4–3.5, p=0.67

Associations between intensities of PT/OT interventions and bleeding complications in patients ages 9–18

Table 8:

Intensity	No bleeding complications	Bleeding complications
Very light	11 (100%)	0
Light	67 (100%)	0
Moderate	67 (99%)	1 (1%)
Intensive	108 (96%)	4 (4%)

Note: There were no bleeding complications in patients <=5 years

Odds ratio: 4.0 (per increase in intensity), 95% CI: 0.7–21.6, p=0.11