

Exercise and Physical Function in the Paediatric Solid Organ Transplant Population.

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CLINICAL SCENARIO:

Paediatric solid organ transplantation is a life-saving therapy for many children, but it is not a cure. End-stage organ disease is replaced by a chronic condition with many associated comorbidities (Ng et al., 2008; Nobili & de Goyet, 2013). Current literature suggests that activity levels and exercise tolerance of recipients are often reduced (Clark, Cantell, Crawford, & Hamiwka, 2012; Davis et al., 2006; Krasnoff, Mathias, Rosenthal, & Painter, 2006). In the healthy population, physical activity has been demonstrated to produce overall physical, psychological and social benefits, and is an important factor in the development of children's fundamental gross motor skills (Janssen, 2007). In the effort to improve physical functioning post transplant, prescribed exercise for adult recipients has proven to be a successful treatment approach (Didsbury et al., 2013a), however; the unique exercise responses of a growing child prevent the direct translation of adult prescriptions.

FOCUSED CLINICAL QUESTION:

Among paediatric solid organ transplant recipients does exercise improve physical functioning?

SUMMARY of Search, 'Best' Evidence' Appraised, and Key Finding

At present there is limited evidence to demonstrate the effectiveness of exercise to improve the physical functioning of paediatric transplant recipients. An exercise trial has been positively associated with increases in both physical endurance and muscle strength in children post heart and lung transplant in a non-randomized control trial (Deliva et al., 2012a) and a case series pilot study (Patel et al., 2008). Gains in cardiorespiratory fitness were also reported following rehabilitation in a single heart retransplantation case (Chang et al., 2013). Two case control studies have highlighted the importance of physical activity in which a higher number of steps/day were positively correlated with improved health related quality of life and higher levels of aerobic endurance in children post renal transplant (Hamiwka, Cantell, Crawford, & Clark, 2009; Lubrano et al., 2012). In both studies the transplant participant group was limited in size (n= 20 or less) and smaller than the control group. There are indications that exercise may have a positive impact on physical fitness and quality of life, but the few available studies are of lower quality with a lack of randomization and small sample sizes that limit generalizability.

CLINICAL BOTTOM LINE:

Physical activity and exercise training may be effective tools to lessen the morbidities of transplant and improve health related quality of life for children post solid organ transplant, but the evidence is insufficient and further study is warranted.

Limitation of this CAT: This critically appraised paper (or topic) was prepared for a graduate course assignment and has been peer-reviewed by an instructor.

SEARCH STRATEGY:**Terms used to guide Search Strategy:**

- **P**atient/Client Group: Children (age <18 yrs.) post solid organ transplant (heart, lung, liver and kidney)
- **I**ntervention (or Assessment): exercise, also represented as physical activity or sports
- **C**omparison: none
- **O**utcome(s): physical functioning measured quantitatively as a subjective HRQOL concept or objectively as an aspect of health related physical fitness (muscle strength, endurance, cardiorespiratory fitness and flexibility) through exercise test, exercise endurance or physical activity levels

Databases and Sites Searched	Search Terms	Limits Used
Cochrane Central Medline CINAHL Embase	<p>exercise, exercise therapy, exercise movement techniques, exercise*, physical activit*, sports, muscle exercise, exercise test, exercise tolerance, physical endurance ,physical fitness, physical function</p> <p>AND</p> <p>organ transplantation, heart transplantation, kidney transplantation liver transplantation, lung transplantation</p> <p>AND</p> <p>child*, adolescen*, teen*, girl*, boy*, youth*, paediatric*, pediatric*</p>	<p>preschool child <1 to 6 years>, school child <7 to 12 years>, adolescent <13 to 17 years>)</p>

INCLUSION and EXCLUSION CRITERIA**Inclusion:**

- Participant population is <18 years of age
- Participants must be solid organ transplant recipients
- Medical clearance to engage in activity/exercise testing

Exclusion:

- Participants had received tissue and stem cell transplants (bone marrow, skin or islet cells)
- Descriptive studies that only measured aspects of fitness and did not analyze its relationship to exercise or physical activity

RESULTS OF SEARCH

Five relevant studies were located and categorised as shown in Table 1

Table 1: Summary of Study Designs of Articles Retrieved

Study Design/ Methodology of Articles Retrieved	Level*	Number Located	Author (Year)
Non-Randomized control trial	3	1	Deliva et al., (2012)
Case control	4	2	Hamiwka, Cantell, Crawford, & Clark, (2009) Lubrano et al., (2012)
Case series (pre and post intervention design)	4	1	Patel et al.,(2008)
Single case design	4	1	Chang et al., (2013)

*OCEBM Levels of Evidence Working Group. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. <http://www.cebm.net/index.aspx?o=5653>

BEST EVIDENCE

The following study (Deliva et al., 2012b) was identified as the 'best' evidence and selected for critical appraisal. Reasons for selection were:

- Most recently published and highest level of evidence available
- Primary outcomes were standardized and validated outcome measures of physical function.
- Single blind study
- Non-randomized but no statistical difference between treatment groups at baseline
- Reflects all aspects of my PICO

SUMMARY OF BEST EVIDENCE

Table 2: Description and appraisal of: Effects of an Acute, Outpatient Physiotherapy Exercise Program Following Paediatric Heart or Lung Transplantation by **Deliva et al., 2012.**

Aim/Objective of the Study/Systematic Review:

"To examine the impact of a hospital-attended or home-based, semi-individualized, physiotherapy (PT) prescribed exercise program following paediatric heart or lung transplantation."(Deliva et al., 2012a, p.879)

Study Design: Non-randomized control trial

Setting: An acute care hospital-attended (HA) or home-based (HB) setting. All outcome assessments were performed in the hospital setting.

Participants: N=39, participants were enrolled in the study during their hospitalization at the time of transplant between October 2002 and February 2008.

Inclusion criteria: Children 6 years and older post heart or lung transplant.

Exclusion criteria: Concomitant diagnoses that would interfere with participation in a structured exercise program.

Participants were assigned to one of two groups:

HA: If the participant lived <30 minute commute to the hospital they performed a hospital attended outpatient exercise program with PT supervision. (control group)

HB: If the participant lived > 30 minute commute to hospital they performed a home exercise program with parent supervision. (intervention group)

Blinding: Assessors were blind to assigned groupings but therapists and participants were not. Outcomes were measured at baseline (discharge), 3 months and 1-year post discharge.

Table 1a: Participant Characteristics at Baseline

	Group 1 HA (n=20)	Group 2 HB (n=19)
Age	13.0 ± 3.1	12.7 ± 2.7
Gender (Male/Female)	8/12	12/8
Type of Transplant: (no.)		
Heart/lung	14/6	13/6
Wait times (days)	156.6±181.8	157±221.5

There was no significant difference in age, gender, transplant type and numbers between groups at baseline.

Three month assessment: 33 participants completed the exercise program HA =15 (4 boys) and HB =18(12 boys)

One year Assessment: 25 participants completed the one year assessment HA=9 (3 boys) and HB=16 (11 boys).

Dropouts (14) were secondary to i) transfer to another facility (3); ii) subject relocation (4) iii) patient deceased (3) iv) infection with prolonged hospitalization (1), v) ongoing multi-system illness (1); vi) complications related to pressure ulcer (1) and vii) recurrent non-attendance (1).

Intervention/Phenomenon Investigated: Both groups performed an exercise program 3 times weekly for 3 months. It consisted of “aerobic and resistance training, gross motor activities and stretching based on individual needs, developmental status and sternal healing” (Deliva et al., 2012a, p.880). Activities were progressed by a physiotherapist weekly in clinic or by phone and home-based exercise was tracked by an activity journal. Exercises: resistance level for strengthening was 20-30% of participant’s maximal load and increased one pound when participant could perform 30 repetitions. Aerobic exercise was based on reported physical exertion using the modified Borg scale with a goal to achieve a minimum of 30 minutes of an intensity of 4-5/10. Stretches were low load and prolonged (>30 sec).

Outcome Measures:**Primary**

1) Exercise capacity: Exercise endurance was measured by Six Minute Walk test (SMW). It is a valid and reliable submaximal exercise test that represents distance covered walking for six minutes. It is standardized and was conducted according to the ATS guidelines.

2) Strength: A Hand-Held Dynamometer (HHD) was used to assess isometric muscle strength of ankle dorsiflexors, knee extensors, hip extensors, abductors and flexors, shoulder abductors and flexors and elbow flexors and extensors. It is a reliable measure when a standardized protocol is used with one assessor as referenced in this study.

3) Flexibility: Goniometry was used to measure Hamstrings (popliteal angle) and gastrocs/soleus. Lower back flexion/extension was measured using the modified-Schober's test. Both are reliable and valid tests. Shoulder flexibility was measured with the "Hand behind Back" method that has no reports of validity or reliability.

Secondary

1) Heart rate, respiratory rate, oxygen saturations: Portable saturation monitor measured all.

2) Exertion: The modified Borg scale is a visual analog scale of the rate of perceived exertion and is a valid and reliable indicator of exercise intensity.

3) Dyspnea: The Dyspnea Index is a 15 count breathlessness score. It is not validated and requires practice for reliability.

Main Findings:

There were no differences at any time point in physical fitness parameters found between HA and HB exercise groups. The entire cohort demonstrated significant improvements in functional exercise capacity, proximal muscle group strength and hamstring, shoulder and low back flexibility at program completion (3 months) and at one year (See Table 1a.). As an entire cohort, older age and male gender were associated with longer SMW distance. There was smaller improvement in SMW distance in males and those with diagnoses other than congenital heart disease.

Table 1a: Significant Changes in Cohort Health Related Fitness over Time

Entire Cohort					
Outcome measured	Baseline	3 month	1 yr.	Initial vs. 3 month (p value)	Initial vs 1 yr. (p value)
Exercise Capacity(metres)					
SMW distance	425.7±109.4	500.6±93.6	528.5±66.6	P=0.0001	P=0.001
Strength (kgs)					
Right shoulder flexion	4.6 ± 3.5	6.2 ± 3.9	6.8 ± 3.9	0.002	0.008
Left shoulder flexion	4.3 ± 3.2	6.3 ± 3.9	6.7 ± 4.0	<0.001	0.006
Left shoulder abduction	4.2 ± 2.9	5.4 ± 2.8	5.9 ± 3.9	0.009	0.09*
Right elbow flexion	6.4 ± 4.4	8.0 ± 4.5	8.5 ± 4.4	0.01	0.02
Left elbow flexion	7.2 ± 9.8	7.4 ± 4.7	8.3 ± 4.5	0.04	0.02
Left hip flexion	9.0 ± 5.2	10.1 ± 5.5	10.6 ± 5.1	0.05	0.11*
Left hip extension	7.4 ± 3.7	9.4 ± 5.2	9.2 ± 5.8	0.03	0.14*
Flexibility					

Right Popliteal angle (°)	153±17	160±11	No change	P=0.02	P=0.05
Left popliteal angle	155±18	161±13	No change	P=0.06**	P=0.05
Right hand behind head(inches)	8.8±6.5	6.2±5.9	3.2±4.9	P=0.002	P=0.001
Left hand behind head	12.5±9.0	n/a	7.7±6.3	n/a	P=0.003
Lumbar flexion	16.5±3.2	18.2±3.0	19.0±2.8	P=0.002	P=0.001

(* p value not significant at one year,** approaching significance)

Conclusions: “This is the first prospective study to examine both HB and HA exercise rehabilitation programs in the recovery following paediatric heart and lung transplantation. Both intervention groups demonstrated improved health related fitness to a similar degree in the first months after transplant. “(Deliva et al., 2012a, p.885).

The results suggest that a PT home exercise prescription may be an effective way to address the gap in community resources for the pediatric population.

Critical Appraisal: There was a focused and well defined research question with an appropriate in depth literature review.

Design: The study was a non-randomized control trial. Rehabilitation programs were the standard of care post thoracic transplant so it was unethical to not provide a treatment program to both groups.

Sample: It was a sample of convenience, described in detail with specific inclusion/exclusion criteria. Group assignment was not randomized and based on patient geographic location with no significant difference in baseline characteristics between groups. Informed consent was attained.

Outcomes: Outcome measures were appropriate. Use of the SMW test represents exercise tolerance but may miss significant physiological differences in true aerobic capacity that could be measured with a peak exercise test. Measures of key outcomes were done pre and post treatment intervention (baseline/3 months) and at one year for long-term effects. Dropouts were reported.

Interventions: Subjects and treating therapists were not blinded. Exercise Intervention was well described.

Results: Point measures and measures of variability were provided for primary and secondary outcomes with means and standard deviations, but confidence intervals were not provided.

Bias:

Allocation Bias: Not randomized, differences between groups that are not measured may impact outcomes

Maturation Bias: Sampling occurred over 5 ½ years. Changes in surgical intervention and medical care may impact participant’s outcomes. Improvements in the entire cohort’s physical outcomes may have occurred just as a result of physical recovery and maturation over time post transplant.

Attrition Bias: Participants lost to follow-up was not equal between groups. Overall loss at 3 months is 14% and 31% at one year. There were also more boys in the HB group. Boys generally have higher physical activity levels, (Colley et al., 2011) which may favour the HB group.

Intervention Bias: Control for contamination or co-intervention is not addressed and the principle of intention to treat analysis is not utilized.

Interpretation of Results:

The transferability of this study is favourable. It represents a participant, setting and intervention consistent with the acute care rehabilitation of this patient population. Clinical

significance may be attributed to changes in the SMW distance as average distances increased in amounts much greater amount than those attributed to maturation (25 metres), (Geiger, 2007).

Minimal clinical difference >25m in both HB and HA group

Table 1b: Change in SMW distance baseline/12 months (metres):

Group	n	mean±SD	CI(5-95)
HB	15	81.79±100.85	32.38-131.2
HA	9	107.6±102.41	40.7-157.01

Between groups: difference of means= 25.81±101.63 Confidence interval= (-61.63-113.25)
There is a clinically significant change within each group but between groups there is uncertainty about the clinical significance and it is not statistically significant p=0.49.

Confidence interval was calculated using: Herbert R. Confidence Interval Calculator (2013). <http://www.pedro.org.au/english/downloads/confidence-interval-calculator/>. Accessed on March 1, 2014.

Summary/Conclusion:

Study results showed no statistically significant differences in physical parameters between groups at any time. Together, the entire cohort showed improvements in fitness outcomes post-intervention and at one year. Lack of randomization and a non-intervention control group created difficulty in determining the effectiveness of the intervention as opposed to the influence of natural recovery on physical performance. A larger multi-centred randomized control trial to develop definitive evidence is warranted.

IMPLICATIONS FOR PRACTICE, EDUCATION and FUTURE RESEARCH

- The health benefits associated with physical activity and exercise have been established in both healthy children and the adult transplant population (Didsbury et al., 2013b; Janssen, 2007). Despite their complex medical needs, children post transplant may benefit from regular participation in physical exercise, although its effectiveness in this population remains to be definitively established.
- Short term rehabilitation is provided in an acute care setting post transplant, although the burden related to travel and missed school, limits the length of intervention. Paediatric rehabilitation programs within the community setting are scarce. As demonstrated in Deliva et al., (2012), a home based exercise program may be an effective way to address the issue of limited community resources.
- Due to the small and complex patient population, research associated with exercise in paediatric solid organ transplant transplantation is sparse and present studies are of low quality. Establishing the effectiveness of exercise post paediatric transplant could lead to increased rehabilitation programs and better health outcomes in this population decreasing health care costs associated with this chronic disease.

References

- American Thoracic Society (2002). ATS Statement: Guidelines for the six-minute-walk test. *Am J Respiratory Critical Care Medicine*, 166, 111–117.
- Chang, K. V., Chiu, H., Wang, S., Lan C., - Chen,S.Y., Chou, N., Wu, M., . Lai, J. S. (2013). Cardiac rehabilitation in a pediatric patient with heart retransplantation. A single case study.*European Journal of Physical Rehabilitation Medicine*. Advanced online publication retrieved from www.minervamedical.it/en/getfreepdf/BXKa3osq%252BqpCDXf6whUasAbSZup7ft
- Clark, C., Cantell, M., Crawford, S., & Hamiwka, L. (2012). Accelerometry-based physical activity and exercise capacity in pediatric kidney transplant patients. *Pediatric Nephrology*, 27(4), 659-665. doi:10.1007/s00467-011-2054-z
- Clarkson, H.M, Gilwich, GB.(1989). *Musculoskeletal Assessment: Joint Range of Motion and Manual Muscle Strength*. Baltimore: Williams & Wilkins.
- Colley, R. C., Garriguet, D., Janssen, I., Craig, C. L., Clarke, J., & Tremblay, M. S. (2011). Physical activity of canadian children and youth: Accelerometer results from the 2007 to 2009 canadian health measures survey. *Health Reports*, 22(1), 15-23.
- Davis, J. A., McBride, M. G., Chrisant, M. R. K., Patil, S. M., Hanna, B. D., & Paridon, S. M. (2006). Longitudinal assessment of cardiovascular exercise performance after pediatric heart transplantation. *Journal of Heart and Lung Transplantation*, 25(6), 626-633. doi:10.1016/j.healun.2006.02.011
- Deliva, R. D., Hassall, A., Manlhiot, C., Solomon, M., McCrindle, B. W., & Dipchand, A. I. (2012a). Effects of an acute, outpatient physiotherapy exercise program following pediatric heart or lung transplantation. *Pediatric Transplantation*, 16(8), 879-886. doi:10.1111/petr.12003

- Deliva, R. D., Hassall, A., Manlhiot, C., Solomon, M., McCrindle, B. W., & Dipchand, A. I. (2012b). Effects of an acute, outpatient physiotherapy exercise program following pediatric heart or lung transplantation. *Pediatric Transplantation*, *16*, 879-886. doi:<http://dx.doi.org/10.1111/petr.12003>
- Didsbury, M., McGee, R. G., Tong, A., Craig, J. C., Chapman, J. R., Chadban, S., & Wong, G. (2013a). Exercise training in solid organ transplant recipients: A systematic review and meta-analysis. *Transplantation*, *95*(5), 679.
- Geiger, R. (2007). Six-minute walk test in children and adolescents. *J Pediatr*, *150*(4), 395-399.e2.
- Hamiwka, L. A., Cantell, M., Crawford, S., & Clark, C. G. (2009). Physical activity and health related quality of life in children following kidney transplantation. *Pediatric Transplantation*, *13*, 861-867. doi:<http://dx.doi.org/10.1111/j.1399-3046.2009.01195.x>
- Janssen, I. (2007). Physical activity guidelines for children and youth. *Applied Physiology, Nutrition, and Metabolism*, *32*, S109.
- Krasnoff, J. B., Mathias, R., Rosenthal, P., & Painter, P. L. (2006). The physical fitness of pediatric kidney and liver transplant recipients: 976. *Medicine & Science in Sports & Exercise*, *38*, S93.
- Lubrano, R., Tancredi, G., Bellelli, E., Gentile, I., Scateni, S., Masciangelo, R., . . . Elli, M. (2012). Influence of physical activity on cardiorespiratory fitness in children after renal transplantation. *Nephrology Dialysis Transplantation*, *27*, 1677-1681. doi:<http://dx.doi.org/10.1093/ndt/gfr434>
- Ng, V. L., Fecteau, A., Shepherd, R., Magee, J., Bucuvalas, J., Alonso, E., . . . and the Studies of Pediatric Liver Transplantation Research Group. (2008). Outcomes of 5-year survivors of pediatric liver transplantation: Report on 461 children from a north american multicenter registry. *Pediatrics*, *122*(6), e1128-e1135. doi:10.1542/peds.2008-1363
- Nobili, V., & de Goyet, J. (2013). Pediatric post-transplant metabolic syndrome: New clouds on the horizon. *Pediatric Transplantation*, *17*(3), 216-223. doi:10.1111/petr.12065

Patel, J. N., Kavey, R., Pophal, S. G., Trapp, E. E., Jellen, G., & Pahl, E. (2008). Improved exercise performance in pediatric heart transplant recipients after home exercise training. *Pediatric Transplantation*, *12*, 336-340. doi:<http://dx.doi.org/10.1111/j.1399-3046.2007.00806.x>

Prasad S, Randall, S., Balfour-Lynn, I. (2005) Fifteen-count breathlessness score: An objective measure for children. *Pediatric Pulmonology*, *30*, 56–62.

Schneiderman-Walker, J., Wilkes, D. L., Strug, L., Lands, L. C., Pollock, S. L., Selvadurai, H. C., . . . Corey, M. (2005). Sex differences in habitual physical activity and lung function decline in children with cystic fibrosis. *The Journal of Pediatrics*, *147*(3), 321-326.