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The efficacy of resistance training in addition to usual care for adults with acute burn injury: A randomised controlled trial

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Abbreviations:
QoL: Quality of life
RT: Resistance training
RTG: Resistance training group
CG: Control group
LLFI-10: Lower Limb Functional Index-10 survey
Quick-DASH: Quick Disability of Arm, Shoulder and Hand survey
BSHS-B: Burn Specific Health Scale Brief survey

ABSTRACT

Resistance training immediately after a burn injury has not been investigated previously. This randomised, controlled trial assessed the impact of resistance training on quality of life plus a number of physical, functional and safety outcomes in adults with a burn injury.

Patients were randomly assigned to receive, in addition to standard physiotherapy, four weeks of high intensity resistance training (RTG) or sham resistance training (CG) three days per week, commenced within 72 hours of the burn injury. Outcome data was collected at six weeks, three and six months after burn injury. Quality of life at 6 months was the primary endpoint. Data analysis was an available cases analysis with no data imputed. Regression analyses were used for all longitudinal outcome data and between-group comparisons were used for descriptive analyses.

Forty-eight patients were randomised resistance training (RTG) (n=23) or control group (CG) (n=25). The RTG demonstrated improved outcomes for the functional domain of the Burn Specific Health Scale-Brief ($p=0.017$) and the Quick Disability of Arm Shoulder and Hand ($p<0.001$). Between group differences were seen for C-reactive protein and retinol binding protein ($p=0.001$). Total quality of life scores, lower limb disability, muscle strength and volume were not seen to be different between groups ($p>0.05$).

Resistance training in addition to usual rehabilitation therapy showed evidence of improving functional outcomes, particularly in upper limb burn injuries. Additionally, resistance training commenced acutely after a burn injury was not seen to be harmful to patients.

Keywords: *Burns, Exercise, Resistance training, Rehabilitation, Quality of life, Muscle strength*

INTRODUCTION

Despite the ongoing improvements in burn care, physical impairment and diminished quality of life (QoL) continue to be significant burdens after burn injury. A known and expected outcome for patients after a burn injury is a protracted deficit of skeletal muscle strength which has been demonstrated in both adults [1-4] and children [5-7]. St-Pierre et al. [1] found muscle strength to be significantly reduced in adult patients on average three years after injury when compared to matched, unburned control participants. Similarly, paediatric studies have reported long term skeletal muscle impairment in burn injured children up to four years after injury when compared to non-burned individuals [5-7]. It is considered that muscle mass reduction related to the catabolic response to a major burn injury [8, 9] is a primary cause of reduced force generating capacity of muscle after an injury. Reduction of muscle mass and strength is exacerbated by the deleterious effects of bed rest or unloading [10] imposed upon patients after a burn injury, highlighting the importance of movement and physical rehabilitation.

Skeletal muscle is necessary for movement and locomotion and an association between muscle strength and functional ability has been documented in populations including healthy older adults [11, 12], and in clinical groups with osteoarthritis [13, 14]. Additionally, it is possible that an ongoing reduction in strength and movement in burns patients may play a role in scar contracture formation over time. With these outcomes in mind, loss of skeletal muscle strength after a burn injury will contribute to post-burn disability. Previously, self-reported physical function has been demonstrated to be below baseline levels for up to three years after burn injury [15-18] and further, was noted to be a key factor in the ability of people to return to work after a burn injury [19]. Grisbrook et al. [20], [21] concluded that self-reported function was significantly impaired in a burn injured group when compared to matched controls on average six years after their burn injury. In addition, QoL has been shown to be reduced in both the short-term and long-term after a burn injury [21-25]. Functional deficits after a burn has been a concept usually reserved for major burn injuries. However, minor severity burn injuries have been demonstrated to have a sustained negative impact on physical function [26] and QoL [25, 27, 28], suggesting that all severities of burn injury may necessitate rehabilitation in an attempt to ameliorate ongoing impairments and disability.

When prescribed with an appropriate training load, it has been established that resistance training (RT) is an effective method of increasing skeletal muscle mass and muscle strength [29]. As such, it forms part of the recommended exercise guidelines of national bodies and health groups to improve general health, prevent disease and optimise health in clinical populations [29-32]. Regarding the utilisation of RT after a burn injury, our recent systematic review and meta-analysis suggested that RT may have some positive effect on muscle strength, yet there is a lack of available data for patient reported outcome measures assessing function and QoL [33]. It was also established that the current evidence base for RT after burn injury is of low to very low quality and that future longitudinal research should employ robust methodologies to improve the overall quality of data available on this matter [33, 34]. Previous research has not investigated RT in the acute care setting and has only evaluated exercise programmes of at least six weeks in duration which may not be a practicable length of time within an acute care setting. Furthermore, research has been limited to major burn injuries only, meaning that the unique effect of RT across the whole spectrum of burn injury severity remains unknown [35, 36].

Thus, there is a need to conduct high quality randomised trials which investigate the optimal prescription and mode of exercise training, as well as the effect of implementing training within the acute care setting [33, 36, 37]. There are unique challenges for a burn injured patient which make the acute period a difficult time in which to calculate training load and complete exercise. In addition, there is a potential for competing physiological demands such as the breakdown of skeletal muscle as an additional energy source and the desired

hypertrophic response of that muscle to exercise and RT. As such, no study to date has assessed the effect of RT prescription during the acute injury phase, and none have included physiological measures of body composition at this critical time.

To address the uncertainties in the literature, we designed a randomised controlled trial to test a unique RT programme for use in acute burn injury rehabilitation. The primary aim of this study were to examine whether participation in early RT improves QoL. Secondary aims examined self-report physical disability, muscle strength and body composition after burn injury. Patient length of stay, as well as the safety and feasibility of a progressive, high load RT program in patients with acute burn injury was also examined.

METHODS

Trial Design

This study is a parallel, randomised, controlled intervention trial. Ethics approval was granted from University of Notre Dame Australia HREC (014138F) and Royal Perth Hospital HREC (2014-008). It was registered on the Australian and New Zealand Clinical Trial Registry (ACTRN12614001156673). The registered trial describes a study that planned to randomise 60 participants. This sample size was derived from a sample size calculation utilising the primary outcome of quality of life. This study has been closed prior to completion of the recruitment target due to a slower than anticipated recruitment rate and exhaustion of funding. This report represents an analysis of the data available at the time of trial closure.

Participants

Participants who met inclusion criteria were recruited by the primary investigator upon admission to the adult burns unit between August 2014 and December 2017. Participants were deemed eligible if they were over 18 years of age, had a burn injury of 5% – 40% TBSA, were able to provide consent and able to commence exercise training within 72 hours of the burn injury. If patients were initially admitted to the intensive care unit, they were allowed to participate in the study if they were transferred to the burns unit and could commence training within one week of injury. Patients were excluded if they were admitted later than 72 hours after their injury, had surgery prior to recruitment, sustained an electrical burn injury, palmar hand burn injury, associated injuries or emergency surgery affecting participation in exercise training, including fracture, amputation, acquired brain injury or peripheral neural injury or any pre-existing medical condition which may affect exercise participation.

After providing consent to participate within 72 hours of injury, subjects were assigned into the control group (CG), or the RT group (RTG). Allocation to treatment group was via a concealed randomisation process. Randomisation tokens stating allocation to the CG or RTG were placed into sealed, opaque envelopes with an equal allocation ratio. After entry into the study an independent staff member drew an envelope to allocate participants to a

treatment group. Upon allocation, assessment and exercise training for the study commenced immediately in a supervised rehabilitation gym on the burns unit. Those allocated to the CG undertook usual physiotherapy rehabilitation plus sham RT whereas those in the RTG group undertook usual physiotherapy rehabilitation plus progressive RT. Participation in the study exercise programme was for four weeks after enrolment for both groups. Outcome assessment was planned to occur at multidisciplinary review clinics at six weeks, three months and six months after the burn injury.

Control Intervention

Standard physiotherapy for all participants in this study consisted of respiratory care, extensive mobilisation from the day of injury and all exercise other than RT including stretching, active range of movement, balance and postural exercises, as well as the use of the treadmill, stationary bike and upper limb cycle ergometer. Assessment of maximum voluntary isometric contraction (MVIC), as described in the outcome measurement section, was completed for elbow flexion, elbow extension, shoulder abduction, shoulder press, knee extension, leg press and grip strength for three trials on both left and right sides using a hand held Lafayette Muscle Meter no. 01165 (SI Instruments, SA, Australia). The assessment methodology has been described in detail in a prior publication [38]. After testing, sham RT was implemented for the CG, in place of standard physiotherapy, three days per week for four weeks from enrolment. These sessions included bilateral bicep curls, lateral deltoid fly, overhead shoulder press, knee extensions and leg press. Three sets of 10 repetitions of each exercise were completed using 1kg dumb-bells or with minimum resistance set on a cable weighted multi-gym (BodyCraft Xpress Pro, BodyCraft, Ohio). Sham RT sessions were completed under supervision of a physiotherapist or exercise physiologist and in isolation from other burns patients in order to maintain blinding. A verbal pain score using a scale of 0 (no pain) to 10 (most extreme pain) was asked prior to commencing each session to determine baseline pain intensity and 10 minutes after the completion of each session to determine highest pain intensity experienced during training. Patients were asked to inform the supervising therapist if pain exceeded 7/10 during the exercise session and if they wished to cease the session.

Experimental Intervention

Participants in the RTG group also received standard physiotherapy. In addition, a RT programme was undertaken three times per week, utilising continual reassessment of muscle strength to prescribe intensity. The RT sessions were completed in place of standard physiotherapy for that day's treatment. This was continued for a four-week period after enrolment. All intervention sessions related to this study were completed in the burn unit gymnasium in isolation from other rehabilitating patients to maintain participant blinding to group allocation. Exercise sessions were completed with the supervision of a qualified Physiotherapist or Exercise Physiologist. At each session, MVIC was measured in kilograms of force for muscles previously described for the control group. This was followed by a RT

session of bilateral bicep curls, lateral deltoid fly, overhead shoulder press, knee extensions and leg press using both free weights and a cable weighted multi-gym. The intensity of RT exercise was prescribed at 70% of MVIC for that day, thereby titrating the training load to reflect current capacity. The prescription of RT utilised in this study was informed by strength training recommendations from the American College of Sports Medicine Position Stand [29]. This study adapted the definition of high intensity RT for novice exercisers as 70% of one-repetition maximum and volume was prescribed at three sets of 8-12 repetitions for each exercise. A verbal pain intensity score was collected and utilised as described in the *control intervention* section above. Gym-based exercise was stopped for two days for all patients after surgical intervention to repair the burn wounds, as per our burn service protocols.

Outcome Measurement

Comprehensive assessments of QoL, self-report physical disability, muscle strength, body composition and adverse events were completed at clinic reviews planned for six weeks, three months and six months after the occurrence of the burn injury.

Primary Outcome

The primary outcome for this study was patient reported QoL, as assessed by the Burn Specific Health Scale-Brief (BSHS-B) at six months after burn injury. The BSHS-B is a 40-item burn specific assessment of QoL validated for use in both minor and severe burn injuries [27, 39, 40]. The BSHS-B assesses QoL across nine separate domains as well as providing a total score [39]. Subsequent work has shown that the nine BSHS-B domains can be further simplified into three main domains; "*Function", "Affect and Relations"* and *"Skin Involvement",* plus the subscale of *"Work"* [40]. In all cases, a higher score indicates greater QoL. The total score and function domain scores were used for longitudinal analysis in this study. Outcome assessor blinding was achieved for the primary outcome measure as participants were blinded to their group allocation throughout the six-month enrolment period and act as their own assessor in self-report surveys.

Secondary Outcomes

Self-reported disability

Physical disability was assessed using patient-reported surveys. The Quick Disability of Arm, Shoulder and Hand (Quick-DASH) was utilised for participants with burns to the upper limbs and the Lower Limb Functional Index-10 (LLFI-10) for those with burns on the lower limb. These surveys have previously been found to be reliable and valid for use with patients recovering from a burn injury [41, 42]. For both surveys, a low score indicates less disability. Outcome assessor blinding was achieved as participants were blinded to their group allocation and acted as their own assessor when completing these surveys.

Muscle Strength

Muscle strength was measured as an MVIC in kilograms of force by belt stabilised, hand held dynamometry using a previously validated assessment protocol [38, 43]. Pre-selected key muscle groups for upper and lower limbs were biceps, quadriceps and grip strength. These were used for ongoing outcome assessment of muscle strength after the intervention period. To minimise confounding from learning effects, the first effort was discarded and only data from the second and third attempt combined for analysis [38]. Using data from the second and third assessments of MVIC, a mean strength value was generated for combined left and right sided elbow flexion, knee extension and grip strength. These were also combined to create a total single strength measure for each assessment time point. This outcome was assessed by a researcher who was not blinded to group allocation.

Body Composition

A series of estimates of body composition using bioimpedance spectrospcopy (BIS) were also evaluated. Patients were asked to lie supine and electrodes were place on one upper limb and the ipsilateral lower limb as per manufacturer's instructions for a tetra-polar arrangement of electrodes. Whole body BIS measures were taken using the SFB7 (Impedimed ®, Queensland, Australia) in triplicate with one second intervals between measurements. Assessment of BIS was undertaken by non-blinded research personnel. Bioimpedance spectroscopy measures the impedance to an electric current through the body at various frequencies to calculate the fat mass, fat free mass, intracellular water and extracellular water components of body composition. Resistance (R) is the impedance to flow of the electrical current from the intra- and extracellular water [44]. At zero frequency, BIS measures only the extracellular water component (Ro). At high frequency, BIS measures both intra- and extracellular water components (Rinf) [44]. These values are used to determine the intracellular resistance (Ri) using the equation:

(Ri = Rinf – Ro)

Intracellular water volume is represented by Ri and is used in this study as an estimate of muscle cell volume. Low Ri values are representative of higher intracellular volume and for this study is an estimate of greater muscle cell volume. Bioimpedance spectroscopy has been demonstrated to be reliable and valid for measuring compartment volumes in acute burn injury [45, 46]

Length of Stay

All participants entered into the study were inpatients. The impact of RT on length of stay was calculated by a blinded assessor as the number of days each patient was resident in the burns unit for inpatient management.

Feasibility

Resistance training in this study population has many inherent challenges due to the acuity of the burn injury. The feasibility of undertaking RT in an acutely burn injured population

was assessed through an examination of the number of complete and incomplete exercise sessions and for each group.

Adverse Events & Blood Markers of Inflammation and Protein Turnover

Patient reported pain intensity in excess of pre-defined limits for ceasing exercise (a rating of greater than 7/10) and the requirement for more than one surgical procedure were considered adverse events for this study.

C-reactive protein (CRP) was included as a marker of systemic inflammation. A high concentration of CRP is indicative of inflammation [47]. Retinol binding protein (RBP) was included in this study as an indication of nutritional status and protein turnover. It is a high turnover visceral protein which has been noted to be at low concentration during a state of protein depletion and higher concentrations after nutritional correction [48]. The concentration of RBP is expected to decline immediately after trauma reaching a maximal decrease in up to nine days after injury. It is then expected to increase in concentration with recovery [49, 50]. In this study, these markers were included to monitor for adverse events related to progression of the inflammatory response, muscle protein catabolism or nutritional impairment which may be related to the intervention. Blood samples were collected from a subset of 31 participants by venepuncture at admission, weekly during the training period, as well as six weeks, three months and six months after enrolment. The number of participants providing blood samples was limited by funding to undertake the analyses of samples. After centrifugation of the sample, CRP was analysed immediately and serum aliquots were stored at -80^{O}C for batch analysis of RBP by ELISA immunoassay (R&D Systems Inc., Minneapolis, USA).

Sample Size

A sample size calculation was undertaken using the BSHS-B total score. To achieve 90% power to detect a difference of 10.0 with a standard deviation of 16.0 (based on a past WA burn cohort, unpublished data) in the BSHS-B total score with a significance level of 0.05, 30 participants in each group were required with 3 repeat measurements.

Data Analysis

Data analysis was completed using STATA v 14.0 (StataCorp, Chicago, IL). Descriptive statistics were used to describe the demographic and clinical characteristics of the sample, as well as elements of safety and feasibility of the exercise program. Baseline comparison of variables was completed using Wilcoxon Rank Sum and Chi Square tests. An assessment of missing data for both groups at six weeks, three months and six months was completed using descriptive statistics. The number of complete and incomplete RT sessions for each group was used as an assessment of the feasibility of RT in this group. Data analysis was an available cases analysis, all participants' data were analysed based on their group allocation but no missing data were imputed.

The regression analyses used to analyse Qol, disability, muscle strength and body composition were all conducted including the fixed effects for group, time from burn injury (in weeks) and the interaction of these two variables. The interaction term acted as the test of hypothesis for these analyses. Time from burn injury in weeks was included as a continuous variable to account for the variability in timing of follow up assessments between groups. Covariables which displayed $\alpha \leq 0.1$ were included in multivariable regression analysis and the final model was determined using manual backward removal of variables based on magnitude of coefficients and p-values where a significance level of $\alpha \leq 0.05$ was used.

Quality of Life

Due to left skew of BSHS-B data, a dichotomous variable was generated for both the total BSHS-B score and the functional domain score. These dichotomous variables signify whether or not participants had reached a level of recovery equivalent to the upper 95% confidence level of mean scores for Western Australia population data by gender and age [51]. Due to the injury specific nature of the survey, population data was not available to create a dichotomous variable for analysis of the other domains of the BSHS-B. To assess the effect of the intervention on QoL, a logistic regression model with a robust estimator clustered by subject was used. Total burn surface area, age and gender were included as covariables in these regression models.

Secondary Outcome Analysis

All other outcomes assessed in this study were secondary outcomes and should be viewed as exploratory analyses.

Self-reported disability

To assess the effect of treatment on self-reported disability, separate analyses were undertaken for those with upper limb (Quick-DASH) and lower limb burns (LLFI-10). These analyses included all collected questionnaires. Where a participant had both upper and lower limb burns, both surveys were completed and data from these individuals were included in both analyses. Negative binomial mixed effects regression was chosen due to the over-representation of true zero scores, indicating 0% disability, in both surveys. This model treats the scores for the surveys as counts. As such, any scores that fell between two integers were rounded to the nearest whole number to allow for this model to be used. Clinically relevant covariables of age, gender, TBSA and muscle strength were assessed in this regression model. For LLFI-10 only quadriceps muscle strength was included whilst for Quick-DASH the combined biceps and grip strength was used.

Muscle Strength

Strength data was summarised using mean ± SD for both groups. The effect of treatment on muscle strength was assessed using mixed effects linear regression with maximum likelihood estimation for the combined muscle strength value. Muscle strength at time of enrolment (baseline) was included as a covariable to adjust for differences in initial muscle strength values between the two groups. To assess the impact of clinically relevant covariables on the outcome variable, adjustment for gender, age, TBSA and RT history prior to enrolment was undertaken. Similar analysis was undertaken for individual muscle groups; biceps, quadriceps and grip strength with left and right sided values combined.

Body Composition

Triplicate measures of BIS from each assessment were averaged to produce an average Ri value for analysis. Clinically relevant covariables of age, gender and TBSA were assessed using linear regression. Baseline Ri was assessed as a covariable to adjust the model for differences in baseline readings between the groups. Random effects for participants were included in all models.

Length of Stay

Length of stay was compared between groups using ranksum assessment.

Adverse Events & Blood Markers of Inflammation and Protein Turnover

Repeat surgery and the number of sessions in which pain scores exceeded 7/10 were reported by group to investigate safety of the RT intervention. Exploratory analyses of CRP and RBP on a subset of study participants were undertaken. C-reactive protein results were rounded to the nearest whole number to perform a mixed effects negative binomial regression analysis. Retinol binding protein was analysed using a random intercept linear regression model. Clinical and patient factors were included in both analyses as covariables and were removed in a stepwise manner as determined by coefficients and p-values which were considered significant at $\alpha \leq 0.05$ to determine the final model of each. For CPR analysis a (0, 0, 0.5) fractional polynomial transformation of days since burn injury was identified as best describing this mixed data. For RBP analyses, an inverse square root transformation was completed for time since burn injury in weeks due to the non-linear relationship with RBP.

RESULTS

The flow of participants through the study is outlined in Figure 1. During the study recruitment period, 224 patients were screened and 66 patients were approached for recruitment. Fifty participants consented to participate and were allocated to a treatment group. One participant from each group requested to be withdrawn from the study after randomisation at their request to cease participating. Forty-eight participants were therefore included in the final sample for data analysis. All data for the two participants who

requested withdrawal from the study was removed and not included in any analysis. Three participants of the original 48 were lost to all three of these follow up assessments and were not able to be contacted. Data were available for analysis for the primary outcome from 38 participants (79%) at 6 weeks, 35 participants (73%) at 12 weeks and 34 participants (71%) at 26 weeks. For secondary outcomes, the number of participants with available data for analysis differed from the numbers described for the primary outcomes. This was principally related to the inability to collect physical follow up data from patients who chose not attend in person for review and/or chose not to return surveys via post. Demographic and clinical characteristics of both groups are outlined in Table 1. There were no significant baseline differences between groups for any of the measured demographic or clinical variables (Table 1). A descriptive assessment of missing data throughout the study was completed from which there was no indication of significant bias introduced to the study (Supplementary Table 1).

Thirty-eight participants (79%) completed at least seven training sessions (CG n=19, RTG n=19), the equivalent of at least two days of RT per week. Thirty-eight sessions (9.5 % of all sessions) were not completed in their entirety during the study. Ten participants from the CG and nine participants from the RTG group recorded 15 and 23 incomplete sessions respectively for reasons including pain, fatigue, nausea during a session, or, limitations to testing related to dressings and surgical limitations.

Primary Outcome

The observed proportions of participants meeting the pre-defined level of recovery as described in the data analysis section for the BSHS-B are summarised in Table 2. There was no difference in the odds of recovery across time between the RTG and CG group based on the total BSHS-B total score (OR=0.991, p=0.802). In contrast, for every increase of one week, the *Function* domain of the BSHS-B demonstrates a further 20% increase in the odds of recovery in the RTG group, compared with the CG (OR =1.21, p=0.017) (Table 3). Figures 2a & 2b show the predicted probability of recovery for both groups across time.

Secondary Outcomes

Self-reported disability

A summary of functional outcome survey results are shown in Table 4. The rate of change of the LLFI-10 score across weeks was not different between groups (IRR 0.978; 95% CI 0.944 to 1.01; p=0.223) (Table 5). Figure 3a represents these data graphically. For the Quick-DASH, the RTG demonstrated a significantly greater rate of recovery compared to the CG (IRR 0.770; 95% CI 0.670 to 0.886; p<0.001) (Table 5). Upper limb function was dependent on severity of injury in this model, where as expected, higher TBSA was related to greater reported disability (IRR 1.08; 95% CI 1.02 to 1.14; p=0.014). Figure 3b presents data for the Quick-DASH graphically.

Muscle Strength

Average values for muscle strength of the two groups across the study period are shown in Table 6. The rate of change in muscle strength was not significantly different between groups as indicated by the interaction term after adjustment for baseline muscle strength, TBSA and gender (co-eff 0.637; 95% CI -0.111 to 1.38; p=0.095). Muscle strength improved significantly over time for the CG (co-eff 1.25; 95% CI 0.716 to 1.78; p<0.001) and no significant difference in muscle strength between the treatment groups was seen (Table 7). Figure 4 presents these data graphically. A similar effect was seen for individual muscle groups. Biceps, quadriceps and grip strength improved over time, but there was no significant difference between groups. These results can be found in Supplementary Table 2.

Body Composition

There was no difference in the interaction term for the change of Ri over time between the CG and RTG after adjustment for baseline Ri, TBSA and gender (co-eff 3.11; 95% CI -1.83 to 8.07; p=0.217).However, overall Ri did decrease with weeks since the burn injury (co eff -4.18; 95% CI -8.14 to -0.225; p=0.038) (Table 8). Figure 5 represents this graphically.

Length of Stay

Median length of inpatient hospital stay was 13 days (IQR 9-16) for the CG and 12 days (IQR 9-16) for the RTG. The difference in length of stay between groups was not statistically significant (z=0.300, p = 0.764).

Adverse Events & Blood Markers of Inflammation and Protein Turnover

A total of 6 participants (12 %) required repeat surgery to their burn wounds, these were distributed equally between the CG and RTG. Two participants in each group required a total of two surgeries and one participant from each group required three surgeries. Participants rated their highest pain as >7/10 in 57 exercise sessions (15.1% of total sessions: CG=30 sessions, 15 subjects, TBSA 6-27% & RTG=27 sessions, 13 subjects, TBSA 6-40%). Nine of these sessions were ceased at request of the participants due to excessive pain (CG=6 session, RTG=3 sessions).

C-reactive protein increased initially after injury then reduced over time for the study population. After adjustment for TBSA and age, there was a significant interaction for treatment group and days since injury and the RTG tended to have a lower peak and faster reduction in CRP concentration. Figure 6 demonstrates this graphically. The RBP concentration increased for the first two weeks after injury then plateaued for the study population. After adjustment for weeks after burn injury, gender, age and RT history, RBP concentrations were on average higher in the RTG (8.16 μg/mL; 95% CI 3.26, 13.06; P=0.001) (Table 9).

DISCUSSION

This study offers support for the potential benefits associated with the use of early RT as an adjunct to our usual, proactive physiotherapy treatment of acute burn injury. While we found no evidence of a difference between RTG and CG for the total BSHS-B QoL score, there was evidence of a significant difference in the function domain in favour of the RTG. Among the secondary outcomes explored in this study, RT was found to have contributed to improving the rate of recovery of upper limb disability after a burn injury. Exploratory analysis indicated a faster improvement in CRP and RBP concentration for the RTG after adjustment for clinical variables. For other secondary outcomes, we found no evidence that RT offered benefits above those obtained with standard physiotherapy care for lower limb function, a composite measure of muscle strength or body composition. Length of inpatient hospital stay was also the same for both groups. Results from trial monitoring and blood analysis indicate that a RT intervention at this acute phase of injury is both a safe and feasible option for this clinical group.

There is plausibility in our findings for QoL in this study as the BSHS-B survey assesses items which are unrelated to physical function and contribute to the total BSHS-B score. These are unlikely to be impacted by RT. Conversely, the survey items related to functional status could conceivably be influenced by RT. Paratz et al. [52] have previously reported improvements in all 4 main domains of the Burn Specific Health Score-Abbreviated (BSHS-A) for their exercise group in comparison to self-management. The BSHS-A is a predecessor version of the Burn Specific Health Scale survey, from which the BSHS-B has been developed in order to improve the clinical use of the Scale to measure QoL after a burn injury. The differences between this study and our results reported here could conceivably stem from differences in the control treatments of the two studies, non-randomised group assignment in the Paratz et al. [52] study, the duration of intervention applied, the difference in acuity of the patient groups and the different QoL assessment tool used.

In the present study, the RTG demonstrated significantly greater recovery of upper limb function compared to the CG. This result is in keeping with Quick-DASH results from a previous non-randomised clinical trial [52] and provides further evidence that RT could form an important aspect of optimal upper limb rehabilitation after a burn injury. However, our study found no evidence of an additional benefit of early RT for lower limb physical function. This result is in contrast to previous work [52] where lower limb function was assessed with a different outcome tool, the Lower Extremity Functional Scale (LEFS) [52], and, as previously mentioned there are numerous clinical and methodological differences between this study and ours. A lack of apparent statistical association between functional ability and muscle strength in this study may relate to the variation of muscle strength in comparison to the very small variation of scores for the LLFI-10 and QuickDASH. Another consideration for this finding is whether lower limb RT exercises offered a training stimulus greater than what was received through standard care alone. Our facility practices a philosophy of early ambulation for all patients as a standard of care. This includes extensive

mobilisation commenced from the day of hospital admission and again within 48 hours after surgery, as well as the use of stairs, stationary bikes and body weight lower limb exercises. It is possible that early RT in the acute injury phase does not provide a substantially greater training load for the lower limbs beyond that gained from this approach.

Our data did not find evidence that the addition of four weeks of RT to standard care leads to an increase in muscle strength or cellular volume greater than that seen in usual care alone. Training in the sub-acute and long term rehabilitation phases of injury have previously shown a benefit for muscle strength in adults where training duration was six weeks or more [2, 52]. Again, the clinical and methodological differences between these studies and ours should be considered when comparing results. A longer duration of RT may be required throughout and beyond the acute injury phase for an ongoing difference in muscle strength and volume to be realised. However, in an adult population, it must be considered that a longer rehabilitation period may be unfeasible due to the demands of returning to work and other social or financial responsibilities which may take priority upon discharge from hospital.

Resistance exercise in this clinical group might have wider implications for patient health as participation in RT was linked to a reduced peak and faster improvement in an inflammation biomarker (CRP). This suggests an anti-inflammatory action from RT after burn injury, though this finding would benefit from further investigation. Exercise and physical activity are established as having an anti-inflammatory effect, particularly when undertaken on a regular basis [53]. A previous systematic literature review and meta-analysis has documented improvements in CRP following exercise training in clinical and non-clinical groups [54]. This review concluded that exercise resulted in small but significant reductions in CRP [54], offering support for the reduction of CRP concentration seen in the RT group in this study.

The RT programme assessed in our study was informed by guidelines for healthy adults as there are no prior guidelines for RT in burn injured adults. In uninjured populations, significant increases in muscle strength [55-59] have been demonstrated to occur within four weeks of the commencement of a RT program. There is also some evidence to support increases of muscle thickness in that same period of time [56, 60]. These studies supported our choice of implementing a four week exercise training protocol in burn injured patients. Further, the duration of RT was deemed to be feasible in the WA context as patients are likely to be still receiving care from the burns service during this time. The shorter training duration assessed in this study would improve the generalisability of RT prescription, as access to ongoing long-term treatment may not be feasible in many services.

Implications in Practice

This study has presented evidence supporting a number of benefits from participation in a novel four week RT program commenced immediately after a burn injury. It is the first study to assess the effect of a RT program in acute burn injury and the four week training duration is shorter than programs previously delivered in burn injured populations, which range from 6 to 12 weeks [2, 7, 52, 61-72]. The beneficial results, safety and feasibility described in this study highlight that early RT is a suitable rehabilitation practice for patients with an acute burn injury.

Assurances about the safety of RT in such an acute population are important. The addition of a high intensity RT programme to our standard of care, early mobilisation approach was not of detriment to our study group. In fact, there is evidence of improvement in outcomes from participation in prescribed, early RT. We detected no negative effects on QoL, disability, muscle strength or muscle volume related to participation in early RT. Additionally, RT was not seen to impair protein turnover or nutrition status as assessed by RBP concentrations. It is also unlikely that RT was the primary cause of requiring more than one operative procedure given the equal distribution of these cases across both groups. Our data suggests that the majority of patients voluntarily continued to exercise beyond a recommended stopping point of greater than 7/10 pain intensity. Eighty percent of the sample completed at least seven exercise sessions, or, the equivalent of two training days per week, a frequency which is supported by the literature to provide benefit from RT [29, 73]. Additionally, there was a similar number of discontinued or incomplete RT sessions recorded across both groups in this study indicating that RT is a practical rehabilitation mode in acute burn injury.

The use of hand held muscle dynamometry (HHD) to assist in the prescription of training load was another novel concept used in this study. We have validated the use of HHD as a method to assess muscle strength outcome in burn injuries [38, 43] and it has been shown to be able to accurately predict the reference standard assessment of one-repetition maximum of chosen muscle groups [74]. This study demonstrates the first standardised method for HHD being used in the prescription of RT load in burn injured patients. It was found to be a time-efficient method of assessment and prescription. Given the relatively low cost of the equipment used, particularly in comparison to tools such as isokinetic dynamometry, it is also likely a cost–effective assessment tool. Having a time and cost effective method of assessing muscle strength enabled us to optimise training load on a daily basis, an important consideration in the acute care setting where large fluctuations in capacity are common.

Limitations

The findings presented here need to be interpreted with the study limitations in mind. This study was closed earlier than anticipated, as a result the number of subjects enrolled did not meet the pre-planned recruitment target. However, in its current form this study is the

largest exercise trial conducted with an adult burn injured population. Larger studies, ideally from multiple centres would be required to improve the precision of the inferences drawn from the trends shown in the current study. Other limitations of this study relate to the introduction of performance, detection and attrition bias.

Therapists were not blinded to group allocation, so the results presented here may be subject to some performance bias. The secondary outcomes of muscle strength and body composition were collected by a non-blinded assessor so may be confounded by detection bias, though as we found no between group difference in muscle strength or body composition, this is unlikely to change the interpretation of the results. There is some evidence of attrition bias in the current study. For the primary outcome, data was available from approximately 80% of participants at the 6 week review and approximately 70% of participants by the 6 month review. Missing data was accounted for by the use of repeated measures and statistical analyses which were robust to missingness, including the use of regression models utilising maximum likelihood estimation. However, this study does contain a number of methodological strengths. Allocation was random and concealed and the baseline equivalence suggests randomisation was successful in controlling for selection bias. Participants were blinded to group allocation and all assessments and treatment occurred in isolation to help maintain blinding for the duration of the study. Also, assessors were blinded for the primary outcome measure and available cases were analysed in the group they were originally assigned.

It is acknowledged that grip strength was used as part of the muscle strength outcome measurement, yet exercises which directly trained grip strength were not included in the training protocol. Grip strength can be used as a surrogate measure of global muscle strength in healthy people and hospitalised patients [75-77] and was included in this study as such. Future studies may consider including grip specific exercises into their protocol. In the present study, we assessed and trained muscle groups as described in the methods section, however long term outcome was based on select, sentinel muscle groups for the upper limb and lower limb. This was done as a way of obtaining quality long term muscle strength data, whilst also reducing the assessment burden on participants who were required to undergo multidisciplinary reviews during these follow up visits to the service. It may be that a different mode of muscle strength assessment would return different results to those reported here.

We were not able to limit fluid intake during exercise or assess the hydration status of participants prior to measurement of body composition using BIS. We appreciate that this is a factor which may influence the calculated values provided by the BIS device. To manage this, we utilised and analysed only the raw BIS values which will improve the interpretability of the data and the validity for comparisons within an individual.

Future Research

Multi-centre research projects are essential to increase the precision of estimates of treatment effects and generalisability of findings in this group of patients. To ascertain the precision of MVIC to be able to prescribe dynamic RT, further patient group specific investigation may be warranted. Investigation of exercise rehabilitation during the acute injury period should continue to explore different dosages of exercise training as rehabilitation during this important time period has previously been untested. Short duration training programs would be recommended to improve the practicality of research, particularly in adult populations who have social and financial responsibilities to attend to as soon as possible after a burn injury. However, further data is required to fully assess the efficacy of short duration training programs. Understanding the physical and psychological outcomes of exercise training across the continuum of burn injury recovery will enable treating teams to be able to provide best practice rehabilitation and provide the best opportunities for optimal recovery. All future rehabilitation research must be undertaken with robust methodology, adequate sample size and accurate reporting which are vital to continue to improve the quality of rehabilitation data available in this patient group.

CONCLUSION

Progressive RT in addition to usual physical rehabilitation appears both safe and feasible in the acute phase post burn injury. There is evidence that progressive RT leads to improvements in QoL and disability in this population, though this is primarily apparent in patients with upper limb burns. There is no evidence of harm to patients participating in an early RT programme after a burn injury.

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CONFLISTS OF INTEREST

No conflicts of interest to declare.

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Table 1: Sample Descriptive Statistics.

	CG[1]	RTG[2]	Test Statistic	p-value
Number of Participants	25	23		
Age (years) [median (IQR)]	33 (24 – 43)	30 (25 – 33)	z = 0.981	0.327
Gender [n (%)]			Chi^2= 0.012	0.913
	22 (88%)	20 (87%)		
• **Male**	3 (12%)	3 (13%)		
• **Female**				
RT[3] History [n (%)]			Chi^2 =0.763	0.382
	18 (72%)	19 (83%)		
• **No**	7 (18%)	4 (17%)		
• **Yes**				
Total Burn Surface Area [Median (IQR)]	14 (9 – 20) %	12 (10 – 20) %	z = 0.289	0.772
Number of Surgeries [n (%)]			Chi^2 = 1.14	0.768
	0 (0%)	1 (4%)		
• **0**	22 (88%)	19 (83%)		
• **1**	2 (8%)	2 (9%)		
• **2**	1 (4%)	1 (4%)		
• **3**				
Surgery Type [n (%)]			Chi^2 = 5.23	0.156
	0 (0%)	1 (4%)		
• **Nil**	10 (40%)	3 (13%)		
• **ReCell Only**	13 (52%)	17 (74%)		
• **SSG[4] & ReCell**	2 (8%)	2 (9%)		
• **SSG Only**				
Location of Burn [n (% of group)]				
	19 (76%)	17 (74%)	Chi^2 = 0.028	0.868
• **Arm Burn**	20 (80%)	19 (82%)	Chi^2 = 0.054	0.817
• **Leg Burn**	15 (60%)	15 (65%)	Chi^2 = 0.139	0.709
• **Hand Burn**				

[1] Control group
[2] Resistance training group
[3] Resistance Training
[4] Split Skin Graft

Table 2: Observed proportions of participants categorized as below or above the upper 95%CI for population normal scores on the Burns Specific Health Scale-Brief (BSHS-B) total scores and function domain scores at each follow up assessment [n (%)]. Range of weeks of assessment after burn injury included.

	BSHS-B Function CG[1]	**BSHS-B Function RTG[2]**	**BSHS-B Total CG**	**BSHS-B Total RTG**
6 week review				
Below	10 (53%)	14 (74%)	16 (84%)	17 (89%)
Above	9 (47%)	5 (26%)	3 (16%)	2 (11%)
n	19	19	19	19
Week of review (min, max)	5.57, 11.7	4.86, 9.57	5.57, 11.7	4.86, 9.57
12 week review				
Below	7 (41%)	6 (33%)	14 (82%)	12 (67%)
Above	10 (59%)	12 (67%)	3 (18%)	6 (33%)
n	17	18	17	18
Week of review (min, max)	11.4, 19.5	10.4, 19.7	11.4, 19.5	10.4, 19.7
26 week review				
Below	5 (31%)	1 (5%)	9 (56%)	11 (61%)
Above	11 (69%)	17 (95%)	7 (44%)	7 (39%)
N	16	18	16	18
Week of review (min, max)	23.4, 38.7	22.3, 40.7	23.4, 38.7	22.3, 40.7

[1] Control Group
[2] Resistance Training Group

Table 3: Final logistic regression model for the Burn Specific Health Scale-Brief (BSHS-B) total score and function domain. No adjustment for total score. Adjustment for TBSA for the function domain (n=43, obs=107).

BSHS-B	**Variable**	**Odds Ratio**	**95% CI**	**p-value**
Total Score	Group#Weeks	0.991	0.926, 1.06	0.802
	Group (RTG[1])	1.28	0.228, 7.21	0.778
	Weeks	1.05	0.989, 1.11	0.106
Function Domain	**Group#Weeks**	**1.21**	**1.03, 1.41**	**0.017***
	Group (RTG)	**0.107**	**0.017, 0.656**	**0.016***
	Weeks	**1.05**	**1.01, 1.11**	**0.038***
	TBSA[2]	**0.893**	**0.815, 0.978**	**0.015***

*p <0.025
[1] Resistance training group
[2] Total Burn Surface Area

Table 4: Summary of group scores for functional assessments Lower Limb Functional Index-10 (LLFI) & Quick Disability of Arm Shoulder and Hand (QDASH) [median (IQR)]

	Control Group		**RT Group**	
	n	**Median (IQR)**	**n**	**Median (IQR)**
LLFI Domain 1 – Baseline	18	0.0 (0.0 – 0.0)	15	0.0 (0.0 – 0.0)
LLFI Domain 1 – 6 week	17	1.5 (0.0 – 3.0)	12	2.5 (1.5 – 4.5)
LLFI Domain 1 – 12 week	15	0.5 (0.0 – 2.5)	14	0.75 (0.5 – 3.0)
LLFI Domain 1 – 26 week	14	1.0 (0.0 – 2.0)	13	0.5 (0.0 – 2.0)
QDASH General – Baseline	18	0.0 (0.0 – 2.27)	14	0.0 (0.0 – 0.0)
QDASH General – 6 week	17	18.18 (9.09 – 25.0)	13	18.18 (9.09 – 22.73)
QDASH General – 12 week	15	6.82 (0.0 – 20.45)	10	2.27 (0.0 – 2.27)
QDASH General – 26 week	14	0.0 (0.0 – 9.09)	10	0.0 (0.0 – 0.0)

Table 5: Final negative binomial regression models for Lower Limb Functional Index-10 scores (n=33, obs=86) & Quick Disabilities of Arm Shoulder and Hand scores with adjustment for TBSA (n=80 observations, 32 groups).

	Variable	***IRR*[1]**	***95% CI***	***p-value***
LLFI-10	Group # Weeks (RTG[2])	0.978	0.944, 1.01	0.223
	Group (RTG)	1.76	0.782, 3.95	0.172
	Weeks	0.979	0.956, 1.00	0.093
Quick-DASH	**Group # Weeks (RTG)**	**0.770**	**0.670, 0.886**	**<0.001***
	Group (RTG)	**7.91**	**1.65, 37.9**	**0.010***
	Weeks	**0.931**	**0.899, 0.964**	**<0.001***
	TBSA[2]	**1.08**	**1.01, 1.14**	**0.014***

* p<0.05

[1] Incident Rate Ratio

[2] Resistance training group

[3] Total Burn Surface Area

Table 6: Observed total combined muscle strength for average scores of left and right sided elbow flexion, knee extension and grip strength in kilograms, by group allocation [mean (SD)]. Range of actual week of assessment after burn injury included.

	Control Group	**n**	**Weeks**	**Resistance Training Group**	**n**	**Weeks**
Baseline	185.6 (51.9)	25	0.142, 0.571	172.6 (54.5)	23	0.142, 0.857
6 Week Assessment	194.1 (46.3)	23	5.57, 8.71	195.9 (48.4)	16	4.86, 9.57
12 Week Assessment	195.1 (45.3)	16	11.4, 15.8	211.8 (41.2)	15	10.4, 17.4
26 Week Assessment	204.5 (39.0)	17	23.4, 40.3	219.3 (53.1)	16	22.3, 40.7

Table 7: Final multivariable mixed effects linear regression model for combined muscle strength adjusted for gender, TBSA & baseline muscle strength.

Muscle Strength	*Variable*	*β Co-eff*	*95% CI*	*p-value*
Combined (n=48)	Group # Weeks (RTG[1])	0.637	-0.111, 1.384	0.095
	Group (RTG)	-13.4	-27.7, 0.834	0.065
	Weeks	**1.25**	**0.716, 1.786**	**<0.001***
	Baseline muscle strength	**0.320**	**0.140, 0.499**	**<0.001***
	Gender (Female)	**-47.1**	**-76.0, -18.2**	**0.001***
	TBSA[2]	**-1.90**	**-2.88, -0.927**	**<0.001***

* p <0.05
[1] Resistance training group
[2] Total Burn Surface Area

Table 8: Final multivariable mixed effects linear regression model for average Ri (avri) adjusted for gender, TBSA & baseline avri (n=29, obs=58)

Variable	*β Co-eff*	*95% CI*	*p-value*
Group # Weeks (RTG)	3.12	-1.83, 8.07	0.217
Group (RTG)	-0.548	-117.8, 116.7	0.993
Weeks	**-4.18**	**-8.14, -0.225**	**0.038***
Baseline avri	**0.407**	**0.256, 0.558**	**<0.001***
Gender (Female)	**176.4**	**33.5, 319.4**	**0.016***
TBSA[2]	**22.4**	**14.8, 30.0**	**<0.001***

* p <0.05
[1] Resistance training group
[2] Total Burn Surface Area

Table 9: Final mixed effects linear regression model for Retinol Binding Protein. Adjusted for age, RT History, sex and time from burn injury (inverse square transformation).

	Abs diff mean RBP[1]	**95% CI**	**p-value**
Group (CG[2])	**8.16**	**3.26, 13.06**	**0.001***
Age	**0.42**	**0.15, 0.69**	**0.003***
RT[3] history	**12.85**	**5.96, 19.75**	**<0.001***
Sex (male)	**-9.01**	**-17.33, -0.69**	**0.034***
Weeks since injury[4]	**-126.12**	**-149.66, -102.57**	**<0.001***

[1] Absolute mean difference for Retinol Binding Protein
[2] Control group
[3] Resistance training
[4] Inverse square transformation of weeks since burn injury
* p<0.05

Supplementary Table 1: Comparison of key baseline variables between those that were and weren't available at each time point, by group.

	6 Week				12 Week				26 Week			
	CG[1]		RTG[2]		CG		RTG		CG		RTG	
	Avail*	Miss[#]	Avail	Miss	Avail	Miss	Avail	Miss	Avail	Miss	Avail	Miss
Baseline Mean Combined Strength	171.4 (n=22)	238.6 (n=3)	169.9 (n=19)	185.0 (n=4)	176.4 (n=18)	187.4 (n=7)	171.3 (n=18)	177.2 (n=5)	171.3 (n=17)	196.9 (n=8)	173.5 (n=19)	168.4 (n=4)
TBSA[1] (median)	13.5 (n=22)	20.0 (n=3)	12.0 (n=19)	14.8 (n=4)	13.5 (n=18)	20.0 (n=7)	12.0 (n=18)	16.0 (n=5)	14.0 (n=17)	14.0 (n=8)	12.0 (n=19)	15.5 (n=4)
Age (median)	34.0 (n=22)	24.0 (n=3)	30.0 (n=19)	27.0 (n=4)	37.5 (n=18)	23.0 (n=7)	29.0 (n=18)	32.0 (n=5)	36.0 (n=17)	25.5 (n=8)	28.0 (n=19)	35.0 (n=4)
LOS[2] (median)	12.5 (n=22)	15.0 (n=3)	11.0 (n=19)	14.0 (n=4)	12.5 (n=18)	15.0 (n=7)	11.5 (n=18)	12.0 (n=5)	13.0 (n=17)	13.0 (n=8)	11.0 (n=19)	13.0 (n=4)
Number RT Sessions (median)	9 (n=22)	8 (n=3)	10 (n=19)	5.5 (n=4)	9.0 (n=18)	6.0 (n=7)	10.0 (n=18)	6.0 (n=5)	9.0 (n=17)	6.0 (n=8)	10.0 (n=19)	6.5 (n=4)
Gender Male	86.4% (n=19)	100% (n=3)	89.5% (n=17)	75.0% (n=3)	83.3% (n=15)	100% (n=7)	88.9% (n=16)	80.0% (n=4)	82.4% (n=14)	100% (n=8)	89.5% (n=17)	75.0% (n=3)
No prior RT History	68.2% (n=15)	100% (n=3)	84.2% (n=16)	75% (n=3)	72.2% (n=13)	71.4 (n=5)	77.8% (n=14)	100% (n=5)	70.5% (n=12)	75.0% (n=6)	79.0% (n=15)	100% (n=4)

* Available cases at follow up time point

[#] Missing cases at follow up time point

[1] Control group

[2] Resistance training group

[3] Total burn surface area

[4] Length of inpatient hospital stay

Supplementary Table 2: Final multivariable mixed effects linear regression model for biceps, quadriceps, grip muscle strengths adjusted for gender, TBSA & baseline muscle strength.

Muscle Strength	***Variable***	***β Co-eff***	***95% CI***	***p-value***
Biceps (n=48)	Group # Weeks (RTG[1])	0.078	-0.116, 0.272	0.431
	Group (RTG)	-3.19	-7.44, 7.05	0.140
	Weeks	**0.512**	**0.371, 0.654**	**<0.001***
	Baseline muscle strength	**0.647**	**0.495, 0.799**	**<0.001***
	TBSA[2]	**-0.600**	**-0.899, -0.302**	**<0.001***
Quadriceps (n=46)	Group # Weeks (RTG[1])	0.202	-0.149, 0.554	0.259
	Group (RTG)	-6.99	-14.6, 0.609	0.071
	Weeks	**0.496**	**0.237, 0.756**	**<0.001***
	Baseline muscle strength	**0.399**	**0.194, 0.604**	**<0.001***
	TBSA[2]	**-0.605**	**-1.12, -0.085**	**0.022***
Grip (n=47)	Group # Weeks (RTG[1])	-0.078	-0.373, 0.217	0.605
	Group (RTG)	2.02	-3.10, 7.14	0.440
	Weeks	**0.576**	**0.365, 0.786**	**<0.001***
	Baseline muscle strength	**0.664**	**0.559, 0.769**	**<0.001***

* $p < 0.05$

[1] Resistance training group

[2] Total Burn Surface Area

Figure 1: Flow of participants through the study

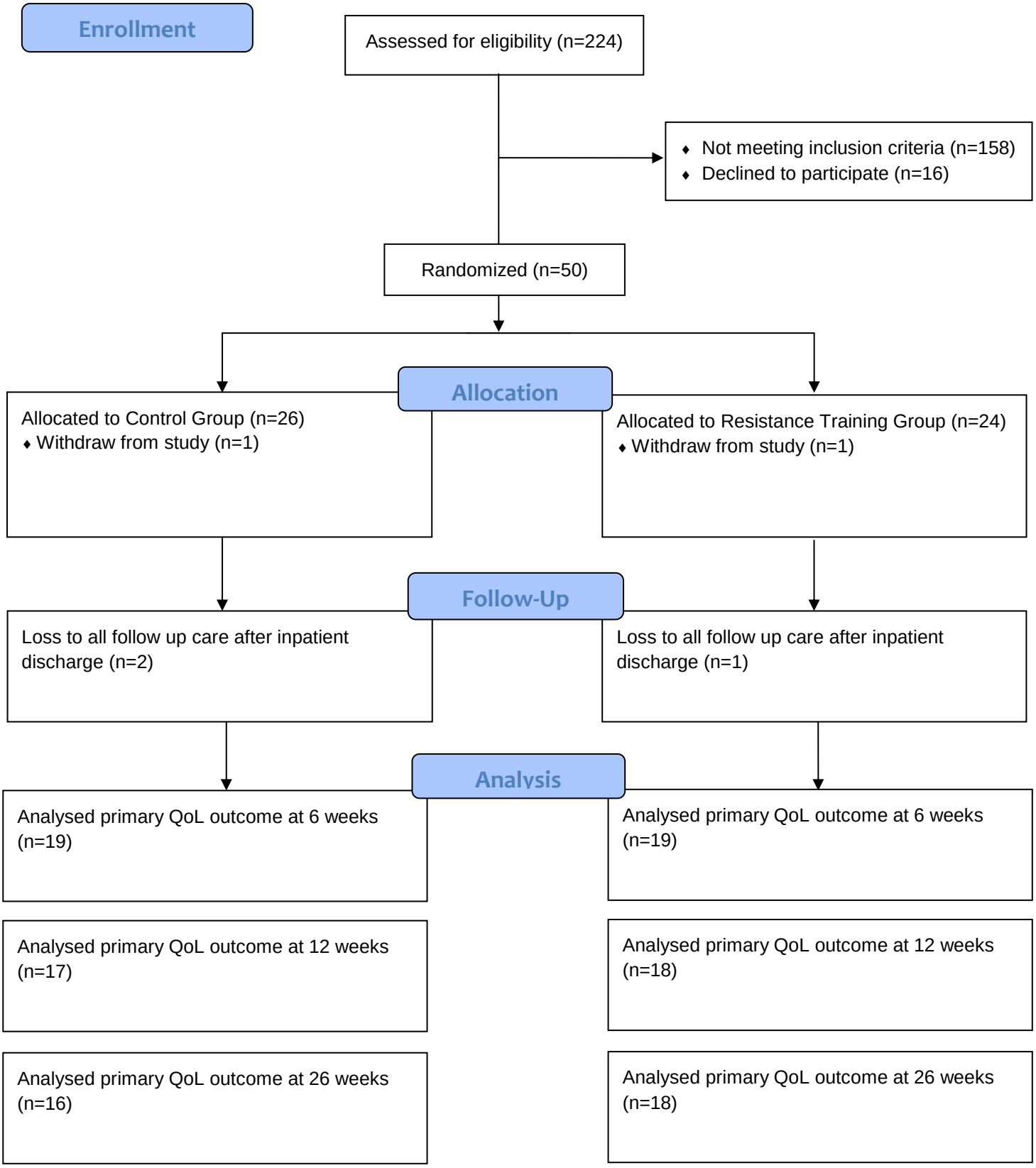

Figure 2: Predicted probabilities of achieving recovery at 6 weeks, 12 weeks & 26 weeks after burn injury on the total score of the Burn Specific Health Scale with no covariable adjustment (Figure 2a), and the function domain score of the Burn Specific Health Scale Brief with adjustment for TBSA (Figure 2b).

Figure 2a

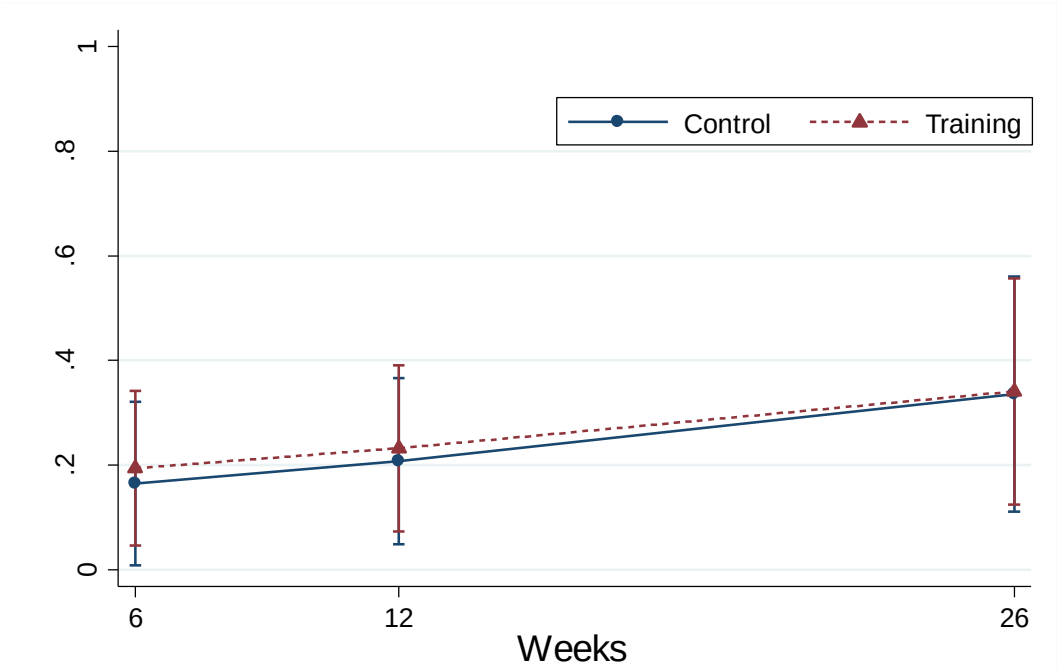

Figure 2b

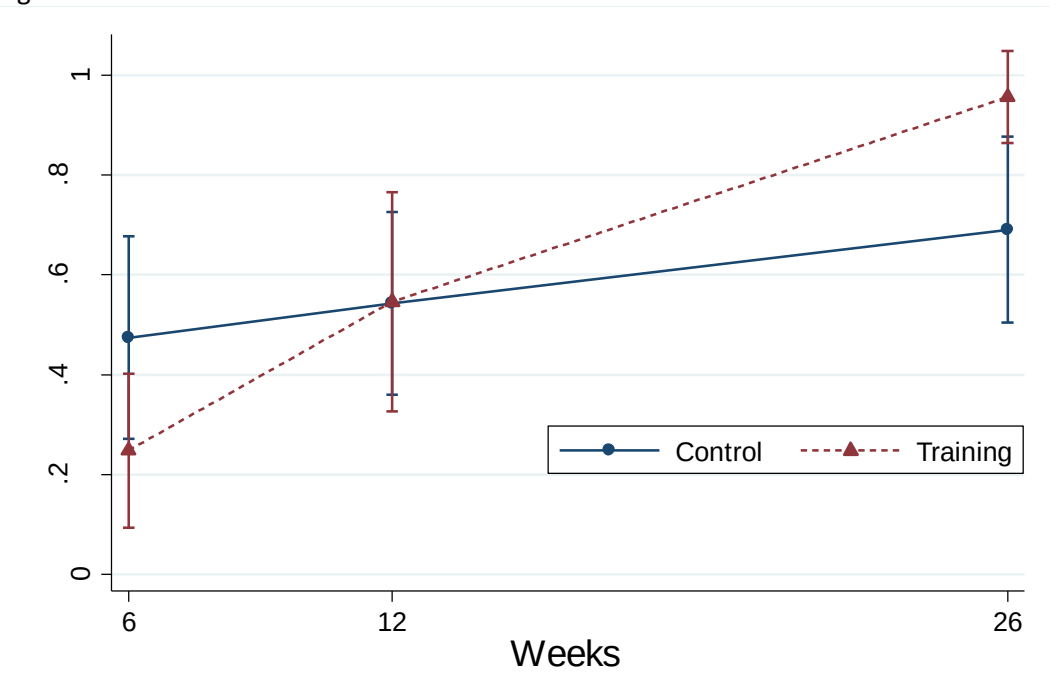

Figure 3: Predicted Lower Limb Functional Index-10 (LLFI-10) scores at 6 weeks, 12 weeks & 26 weeks after burn injury, no covariate adjustment (Figure 3a). Predicted Quick Disability of Arm, Shoulder and Hand survey (Quick-DASH) scores at 6 weeks, 12 weeks & 26 weeks after burn injury, adjusted for TBSA (Figure 3b).

Figure 3a

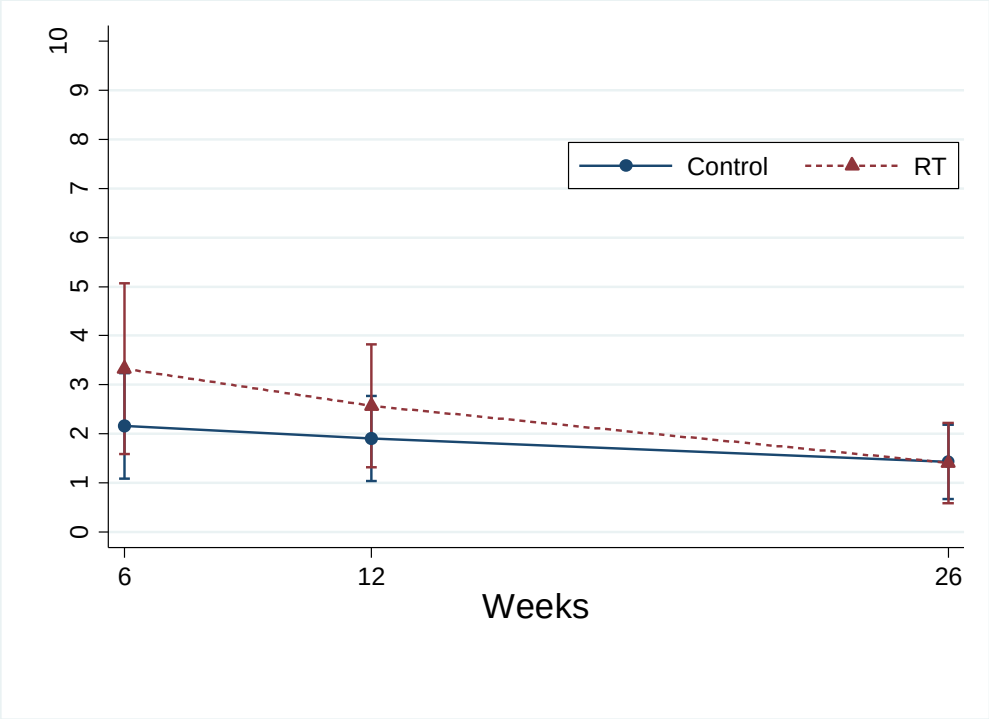

Figure 3b

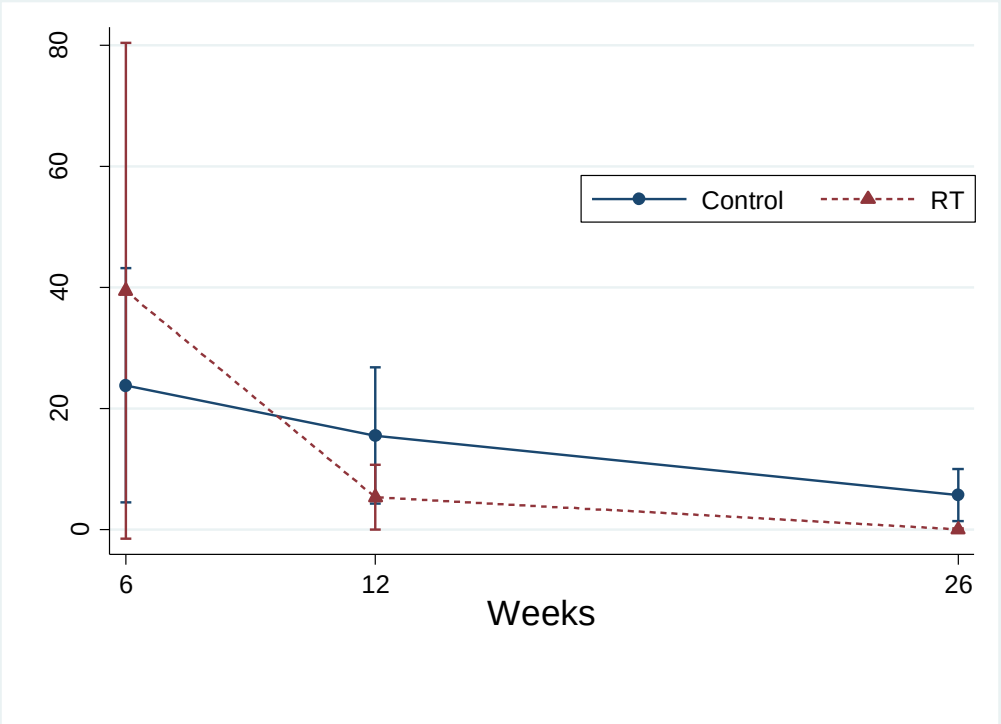

Figure 4: Average combined mean muscle strength at 6 week, 12 week & 26 weeks after burn injury adjusted for gender, TBSA & baseline muscle strength.

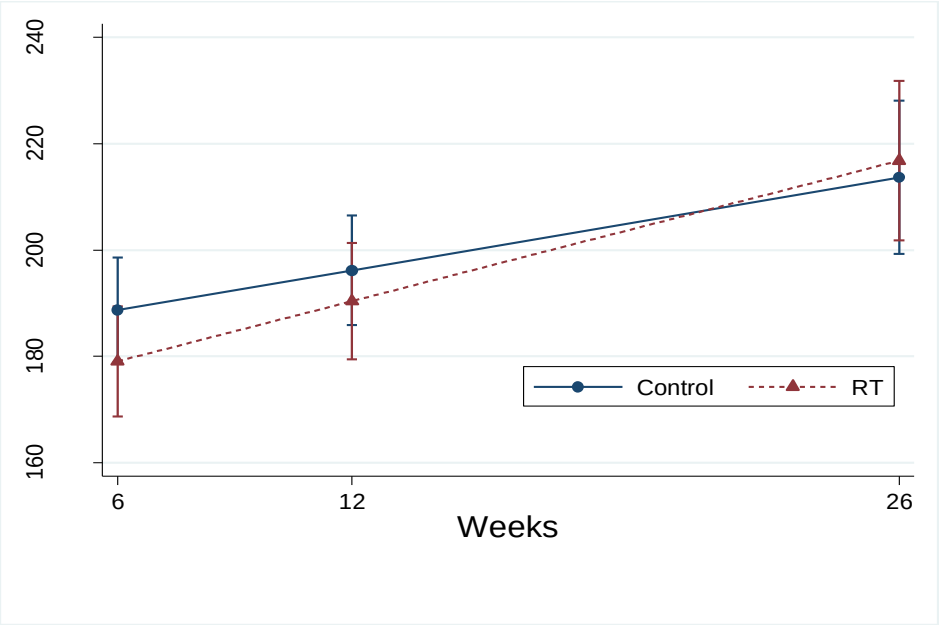

Figure 5: Bioimpedance spectroscopy scatter plot for CG & RT groups with fitted predicted mean line.

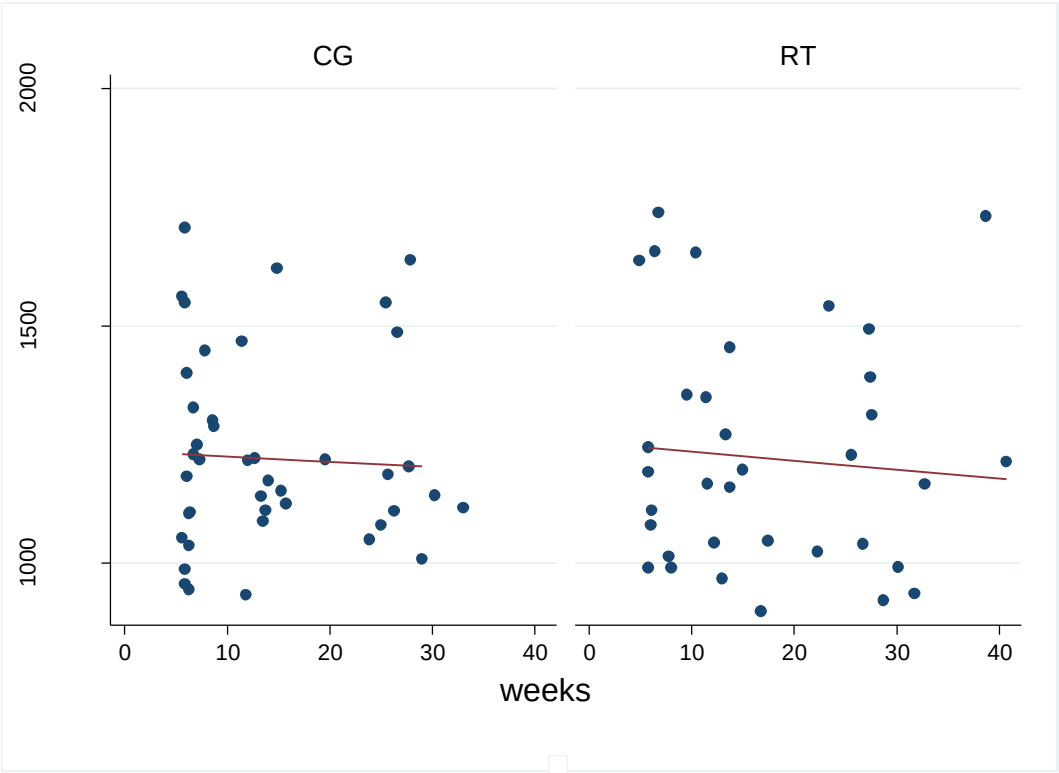

Figure 6: Predicted mean C-Reactive Protein over time. Shaded areas represent 95% CI's for the treatment groups predicted curve.