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Feasibility of Exercise Training in Cancer Patients Scheduled for Elective Gastrointestinal Surgery

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Key Words
Preoperative exercise · Prehabilitation · Oncological surgery

Abstract
Background/Aims: This study examines the feasibility of a preoperative exercise program to improve the physical fitness of a patient before gastrointestinal surgery. ***Methods:*** An outpatient exercise program was developed to increase preoperative aerobic capacity, peripheral muscle endurance and respiratory muscle function in patients with pancreatic, liver, intestinal, gastric or esophageal cancer. During a consult at the outpatient clinic, patients were invited to participate in the exercise program when their surgery was not scheduled within 2 weeks. ***Results:*** The 115 participants followed on average 5.7 (3.5) training sessions. Adherence to the exercise program was high: 82% of the planned training sessions were attended, and no adverse events occurred. Mixed model analyses showed a significant increase of maximal inspiratory muscle strength (84.1–104.7 cm H_2O; p = 0.00) and inspiratory muscle endurance (35.0–39.5 cm H_2O; p = 0.00). No significant changes were found in aerobic capacity and peripheral muscle strength. ***Conclusion:*** This exercise program in patients awaiting oncological surgery is feasible in terms of participation and adherence. Inspiratory muscle function improved significantly as a result of inspiratory muscle training. The exercise program however failed to result in improved aerobic capacity and peripheral muscle strength, probably due to the limited number of training sessions as a result of the restricted time interval between screening and surgery.

Introduction

Surgical resection is the cornerstone of the curative treatment for gastrointestinal malignancies. Although postoperative outcomes have improved during the last decades as a result of the implementation of clinical pathways and improved surgical and anaesthesia techniques, there is still a substantial risk of postoperative complications. Besides the type of surgery, this risk is mainly determined by the preoperative status of the patient. In addition to age and comorbidities, several studies identify preoperative functional performance as an important predictor of postoperative outcome [1–4]. Functional limitations and inadequate activity levels are associated

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with worse postoperative outcomes, and this highlights the importance of good preoperative physical fitness of patients awaiting a major invasive operation like gastrointestinal surgery [1–5].

To decrease the risk of unwanted postoperative outcomes, optimising the health status of a patient before (oncological) surgery is increasingly regarded as an important part of the preoperative treatment process [6–9]. Optimising functional performance by an exercise program before a major invasive surgical procedure is called prehabilitation. Improved preoperative physical performance and health status may put a patient in a more favourable position to withstand the surgical stress [10–13].

Inspiratory muscle training (IMT) is an example of a prehabilitation modality. IMT improves ventilatory capacity by increasing inspiratory (mainly diaphragm) muscle strength and endurance, which may prevent the imbalance between ventilatory demand and ventilatory capacity provoked by surgery [14]. IMT should not be confused with incentive spirometry and has shown to decrease postoperative pulmonary complications in several studies and is therefore regarded as a promising prehabilitation intervention [15–18]. Research on prehabilitation programs aimed at improving the overall exercise capacity and muscle strength before surgery is less common. Only a few pilot studies have investigated the effect of an exercise program before oncological surgery [9, 19]. For this reason, a preoperative exercise program was designed to improve the physical status of patients scheduled for gastrointestinal oncological surgery. This study examined the feasibility of this exercise program and its effectiveness on improving physical fitness.

Materials and Methods

Participants and Study Design

The exercise program was designed for patients diagnosed with pancreatic, liver, intestinal, gastric or esophageal cancer who were scheduled for oncological surgery at the University Medical Center Utrecht. All patients were planned for surgery with curative intent, and the patients with gastric or esophageal cancer received perioperative chemotherapy treatment [20]. When the indication for surgery was given, patients were seen by a nurse practitioner at the outpatient clinic where they were educated about optimizing preoperative physical status regarding postoperative recovery. When the surgery was not scheduled within 2 weeks, patients were invited to undergo health status measurements and were asked to participate in the supervised outpatient exercise program. Patients who agreed to participate in the exercise program started the exercise program preferably within one week of consultation with the nurse practitioner.

Exercise Program

The participants of the exercise program followed 2 group training sessions a week at the outpatient clinic under supervision of a physiotherapist. The aim of the preoperative exercise program was to increase aerobic capacity, peripheral muscle endurance and respiratory muscle function. One training session consisted of 2 sessions of 20–30 min each on a stationary bike, a cross trainer or a row-ergometer. Training intensity was set at 60–85% of the maximal heart rate reserve calculated with the formula of Karvonen et al. [21]. To increase peripheral muscle endurance, the physical rehabilitation training (PRT) systems method was used [22]. The PRT method consists of 7 systems (A–F) in which the training load is the lowest in system A (aerobic endurance training) and the highest in system F (maximal strength training). Resistance training started with PRT-system B (3 series of 20–25 repetitions, 60–90 s rest in between) followed by the PRT-system C (3 series of 13–20 repetitions, 90–120 s rest between series). Both systems are aimed at improving aerobic muscle endurance. The exercises consisted of leg press, bench press, lateral pull down, back extension and abdominal flexion exercises.

Alongside the exercise program, participants were instructed to start IMT at home to improve inspiratory muscle function. IMT is performed with an inspiratory muscle trainer (Threshold IMT, Respironics New Jersey, USA), which increases the inspiratory load. The load of this device (range 9–41 cm H_2O) can be adjusted manually. Patients had to breathe in and out through the inspiratory muscle trainer for 20 min daily starting at an inspiratory resistance of 30% of their maximal inspiratory pressure (MIP) [16]. When the rate of the perceived exertion after a training session was below 5 (range 0–10), patients increased the training load by 5% [16]. Participants were instructed to report their training parameters in a daily training log. IMT progress was evaluated weekly during one of the training sessions by the physiotherapist by assessing inspiratory muscle function. Furthermore, training load was adjusted when indicated. Additionally, participants were advised to perform 30 min of moderately intensive physical activities at least at 5 days a week according to the WHO and Dutch Health Enhancing Physical Activity guidelines [23].

Health Status Measurements

Demographic and anthropometric variables that were collected at baseline included age, gender, weight, height, tumor location, type of surgery and ASA (American Society of Anesthesiologists) classification [24]. During the consultation with the nurse practitioner, all patients (participants and non-participants) were asked to undergo several non-invasive baseline measurements to assess contraindications for training, fatigue, quality of life (QoL), aerobic capacity, peripheral muscle strength and respiratory muscle function. For the participants of the exercise program, aerobic capacity, peripheral and respiratory muscle function follow-up measurements were planned weekly during one of the group training sessions.

Physical Activity Readiness, Fatigue and QoL

To identify patients for whom physical training might be contraindicated, the self-administered Physical Activity Readiness Questionnaire was used [25]. The number of times a question was answered positive was recorded, with a maximal possible score of 7. In case of one or more positive answers, the nurse practitioner was contacted to discuss if a patient could participate in the exercise program.

The Fatigue Severity Scale (FSS) was used to assess the level of perceived fatigue and its impact on daily life and activities. A higher score correlates with higher levels of fatigue. The minimum score is 9; the maximum score is 63 [26]. A cut-off value of 42 has been reported in cancer patients to indicate severe fatigue [27].

QoL was assessed using the RAND-36 and the EORTC QLQ-30 questionnaires. The RAND-36 consists of 36 questions that are grouped into 8 domains. Two summary scores can be derived from the domain scores: the Physical Component Summary (PCS) and Mental Component Summary (MCS) measures [28]. The EORTC QLQ-30 is an integrated system for assessing the health-related QoL of cancer patients and includes 5 functional scales, 3 symptom scales, a global health status scale, and 6 single items. In both questionnaires, a higher score correlates with better QoL (range 0–100).

Aerobic Capacity

The Åstrand test is a submaximal exercise test, providing an indirect estimation of the maximal oxygen consumption (VO_2max), which can be taken as an indicator for aerobic capacity [29]. Prior to each test, heart rate, blood pressure and saturation at rest were measured. Patients started pedaling on the ergometer for 6 min with a frequency of 50 rounds per minute. The workload (Watt) was determined by the physiotherapist based on an estimated fitness level of the patient. Heart rate was recorded every minute. The average heart rate between 5 and 6 min was considered the mean steady state value and used to estimate VO_2max (ml/kg/min) using the Åstrand nomogram [30].

General Muscle Strength

To evaluate peripheral muscle function, handgrip strength, elbow flexion strength and knee extension strength were assessed. Three consecutive measurements were carried out for each muscle group on each side, with standardized verbal encouragement. The mean value for all measurements per muscle group was used in the analyses. Handgrip strength was assessed with a handheld dynamometer (JAMAR, USA) which has shown high test–retest reliability and has been recommended for clinical use [31, 32]. The elbow flexion and knee extension strength measurements were carried out using a microFET-2 handheld dynamometer (Hoggan Health Industries, USA) according to the 'make' technique, a valid and reliable method to measure maximal isometric contraction [33, 34].

Inspiratory Muscle Function

For the evaluation of inspiratory muscle strength, MIP was measured with the microRPM hand-held respiratory pressure meter (MircoMedical, USA). Five successive measurements were taken and the maximum difference allowed between the measurements was 10%. The highest value obtained was recorded as MIP-max [35].

The incremental inspiratory muscle endurance was tested starting at a resistance of 30% of the MIP, which was then increased by 8% every minute. The maximum resistance that could be tolerated for 1 min (MIP-endurance) was used to calculate the incremental inspiratory muscle endurance ((MIP-endurance/MIP-max)*100).

Feasibility Outcomes

Baseline characteristics, including the health status measurements described above, were compared between participants and non-participants to check for sampling bias. To determine the feasibility of the program, several indicators were evaluated. The percentage of patients that agreed on following the training and the reasons for non-participation were recorded. During the exercise program, adherence to the group training sessions and reasons for non-attendance were recorded. Furthermore, adverse events reported by patients participating in the exercise program were documented.

Effectiveness of the Training Program

To evaluate whether the exercise program actually met the goal of increasing preoperative physical fitness, the aerobic capacity, peripheral muscle strength and inspiratory muscle function of the participants were measured weekly during the exercise program.

Analysis

Descriptive statistics were used to analyze the demographic and measurement variables at baseline. Summary statistics are presented as numbers with percentages in the case of categorical variables and as means with SDs in the case of continuous variables. The baseline variables were tested for between-group differences with an independent samples t test or chi-square test.

The repeated measures performed in the participants of aerobic capacity, peripheral muscle strength and inspiratory muscle function were analyzed using mixed models with random intercept and random slope. The covariates gender, age and tumor location were entered in the mixed models. Participants and non-participants could not be compared for the follow-up measurements, since non-participants underwent measurements only at baseline.

Results

Between July 2006 and April 2008, approximately 310 patients underwent pancreatic, liver, intestinal, gastric or esophageal cancer surgery. After the outpatient consult, 168 patients underwent the health status measurements, of which 115 participated in the exercise program (fig. 1).

Baseline Variables

Baseline characteristics of the participants and non-participants are summarized in table 1. No information is available of the patients that did not undergo the health status assessment. Based on the ASA classification scores, participants had less severe systemic disease compared to the non-participants ($p = 0.04$) and the tumor location was not evenly divided across both groups ($p = 0.02$). Patients were comparable for the health status measurements.

The mean FSS score in both groups fell below the cut-off value of 42 points for severe fatigue [27]. The mean reported EORTC scores in both groups (66.7 and 65.6) were higher than the reference values of cancer patients (61.3) [36] and the mean RAND-36 scores PCS (40.3 and 41.1) and MCS (39.0 and 39.8) were lower compared to the Dutch references values of the general population of

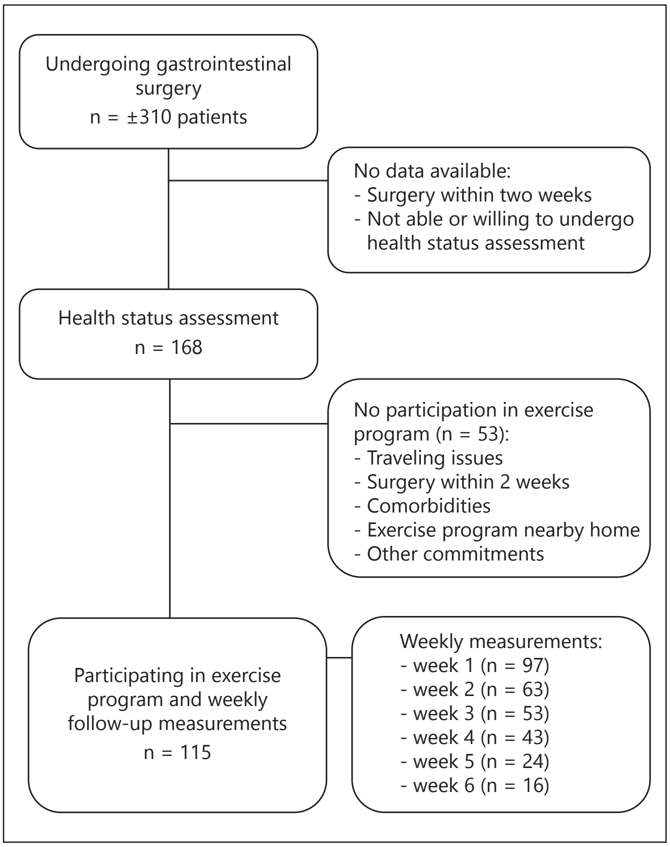

Fig. 1. Flowchart of recruitment and performed measurements.

56–65 years (46.8 and 50.7, respectively) [28] indicating decreased QoL in both groups.

Although not statistically different, the travel distance for the non-participants was longer (39.1 km) than that of the participants (25.7 km).

Feasibility

Of all patients undergoing gastrointestinal surgery, 168 (54%) underwent the health status assessment and of those 115 (37%) participated in the exercise program. The main reasons for not participating in the exercise program were related to the transport: traveling distance (n = 18) and no transport (n = 3). Other reasons for non-participation were: surgery within 2 weeks (n = 3), other commitments (n = 3), comorbidities (n = 2), prefer exercise program nearby their home (n = 2). In the participants, the mean (SD) number of days between the invitation for the exercise program and the first training session was 6.3 (5.8). The average number of days between the first training session and surgery was 30.9 (19.4). On average, 5.7 (3.5) training sessions were attended and 1.2 (1.6) training sessions were missed. Of the participants, 56 (48%) did not miss a single session. Of the 844 scheduled training sessions, 694 were attended, resulting in an overall training adherence of 82%. The main reasons for missing a session were other appointments at the hospital (26.5%) and (public) holidays (25.3%). No adverse events were reported during the training sessions.

Effectiveness of the Exercise Program

The participants underwent weekly measurements of their aerobic capacity, general muscle strength and inspiratory muscle function. The time courses of these measurements (with 95% CIs) are displayed in figures 2 and 3. The mixed model analyses showed a significant increase of the mean estimates over time from weeks 1 to 6 of MIP-max (84.1–104.7 cm H_2O; p = 0.00) and MIP-endurance (35.0–39.5 cm H_2O; p = 0.00). A ceiling effect was observed for MIP-endurance since increasingly more patients reached the maximum load of the threshold device of 41 cm H_2O during this test (54% at the first time point up to 95% at the last time point). This is also illustrated by the decreasing ratio of MIP-endurance/MIP-max in figure 2.

No significant changes over time were found in aerobic capacity (28.5–29.0 ml/kg/min; p = 0.12), handgrip strength (34.7–35.7 kg; p = 0.26) and knee extension strength (261.6–282.9 Newton; p = 0.11). The elbow flexion strength showed a non-significant increase from the weeks 1 to 5 (173.2–179.9 Newton; p = 0.08) and a significant decrease between weeks 5 and 6 (166.1 Newton; p = 0.04).

Discussion

The aim of this study was to investigate the feasibility of a preoperative exercise program and its effects on preoperative physical fitness in patients undergoing gastrointestinal oncological surgery. Adherence to the exercise program was high and no adverse events occurred during the program. Due to the short interval between screening and surgery, the number of training sessions attended was low. The exercise program did result in increased inspiratory muscle function but failed to result in increased peripheral muscle strength and aerobic capacity.

Feasibility

The exercise program is highly feasible in terms of adherence to the training sessions and the training itself. The training adherence of 82% and the legitimate reasons

Table 1. Baseline values

Patient characteristics	n	Non-participants (n = 53)	n	Participants (n = 115)	p value (2-sided)
Age, years, mean (SD)	53	65.6 (11.8)	115	62.3 (10.7)	0.74
Male, n (%)	53	32 (60.4)	115	66 (57.4)	0.72
Height, m, mean (SD)	53	172.4 (10.3)	115	172.0 (12.8)	0.91
Weight, kg, mean (SD)	53	76.7 (16.5)	115	77.3 (14.9)	0.70
BMI, kg/m^2, mean (SD)	53	25.7 (4.6)	115	26.6 (9.5)	0.46
Tumor location, n (%)	53		115		0.02
Pancreas		9 (17)		16 (13.9)	
Liver		9 (17)		28 (24.4)	
Colon		22 (41.5)		27 (23.5)	
Esophagus		6 (11.3)		35 (30.4)	
Stomach		7 (13.2)		9 (7.8)	
ASA physical status classification, n (%)	53		115		0.04
I		8 (15.1)		38 (33.0)	
II		36 (67.9)		65 (56.5)	
III		9 (17.0)		12 (10.4)	
Travel distance, km, mean (SD)	53	39.1 (26.1)	115	25.7 (15.8)	0.65
Health status measurements					
PARQ score, n (%)	48		112		0.66
0		18 (37.5)		38 (33.9)	
≥1		30 (62.5)		74 (66.1)	
Inspiratory muscle function, mean (SD)					
MIP-max, cm H_2O	44	68.2 (28.7)	97	75.6 (29.5)	0.13
MIP-endurance, cm H_2O	33	34.3 (7.9)	80	35.2 (7.9)	0.59
MIP-end/MIP-max, %	33	42.2 (8.3)	80	44.3 (11.1)	0.35
Astrand, ml/kg/min, mean (SD)	5	NR	44	28.5 (6.5)	–
Handgrip strength, kg, mean (SD)	24	38.5 (11.6)	72	35.6 (10.5)	0.26
Elbow flexion strength, n, mean (SD)	24	183.7 (55.8)	73	179.2 (57.1)	0.73
Knee extension strength, n, mean (SD)	24	267.7 (71.2)	70	275.4 (80.8)	0.68
FSS score, mean (SD)	21	35.2 (14.7)	75	30.5 (13.6)	0.17
RAND-36, mean (SD)	24		66		0.49
PCS		40.3 (6.4)		41.1 (6.7)	
MCS		39.0 (9.1)		39.8 (7.6)	
EORTC, mean (SD)	20		54		0.85
Global health status		66.7 (24.5)		65.6 (21.2)	

BMI = Body mass index; PARQ = physical activity readiness; NR = not reported due to high volume of missing values.

for missing sessions show that participants were highly motivated to attend the training sessions. No adverse events were reported and all participants stated that they would participate again.

Of around 46% of patients undergoing gastrointestinal surgery, no health status data are available. A majority of these patients were not invited to the exercise program and the accompanying health status assessment, since their surgery was planned within 2 weeks. The overall participation was therefore 37%, which is fairly low. However, of the patients eligible for the exercise program based on the available time until surgery, 68% participated in the exercise program. A participation rate of 68% is reasonable, since other preoperative training studies report lower participation rates [19, 37]. Having to travel to the outpatient hospital clinic twice a week was the most frequently reported reason for non-participation, which is in line with an earlier reported pilot study [19].

We compared the baseline and health status data of the participants with the non-participants to check for selection bias, since selection bias can decrease external valid-

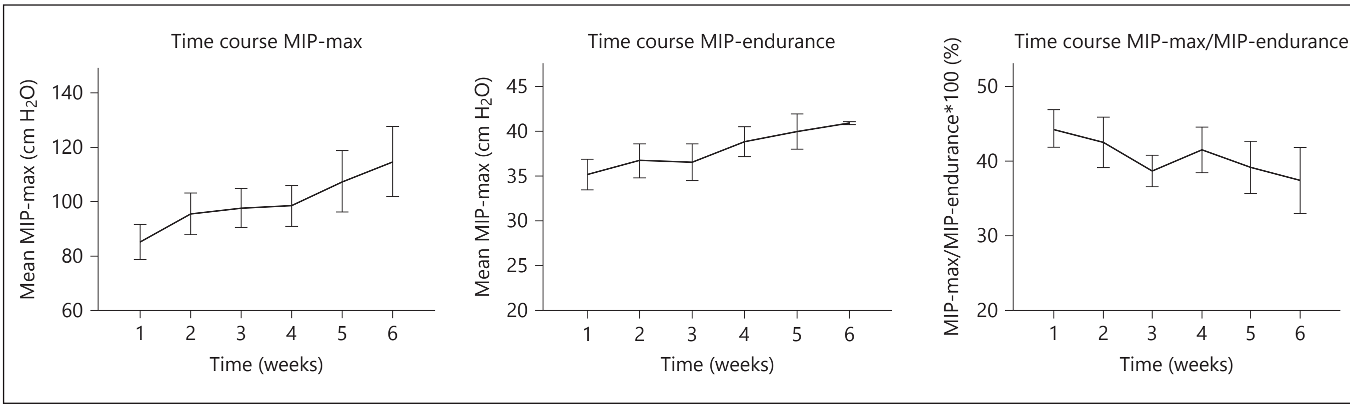

Fig. 2. Time courses of the inspiratory muscle function.

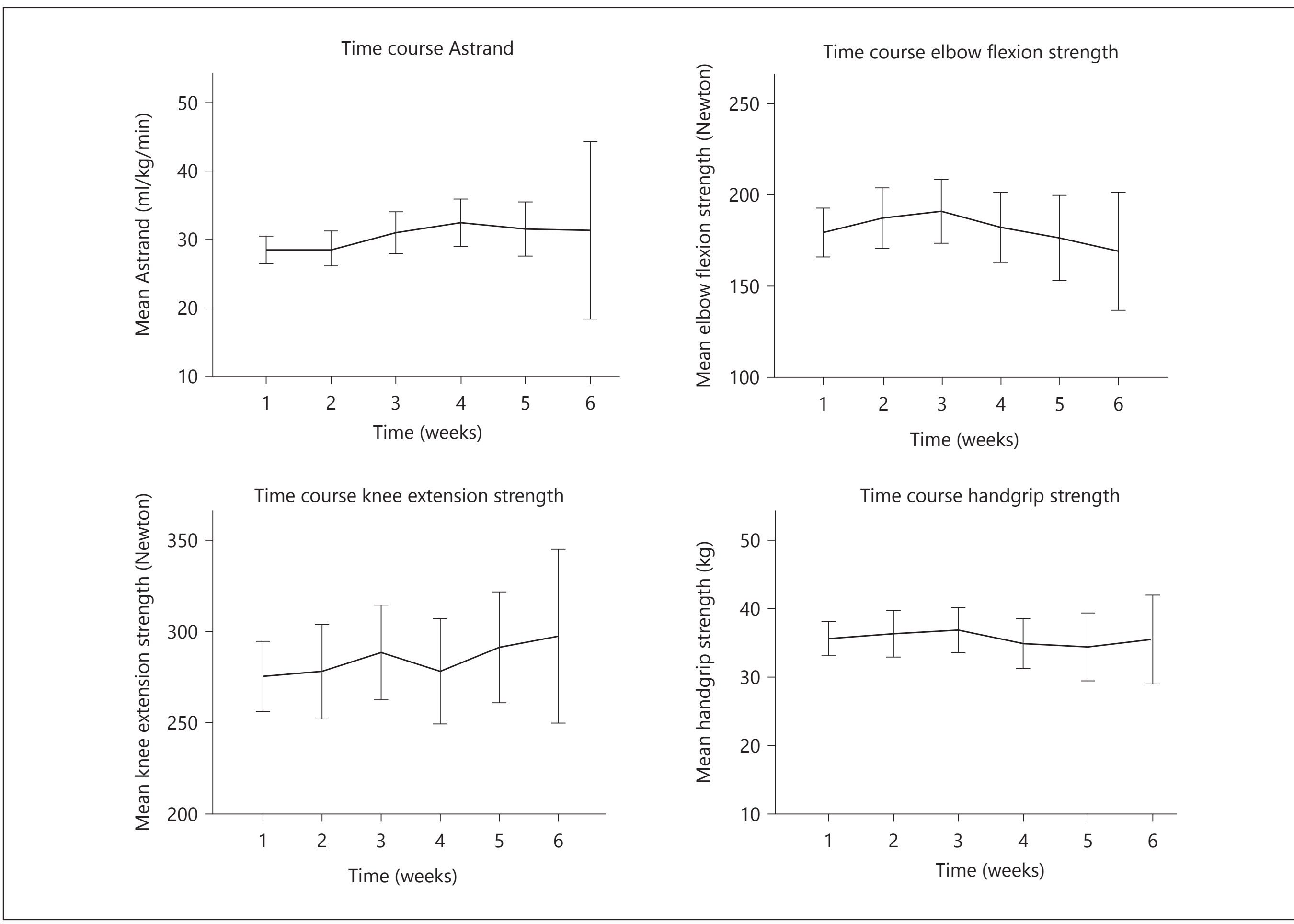

Fig. 3. Time courses of the aerobic capacity and peripheral muscle strength.

ity. For example, it is possible that those interested in following an exercise intervention have a better health status, since they are more likely to be undertaking sports and exercise activities in general. Our results, however, do no confirm this hypothesis, since the scores of participants and non-participants were comparable in terms of the health status measurements at baseline. The feasibility based on the number of followed training sessions was moderate. Participants followed on average 5.7 training sessions. Preferably, patients would have followed more training sessions, but the interval between the first consultation and the date of surgery did not allow a longer intervention period.

Effectiveness of the Exercise Program

Our results show that inspiratory muscle strength improved significantly during the intervention period. This is in line with earlier studies that show that IMT can improve inspiratory muscle strength and endurance after 2 weeks of training in patients undergoing major invasive surgery [16, 38, 39]. Baseline values and the average increase of 20% of MIP-max are also comparable to the results in these studies. In our study, IMT was performed with a threshold device with a range of 9–41 cm H_2O. Patients reported that they reached the maximum load of the training device before the end of their training period, which is confirmed by the ceiling effect reported during the endurance measurements because with time, an increasing number of patients reached a maximum score of 41 cm H_2O. Therefore, the training load was suboptimal and this might have impaired the effects of this training.

No significant improvements were found in aerobic capacity, handgrip strength, knee extension strength and elbow flexion strength. Knee extension strength improved by 7%, which is in line with an earlier pilot study that did find a significant increase in overall muscle strength and aerobic capacity [19]. Patients in the pilot study followed 9 training sessions (median), while our participants on average took part in 5 or 6 training sessions. Studies have found that the optimal conditions to achieve physiological adaptations are exercise programs of 3 months with 3 sessions a week [40–42]. Training programs of 12–18 weeks in cancer survivors have been shown to be successful in improving muscle strength and aerobic capacity [43, 44]. Therefore, presumably our training period was too short to establish physiological adaptations. Another explanation of the lack in aerobic and musculoskeletal progress might be the training intensity. Currently, increasingly more evidence is available that supports the effectiveness of high intensity training [44–46]. A recent commentary investigated the available literature on the key principles of exercise training (frequency, intensity, time, type and progression) in the light of developing a consensus on the design of prehabilitation programs. Their overall conclusion is that individually prescribed and supervised high-intensity interval training is an effective form of exercise therapy prior to surgery [47]. Our program consisted of cardiorespiratory endurance training and low-load muscle endurance training. Although the physiotherapist consistently observed progress in the weight lifted and the number of repetitions performed by the participants, the training load might have been too low to result in increased general muscle strength in the available time period for the exercise program.

Strengths and Limitations

This study is one of the first studies to investigate the feasibility of exercise training in cancer patients awaiting gastrointestinal surgery. When this study was designed in 2005, the general idea was that it was not feasible to train cancer patients. This study proves otherwise. The high number of participants, the high percentage of followed training sessions, and the absence of adverse events during training shows that exercise training before gastrointestinal surgery is possible and feasible. The high number of performed measurements during the exercise program is a big strength of this data and made it possible to investigate the time course of several functional measurements and the effect of the exercise program on these outcomes.

One major downfall of the study is the limited number of followed training sessions by the participants, which likely inhibited the effects of the exercise program on physical fitness.

Another limitation of our data is the amount of missing data in the aerobic capacity and muscle function measurements. About 40–50% of these measurements were missing and it is unclear whether or not this data are missing (completely) at random. When data are not missing at random, this is a violation of the assumptions for using multiple imputations. To avoid a reduced sample size by using standard repeated measure techniques, we chose to analyze the time course of the aerobic capacity and the muscle function measurements with a mixed models analysis. This multilevel approach has been proven to be a useful method to study changes over time in studies with missing data and this method gives unbiased estimates, makes it possible to include covariates and takes into account the dependency between different measurements within a patient [48]. Our data were collected between the years 2006 and 2008 and therefore, current management of oncological surgery patients might have changed. We however believe that our data are still valid nowadays since changes in management of oncological surgery patients mainly involves surgical and postoperative procedures, which do not affect the effectiveness of a preoperative exercise program on preoperative outcomes. Since the design of our training program a decade ago, only a few reports were published on prehabilitation and therefore, we believe this data are still very relevant and can help in the design of future prehabilitation programs.

Recommendations

The current available evidence does not allow the postponement a planned operation in cancer patients in order to complete a prehabilitation program. Therefore, to be able to investigate the effectiveness of a preoperative exercise program on postoperative outcomes and to draw solid conclusions, future scientific efforts are needed to define the most optimal balance of training intensity and frequency in the short time interval between diagnosis and surgery. To achieve physiological adaptations in a short time period, an exercise program incorporated in the preoperative period needs to be effective and time-efficient. A recent commentary and literature summary concluded that high-intensity interval training is an effective form of exercise therapy prior to surgery and therefore we recommend future studies to investigate the effect of a high-intensity exercise program with a higher number of training sessions per week [47]. Furthermore, since travel distance and means of transport were the most frequently mentioned reasons for not participating, offering patients a training program nearby their home should be considered to increase participation numbers. Since IMT proved effective in improving inspiratory muscle function in the available time period, the effectiveness of this training on postoperative outcome is currently being investigated in esophagectomy patients in an international randomized controlled multicenter trial [7].

Conclusions

This preoperative exercise program in patients awaiting oncological surgery is feasible in terms of participation and adherence. Presumably due to the short intervention period, the exercise program failed to significantly increase preoperative peripheral muscle strength and aerobic capacity. The exercise program successfully improved the inspiratory muscle function, providing an opportunity to improve the preoperative pulmonary status of patients undergoing cancer surgery.

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