Post-discharge impact and cost-consequence analysis of prehabilitation in high-risk patients undergoing major abdominal surgery: secondary results from a randomised controlled trial


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Abstract

Background: Prehabilitation may reduce postoperative complications, but sustainability of its health benefits and impact on costs needs further evaluation. Our aim was to assess the midterm clinical impact and costs from a hospital perspective of an endurance-exercise-training-based prehabilitation programme in high-risk patients undergoing major digestive surgery.

Methods: A cost-consequence analysis was performed using secondary data from a randomised, blinded clinical trial. The main outcomes assessed were (i) 30 day hospital readmissions, (ii) endurance time (ET) during an exercise testing, and (iii) physical activity by the Yale Physical Activity Survey (YPAS). Healthcare use for the cost analysis included costs of the prehabilitation programme, hospitalisation, and 30-day emergency room visits and hospital readmissions.

Results: We included 125 patients in an intention-to-treat analysis. Prehabilitation showed a protective effect for 30-day hospital readmissions (relative risk: 6.4; 95% confidence interval [CI]: 1.4–30.0). Prehabilitation-induced enhancement of ET and YPAS remained statistically significant between groups at the end of the 3 and 6 month follow-up periods, respectively (ΔET 205 [151] s; P=0.048) (ΔYPAS 7 [2]; P=0.016). The mean cost of the programme was €389 per patient and did not increment the total costs of the surgical process (€812; CI: 95% €878 – 2642; P=0.365).

Conclusions: Prehabilitation may result in health value generation. Moreover, it appears to be a protective intervention for 30-day hospital readmissions, and its effects on aerobic capacity and physical activity may show sustainability at midterm.

Clinical trial registration: NCT02024776.

Keywords: cost-consequence analysis; exercise therapy; postoperative complications; preoperative care
Major surgical procedures are frequently associated with postoperative complications that have a marked deleterious impact on health-related quality of life, morbidity/mortality, and costs.\(^1\) On average, 20% of patients have major postoperative complications that it is estimated to account for 50% of operational costs.\(^2\) Therefore, the design and implementation of innovative preventive interventions aiming at reducing postoperative complications constitute a relevant milestone with potential positive implications on health outcomes, patient’s experience of care, and cost savings for both healthcare providers and third-party payers, allowing for a more efficient resource reallocation.

Prehabilitation is emerging as a preoperative intervention aiming at improving patient’s aerobic capacity, nutritional balance, and psychological status. Its ultimate aim is to enhance patients’ functional capacity in order to minimise postoperative morbidity and accelerate post-surgical recovery.\(^3\) Several RCTs assessing prehabilitation programmes have shown positive effects of the intervention on aerobic capacity and physical activity, resulting in a significant reduction of both postoperative complications and length of hospital stay.\(^4\) However, the impact of prehabilitation on healthcare costs and service sustainability has been insufficiently analysed.

The current research draws upon the secondary results of a recent RCT exploring the effects of prehabilitation in high-risk candidates for major digestive surgery at the Hospital Clínic de Barcelona (Catalonia), and presents a cost-consequence analysis (CCA). CCA is a form of evaluation of healthcare programmes, in which costs and impacts of the intervention are presented separately.\(^5\) Accordingly, firstly, we explored the effects of the intervention on postoperative recovery during a 6 month period after hospital discharge. Secondly, we evaluated the impact of the prehabilitation service on direct healthcare costs and the midterm sustainability of its clinical benefits.

**Methods**

**Study design**

The current study reports a CCA of a prehabilitation programme, with secondary outcomes from a previously published RCT carried out at the Hospital Clínic de Barcelona (Catalonia).\(^6\) The Ethics Committee for Clinical Research of the centre approved the study (CEIC 2013/8579), for which the protocol was registered at ClinicalTrials.gov (NCT02024776) and it is currently closed. Specific amendments to the original public protocol can be found at https://clinicaltrials.gov/ct2/show/NCT02024776.

Over a 3 yr period (February 3, 2013 to June 13, 2016), a consecutive sample of patients undergoing elective major digestive surgery was included in the trial. The main inclusion criteria were high risk for surgical complications defined by age above 70 yr and ASA physical status 3/4.\(^1\) Patients with a Duke Activity Status Index over 46 were not included in the trial.\(^7\) A minimum waiting period allowing 4 weeks of programme was required as inclusion criterion. Subjects accepting to participate were blindly randomised (1:1 ratio) to control or intervention groups.

**Control group**

Patients included in the control group followed the standard preoperative protocol at Hospital Clínic de Barcelona. It included physical activity recommendation, nutritional counselling, and advice on smoking cessation and reduction of alcohol intake. Moreover, patients suffering from iron deficiency anaemia received i.v. iron, and in those at high risk of malnutrition (Malnutrition Universal Screening Tool \(\geq 2\)) nutritional intervention was carried out by a registered dietician.

**Intervention group**

In addition to the standard preoperative protocol described for the control group, the intervention group was enrolled in a prehabilitation programme with two main objectives: (i) to increase aerobic capacity, and (ii) to enhance physical activity. The prehabilitation programme covered three main actions: (i) a motivational interview, (ii) a hospital-based high-intensity endurance-exercise training programme, and (iii) promotion of physical activity. A specialised physiotherapist was the case manager guiding the patients included in the intervention group throughout the prehabilitation programme. The length of the intervention depended on the waiting time to the surgery. A minimum waiting period allowing 4 weeks of programme was required as inclusion criterion. Patients attending the programme for less than 4 weeks were still included in the intention-to-treat analysis. The detailed characteristics of the trial have been reported previously.\(^7\)

**Clinical outcomes**

The original trial design was powered for postoperative complications. Therefore, the following variables described were planned as secondary outcome variables. Endurance time (ET) measured by a cycling constant work-rate exercise testing at 80% of peak oxygen uptake\(^8\) was assessed at baseline, pre-surgery, and at 3 months after surgery. Physical activity by the Yale Physical Activity Survey (YPAS),\(^9\) self-perceived health status by the Short Form (36) Health Survey (SF-36),\(^10\) and psychological status by the Hospital Anxiety and Depression Scale (HADS)\(^11\) were assessed at baseline, pre-surgery, and at 30 days and 6 months after surgery. Moreover, all-cause mortality at 30 days and at 3 and 6 months was also registered.

**Use of healthcare resources**

Emergency room visits, hospital readmissions, and surgical reinterventions at 30 days for the same condition, 3 and 6 months into the follow-up period after surgery were also registered.
Costs
Total individual costs were prospectively obtained for each group from the hospital perspective, so the cost analysis was restricted to direct healthcare costs. Hospital patient-level data were collected to analyse the impact of the programme on hospital care costs. A combination of diagnostic-related-group-based hospital fees and micro-costing was used to identify and measure the cost allocation. Hospital fees used are specific of the Hospital Clinic de Barcelona, and micro-costing implied direct cost imputation according to individual consumption at a patient level.

The costs of the prehabilitation programme and those from the follow-up period were estimated. Prehabilitation programme costs included (i) a cardiopulmonary exercise testing, (ii) the physiotherapist fees, and (iii) a pedometer device. Follow-up included hospitalisation after surgery, hospital readmissions, surgical re-interventions, and emergency room visit costs at 30 days after hospital discharge. Follow-up postoperative costs included (i) inpatient services (hospital-specific fees), (ii) emergency room visits (hospital-specific fee), (iii) diagnostic procedures (hospital-specific fees), (iv) pharmaceutical consumption (micro-costing), (v) blood products consumption (micro-costing), and (vi) structural costs (hospital-specific fee). Costs are expressed in Euro (€) 2017. No discount rate was used given the short time period used in this study.

For costs, the mean and 95% CI of difference in per-patient costs between the two groups were computed (control-group costs minus prehabilitation-group costs), so that positive values should be interpreted as a savings of the prehabilitation programme. We had to deal with a highly skewed distribution, which is typical of cost data. Right-sided asymmetric distribution appears when some patients incur in high costs, in our case, mainly because of major medical complications. To deal with this, a non-parametric approach (bootstrapping [1000 replications]) was used. Bootstrap analysis yields more robust when dealing with skewed cost data compared with non-parametric tests (such as Mann–Whitney).

Results
Of the initial sample of 144 patients randomised, 19 did not undergo surgery and were excluded from all analyses. Thus, a sample of 125 patients (71 [11] yr; 75% male; adjusted Charlson co morbidity index 7 [9]) was included in an intention-to-treat analysis, as depicted in Fig. 1.

Use of healthcare resources after hospital discharge
Readmission and emergency room visits are presented in Supplementary Table S1. The percentage of patients being readmitted at 30 days after hospital discharge, or still hospitalised during that period, was 10% of the overall sample. It is of note that the prehabilitation group showed a lower rate of 30 day hospital readmissions compared with the usual care group (18% vs 3%; P=0.009). Accordingly, prehabilitation showed to have a protective role for 30 day hospital readmissions with an estimated relative risk (RR) of 6.4 (95% CI: 1.4–30.0). No other significant differences in healthcare use were found during the 6 month follow-up period.
Postoperative functional recovery

Supplementary Table S2 shows the clinical outcomes during the overall study period. Prehabilitation-induced enhancement of aerobic capacity (ET) at Month 3 of the postoperative follow-up period remained significantly higher as compared with the usual care group (Fig. 2, left panel). Moreover, the ET of the intervention group assessed at 3 month follow-up was significantly higher to the measured at baseline (325 [151] vs 535 [401] s in ET; \( P = 0.010 \)).

Likewise, the prehabilitation-induced increase of physical activity levels (YPAS index) remained significantly higher at 6 month follow-up as compared with controls (Fig. 2, right panel). Likewise, the YPAS index at Month 6 of the follow-up period is significantly above the baseline values in the intervention group (34 [16] vs 46 [13] YPAS index values; \( P < 0.001 \)).

Consistently, the prehabilitation group also showed a higher score in the physical component of the SF-36 questionnaire at 30 days and 6 months of follow-up, compared with usual care (Supplementary Table S2). On the other hand, no differences between groups were found in the SF-36 mental component.

In terms of psychological status, the intervention group showed lower anxiety and depression levels (HADS score) at 30 days after surgery, as compared with the usual care group (9 [7] vs 6 [5] HADS score; \( P = 0.008 \)). No other significant differences in clinical outcomes were found between the study groups (Supplementary Table S2).
Cost analysis

Both study groups showed a marked skewness in the distribution of costs, as reported in Supplementary Table S3. Moreover, the control group presented two outliers (common cut-off of 3 so from the mean was used) incurring in high costs (Supplementary Fig. S1). Therefore, in order to provide a robust analysis, we performed the assessment of costs with and without outliers separately. In addition, a bootstrapping approach (1000 replications) was done to calculate the means and 95% CI of the difference in per-patient costs between the two groups.

The mean cost of the prehabilitation programme was €389 per patient, including €230 cardiopulmonary exercise testing, €41 motivational interview, €22 pedometer device, and €96 group endurance-exercise training sessions.

The average cost savings of prehabilitation (Fig. 3) increased by including healthcare use at 30 day follow-up compared with considering only the initial hospitalisation (€333 [745] vs €812 [894]; P < 0.001). However, the prehabilitation programme did not show statistically significant cost savings at 30 days, as presented in Supplementary Table S4 (€812; CI 95% –878 –2642; P = 0.365). Similarly, no statistically significant differences on costs between study groups were found when stratifying by level of surgical aggression or surgical risk (Supplementary Table S5).

Discussion

To our knowledge, this is the first study evaluating midterm clinical impact (3 and 6 months post-surgery) and costs of prehabilitation in patients undergoing intra-cavity surgery. The main findings of this randomised trial are (i) a prehabilitation programme, including hospital-based high-intensity endurance-exercise training and promotion of physical activity, was a protective factor for 30-day hospital readmission in high-risk patients undergoing major digestive surgery; (ii) the prehabilitation-induced benefits on aerobic capacity and physical activity showed sustainability at 3 and 6 months after surgery, respectively; and (iii) prehabilitation fosters health value, as it reduces perioperative complications (RR: 0.5; 95% CI: 0.3–0.8) without increasing direct healthcare costs, which may be interpreted as evidence of higher value for money (cost-effective intervention).

The impact of exercise training on healthcare use and medical costs in chronic stable patients has been widely assessed within the context of cardiopulmonary rehabilitation programmes, reporting significant reductions in the number of hospital admissions, emergency room visits, and direct costs. However, the rehabilitation-induced enhancement of aerobic capacity, in stable pulmonary and cardiac patients and in the absence of any maintenance strategy, appears to diminish over 6–12 months after programme discharge. Consistently, the current trial demonstrated a high protective role of prehabilitation for 30 day hospital readmissions (RR: 6.4; 95% CI: 1.4–30.0) in elderly multimorbid patients (mean age-adjusted Charlson index 7 [9]). Moreover, the prehabilitation-induced effects on aerobic capacity and physical activity showed sustainability at 3 and 6 months post-surgery, respectively. End follow-up ET and YPAS score were lower than preoperative assessments (Fig. 2), but still higher than the baseline measurements. One can speculate that the main reasons of prehabilitation-induced-benefit decline may be the impact of the surgical process, the postoperative co-adjuvant treatment, the progression of the underlying co-morbidities, and patients’ lower adherence to physical activity. Therefore, we strongly believe that there is a need to implement sustainable and modular postoperative programmes in order to (i) optimise the postoperative time required for hospital discharge and functional recovery, and (ii) empower patients and provide long-term support on self-management strategies within an integrated care approach (e.g. promotion of physical activity, nutritional advising, and psychological and disease management).

From our point of view, there is a need of robust perioperative studies assessing both the optimal interventions to be performed and the best duration for the programmes in different subsets of patients. The final outcome would be a sort of modular and patient-oriented programme tailored mainly in terms of type of surgery and patients’ surgical risk.

It is important to highlight that all patients underwent surgery within an enhanced recovery after surgery (ERAS) in-house programme. ERAS was adopted in our hospital more than a decade ago; a dedicated multidisciplinary team collaborates to promote a large number of elements of pre-, intra-, and postoperative care (evidence based) to reduce the physiological and psychological stress of surgery with the aim of improving patient outcome. Our compliance with ERAS recommendations, although the number of ERAS elements depends on the type of surgery, is over 70%, and no patients are excluded from the programme. In this context, we believe that our results should prompt taking prehabilitation programmes into major consideration as an intervention to be included in the ERAS pathway for high-risk patients undergoing major elective surgery.

Our randomised trial presents different design strengths discussed in detail in Barberan-Garcia and colleagues, such as (i) prospective recruitment of patients, reinforcing external validity of the results; (ii) blinding of clinicians collecting perioperative outcomes; (iii) absence of contamination amongst groups, as two different informed consents were used; and (iv) absence of missing data in the exhaustive costs and healthcare use register. However, we acknowledge the fact that the analysis used secondary outcomes of an RCT, which renders the results of the current investigation as ‘hypothesis generating’. Other study limitations to take into account are the lack of assessment of indirect (societal) costs, the possible lack of statistical power to prove the potential cost-saving effect of prehabilitation, the particular characteristics of the population, and the lack of generalisability of the results because it was a single-centre study. We want to point out that costs at 3 and 6 months have not been reported because of the lack of differences on healthcare use between groups during this period of the follow-up (Supplementary Table S1).

From our understanding, future studies should focus on the evaluation, not only of the clinical and economic impact, but also on the implementation practicalities of real-life deployment experiences on prehabilitation, tackling aspects, such as (i) assessment of sustainability and coverage of the service, (ii) identification of factors modulating implementation success and key performance indicators to track the service, and (iii) generation of recommendations for service transferability to other sites, amongst others. In that sense, prehabilitation programmes basing their supervised sessions in the community setting are postulated as interesting strategies to increase accessibility whilst reducing total costs.

We report highly valuable and promising information, which can guide future studies on the topic whilst supporting...
the efficacy and cost-effectiveness of a prehabilitation programme.

Authors’ contributions
Data collection: AB-G, MU, RR, JF.
Data interpretation: all authors.
Intervention: AB-G.
Statistical analysis: AB-G, NP-A.
Writing of first draft: AB-G, MU.
Approval of final version: all authors.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2019.05.032.

Declaration of interest
The authors declare that they have no conflicts of interest.

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