Predicting postoperative outcome in elderly surgical cancer patients - Biomarkers and handgrip strength as predictors of postoperative outcome in elderly

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The primary objective is to study the effects of the inflammatory response to a surgical procedure on postoperative cognitive decline in elderly cancer patients and to compare this to the effects of the inflammatory response on postoperative...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cognitive and attention disorders and disturbances
Study type	Observational invasive

Summary

ID

NL-OMON40429

Source
ToetsingOnline

Brief title
PICNIC B-HAPPY

Condition

- Cognitive and attention disorders and disturbances
- Age related factors
- Gastrointestinal therapeutic procedures

Synonym
1) Postoperative cognitive dysfunction 2) functionloss after surgery; memory- and concentrationproblems and loss of ability to handle daily activities

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Cognitive dysfunction, Elderly, Fuctional decline, Surgery

Outcome measures

Primary outcome

The primary outcome measure is a postoperative change in cognitive functioning. Cognitive functioning will be measured by the scores of the Ruff Figural Fluency (RFFT), the Trailmaking test (TMT) part A en B and Rey*s verbal learning test in comparison to the preoperative scores(26-29). These tests will be submitted at the most 1 month preoperatively and at discharge (or a maximum of 2 weeks postoperatively) and 3 and 12 months postoperatively. There is no uniform definition for POCD in the literature(30). Based on recommendations from a review from Ghoneim and Block our endpoint is defined as a postoperative cognitive decline, which will be analysed by a combined Z-score from the above mentioned tests. With this score predictors of cognitive decline can be investigated. As a reference value for the calculated Z-scores, values of scores on cognitive tests in the general population are available. To increase comparability with other studies the scores on the cognitive tests will also be analysed as continuous endpoints(30).

Comparison to the general population

Cognitive functioning deceases with age(31) and therefore a comparison of outcome on the cognitive tests before and after surgery needs to be corrected for the age-dependent change in outcome which is to be expected.

The RFFT has already been submitted to a large control population comparable in age to the study population (the PREVEND-study: Prevention of REnal and Vascular ENd-stage Disease). Data on performance of the Trailmaking test are also available for the general population which allow comparison.

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Secondary outcome

The secondary outcome measures are: delirium (using the DOS), one-year mortality, morbidity up to 30 days postoperatively (using the Clavien-Dindo classification of morbidity(32)), physical performance status and quality of life (assessed by the SF-36(33)). Physical performance status will be assessed by the ADL and IADL questionnaires, the handgrip strength(34,35) and the TUG(36). The handgrip strength will be measured using a Jamar digital handgrip dynamometer. The TUG measures the time a person needs to get out of a chair, walk 6 meters and sit down again. The tests will be submitted at the most 1 month preoperatively and at discharge (or a maximum of 2 weeks postoperatively) and 3 months and 1 year postoperatively.

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Study description

Background summary

Cancer is a disease that increases in incidence with age(1). As the population is ageing, an increasing number of elderly patients will require surgical treatment for their oncological diagnosis. In contrast to what is generally believed, the knowledge on factors predicting postoperative outcome and quality of life in this elderly population is very limited. Important cognitive postoperative complications include delirium and long term cognitive decline. It seems that an inflammatory response to surgery plays a central role in the development of postoperative complications, especially postoperative cognitive decline and delirium(2-5). We do not know how often these complications occur in this group of elderly patients and what risk factors or regulatory factors for the development of these complications are.

Ageing is characterized by a loss of muscle mass, impaired mobility and increased incidence of malnutrition. Low albumin levels, as a marker of malnutrition, have been associated with morbidity and mortality in hospitalized patients (6) and lower albumin levels are found in elderly (7) and patients with a recent diagnosis of cancer (8). In addition, a state of low-grade inflammation is present in elderly and cancer patients(9,10). A relationship between cancer and nutritional status by means of anorexia and inflammation has been postulated. Biomarkers that represent nutritional and inflammatory status include albumin, D-dimer, CRP, Il-1β, Il-6, Il-10, Il-12 and TNF-α(5,8,11). Furthermore, assumptions can be made on possible precipitating roles of vitamin B12, folic acid and vitamin D deficiencies in the onset of POCD in elderly patients(12-18). Deficiencies of vitamin B12 and folic acid in elderly are prevalent in 10-15% and 30-35% respectively(12,19). Vitamin D deficiency affects nearly 50% of elderly in the Netherlands(20). An even higher prevalence of deficiencies can be expected in elderly cancer patients due to the increased metabolic activity of tumor, catabolism or reduced food intake and less exposure to sunlight.

An inflammatory response has also been observed accompanying loss of intestinal barrier integrity. This has mainly been investigated in animal studies, neonates with necrotizing enterocolitis and children undergoing non-abdominal major surgery(21-25). An association between intestinal hypoperfusion, resulting in enterocyte cell death and loss of tight junction integrity, and consequently a systemic inflammatory response syndrome, multi organ failure or other major postoperative complications have been postulated(22,23). Markers that represent enterocyte cell death and tight junction loss respectively are Intestinal Fatty Acid Binding Protein (I-FABP) and claudin-3.

The heterogeneity of the elderly surgical population makes it impossible to create guidelines for the elderly patients in general. The influence of nutritional status, muscle mass and general functioning on inflammation and outcome in the geriatric surgical patient needs to be investigated so risk factors or predictors of adverse outcome can be determined. Objectifying these characteristics preoperatively will allow us to identify the frail patient at increased risk of poor outcome and the fit elderly patient with a lower risk of adverse outcome. As a consequence appropriate interventions can take place and well-founded treatment decisions can be made.
Since certain biomarkers are increased in elderly and others in cancer patients, the inflammatory response and the influence of potential preoperative confounders on the inflammatory response and thus on the occurrence of cognitive decline, may be more pronounced in certain populations. Hypothesized predictors of poor postoperative outcome in the onco-geriatric surgical population should be investigated in a control group of younger surgical oncological patients as well to assess whether different mechanisms apply to the occurrence of an inflammatory response in age groups.

A pilot study investigating 150 patients aged 65 years and older, undergoing surgery for a solid malignant tumor in the operative center of the University Medical Center of Groningen is ongoing. Interim analysis of this study showed that roughly 15 % of elderly patients experience postoperative delirium and the same amount of patients experience long term postoperative cognitive decline. An inflammatory response was related to the development of postoperative delirium and cognitive decline. Peroperative serum samples of patients experiencing either delirium or long term cognitive decline showed a sharp increase in Il-6 (delirium), Il-10 (delirium) and Il-12 (cognitive decline) levels compared to patients experiencing no cognitive decline or delirium. In aged rats, an association between Il-1β, neuroinflammation and postoperative cognitive dysfunction has been found(3). Due to the limited sample size in this study we were not able to assess the role of potential confounders. Based on the results of this pilot study and the pre-clinical study performed in aged rats further research is proposed.

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Study objective

The primary objective is to study the effects of the inflammatory response to a surgical procedure on postoperative cognitive decline in elderly cancer patients and to compare this to the effects of the inflammatory response on postoperative cognitive decline in a control group of younger patients (<65 years of age) undergoing surgical oncological procedures. Preoperative inflammation level, muscle strength, nutritional status and general functioning will be investigated as possible regulatory factors of this mechanism.
The secondary objectives are to study the association between the inflammatory response and the secondary endpoints and investigate the influence of postoperative cognitive and functional decline on long-term quality of life.

Study design

Observational prospective study with a 1 year follow up.

Study burden and risks

The participating patients will have to complete 6 tests and 5 questionnaires at inclusion in the study which will take about 60 minutes in total. At discharge or at a maximum of two weeks postoperatively 4 out of the 6 tests and 1 questionnaire will be administered again. As no relevant or reliable change is to be expected so soon after surgery at the remaining part of the test and questionnaires, these will not be repeated at this moment. At 3 and 12 months postoperatively the participating patients will be asked to complete the same set of tests and questionnaires as preoperatively. Blood and urine samples will be taken preoperatively, peroperatively and 1 and 2 days postoperatively. The collection of blood samples necessary for this study will be combined with the collection of blood samples used for standard care, if possible. These blood and urine samples or the tests they are asked to complete are not expected to cause an extra burden or discomfort to the participating patients.
Postoperative administration of blood and urine samples are not an indication for a prolonged admission to hospital. Patients will be tested at their place of residence or at the hospital when this can be combined with other appointments. No extra journey to the hospital is needed. No experimental drugs will be used during this study.
By participating in this study, patients will contribute to the collection of data we need to gain more knowledge on the mechanism behind postoperative cognitive decline and on risk factors of adverse postoperative outcome in the onco-geriatric population. This will allow us to identify the frail patient at increased risk of poor outcome and the fit elderly with a lower risk of adverse outcome. As a consequence, appropriate interventions can take place and well-founded treatment decisions can be made.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients over 65 years of age undergoing surgery for a solid malignancy.
Surgery is scheduled more than 24 hours after inclusion in the study as we feel this is the time necessary to obtain test results and plan the intraoperative recording of data.
Surgery under general, local or regional anesthesia.
Written informed consent given according to local regulations.
Patients can only be included in this trial once.;Control group:
Patients <65 years of age undergoing surgery for a solid malignancy.

Exclusion criteria

Any physical condition potentially hampering compliance with the study protocol and follow-up schedule, this includes: severe visual impairment, total deafness or the inability to hold a pencil.
Personal time constraints unabling patients to comply to the study protocol.
Patients unable to comply with the outcome questionnaires (this includes insufficient knowledge of the Dutch language).

Study design

Design

Study type:	Observational invasive
Intervention model:	Other

Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-08-2014
Enrollment:	672
Type:	Actual

Ethics review

Approved WMO

Date:	09-05-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL45602.042.14