ISRCTN03274575 https://doi.org/10.1186/ISRCTN03274575

Enhanced recovery in liver resection surgery

Submission date	Recruitment status	[_] Prospectively registered
18/06/2011	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
28/07/2011	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
09/08/2013	Surgery	

Plain English summary of protocol

Background and study aims
Patients who require an operation to remove a part of their liver currently receive excellent care in the Royal Surrey County Hospital unit. However, it may be possible to make it even better by using an Enhanced Recovery Programme (ERP). An ERP comprises a number of changes to the way in which patients are managed around the time of their operation:
1. Better information for patients about their expected progress and discharge from hospital.
2. Providing special nutritional supplements for the patients prior to their admission to hospital.
3.Tailoring fluid management guided by a LiDCO machine (a minimally invasive device that monitors cardiac functions).
4. Early mobilisation and return to normal living as soon as possible after the completion of the operation.

ERPs have been implemented for patients undergoing colorectal surgery and have improved patients experience, have sped up recovery and been more cost-effective than standard care. This study investigates whether an ERP can produce the same benefits in patients having liver operations. We will compare two groups of patients, one group having the current, excellent care which we provide, the other having an ERP. We will look at the following different elements and compare them between groups:
1. The length of time patients have to remain in hospital following their operation
2. The quality of life for patients in both groups assessed by means of a questionnaire completed by patients both before and after the operation
3. The patientssatisfaction with their care assessed by means of a questionnaire completed by the patients after they leave the hospital
4. The post-operative comfort level assessed by making a daily review of the patientspain
5. The incidence of post-operative complications e.g. chest infections
6. The financial cost of each method
7. The difference in stress response and immune system function (cell-mediated immunity) after surgery in the ERP group compared with the control group

What does the study involve?
During this study, patients will have consented to blood being taken for stress response and cell-mediated immune function analysis on five occasions. The first blood sample will be taken from a cannula. The second and third blood samples will be taken from the patient's central line. The fourth and fifth blood samples will be taken from a peripheral vein at the same time as the

routine post-operative blood samples are being taken. In this way we will ensure that the blood sampling will entail no additional injections/needles thus minimising the inconvenience to patients.
Participants who are allocated to the treatment group (ERP) will have the enhanced recovery information sheet/checklist, which they will be encouraged to complete on a daily basis before and after surgery (eight days in total).
Although this is an additional task, it is key to the treatment as it both educates and empowers patients in their recovery after surgery.
All trial participants will have to complete questionnaires (ten in total). To minimise inconvenience, these questionnaires are as short and simple as possible, and all participants will be shown how to fill them out. All questionnaires after discharge will have a stamped addressed envelope to make it easier for patients to return them by post. The contact details of members of the clinical research team will be given to all patients who can then contact them in the event of any concerns or questions regarding the study.

Who can take part?
All patients due to have an elective open liver resection at the Royal Surrey County Hospital are being invited to participate.

Where is the study run from?
Royal Surrey County Hospital NHS Foundation Trust.

When is the study starting and how long is it expected to run for?
The trial is expected to run from early 2011 to early 2012.

What are the risks to participants?
Undergoing liver resection surgery presents risks. There will be no additional risks for patients who participate in the trial compared with those who do not. The risks from anaesthesia and surgery will be the same for both the treatment and the control group. All the aspects of the enhanced recovery program (including the peri-operative carbohydrate drinks, goal-directed fluid therapy, early mobilisation and early feeding) have been shown to be safe without increasing risk to the patient.

Who is funding the project?
The Research and Development Department of the Royal Surrey County Hospital, together with GUTS (Guildford Undetected Tumour Screening) and LCSA (Liver Cancer Surgery Appeal) charities, are funding the project.

Who is the main contact?
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Contact information

Type(s)
Scientific

Contact name
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Contact details

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
v3

Study information

Scientific Title
Enhanced recovery in liver resection surgery: a single-blinded randomised controlled trial

Study objectives
The post-operative length of stay after liver resection will be significantly shorter in the enhanced recovery and goal-directed fluid therapy (GDFT) group (intervention group, IG) compared to the standard therapy group (control group, CG).

Secondary hypotheses: there will be a reduced morbidity, improved quality of life and patient satisfaction with no difference in pain scores in the IG. The IG will also show improved cost effectiveness compared to the CG. The IG will show a reduced stress response and a lower reduction in cell-mediated immunity when compared to the CG.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approval granted by Surrey Research Ethics Committee on 06/01/2011, and amended on 22/03/2011, Ref: 10/H1109/83

Study design
Single-blinded randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Quality of life

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Liver resection surgery

Interventions
Randomisation patients will be randomised into the IG or CG. Randomisation will be carried out by an independent statistician in the Department of Mathematics, University of Surrey. Concealment will be achieved by the use of brown opaque envelopes containing group allocation for the next patient in the trial.

Sample size The sample size calculation has been based on the level of variation (mean = 9.213, SD = 4.946) of postoperative length of stay determined by a prospective audit of all patients undergoing liver resections at the hospital in the last 12 months. We consider that a clinically (and economically) significant reduction in hospital length of stay is 3 days; this is also what other surgical Event-Related Potentials (ERPs) have achieved. In order to determine (with a power of 80%, using a two-sided two-sample Students t-test), whether the IG group have a 3-day (or 30%) reduction in postoperative length of stay compared to CG, a minimum of 89 patients will be required (i.e. 45 patients in each group). Currently the unit undertakes around 100 liver resections/year. Assuming 30% do not wish to participate or do not meet eligibility criteria, we will need 15 months to meet our achieved sample size. We are assuming no drop out following recruitment, since all patients will have a hospital length of stay.

Blinding Group allocation will be un-blinded to the patient and the clinicians, but to reduce bias both groups will be treated using strict protocols. Two independent assessors (who will be blinded to group allocation) will assess whether the patient is ready to be discharged home (main outcome measure). The patient will only be discharged from hospital if both assessors agree to discharge. The outcome measure of Quality of Life (QoL) and pain will be completed by the patient following a reminder from the Clinical Nurse Specialist (blinded to group allocation). It will not be possible to blind the Research Fellow (RF), so the outcome measures of post-operative morbidity and surgical complications will not be blinded.

The intervention group
(Enhanced recovery and goal-directed therapy group)
Interventions - the patient will receive a comprehensive patient checklist. Patient education is an important part of the ERP. The leaflet explains the daily goals the patient needs to achieve (in terms of nutrition and mobilisation). Although this is an additional burden it actually forms a key part of the treatment by both educating and empowering the patient in their recovery after surgery.

1. Pre-operatively
1.1. Nutritional supplements (Fortisip®- Nutricia) taken for three days prior to surgery (one bottle, three times/day). These supplements will be given to the patients at pre-assessment

clinic by the research fellow (RF), following randomisation into the IG. They will be instructed how and when to take them by the RF and the patient checklist contains written prompts to help remind them.
1.2. Night before surgery (21:00) the patients take 100g carbohydrate drink (preOp Nutricia), and further 50 g 2 hours before surgery. The patients will have been supplied these carbohydrate drinks at the same time as they received the nutritional supplements.
1.3. Pre-operatively 10 ml venous blood taken for stress response analysis.
2. During surgery
2.1. The anaesthetic management is standardised for both groups
2.2. The surgical management and technique is the same for both groups, apart from a more rationalised approach to nasogastric tubes and surgical drain usage in IG i.e. rather than the routine placement of drains and nasogastric (NG) tubes, these will only be used if deemed clinically necessary by the surgical team
2.3. To reduce bleeding, all patients are deliberately fluid restricted during theatre (standard practice). Once the resection is complete the patients in the IG will receive fluid therapy as per the goal-directed fluid therapy (GDFT) protocol with the LiDCO Rapid monitor
3. Post-operatively (afternoon of day of surgery)
3.1. In addition to routine blood tests, 10 ml venous blood taken for stress response analysis from central venous line in patients neck
3.2. The patient will go as normal to a level 2 critical care bed, where the GDFT will continue for 6 hrs
4. Day 1 post-operatively
4.1. In addition to routine blood tests, 10 ml venous blood taken for stress response analysis from central venous line in patients neck
4.2. Oral fluids and diet will be encouraged immediately
4.3. Patients will continue the nutritional supplements (Fortisip®) three times/day. If tolerating this, intravenous (IV) fluids will be stopped
4.4. Patients will be mobilised from bed to chair or marching on the spot by the physiotherapists (morning and afternoon), as their clinical condition allows
4.5. Patients will be started on regular oral analgesia (evening)
5. Day 2 post-operatively
5.1. In addition to routine blood tests, 10 ml venous blood taken for stress response analysis from central venous line in patients neck
5.2. 07:00, 3 mg diamorphine will be administered via the epidural (this is routine practice prior to epidural removal in our unit)
5.3. 09:00, epidural and urinary catheter will be removed. Once the epidurals down, mobilisation will be encouraged in line with the daily goals
5.4. Nutritional supplements will continue until patient is ready for discharge
5.5. Patients will be reviewed twice/day by the researchers to check that daily goals have been met and assess daily pain scores
6. Days 3 onwards post-operatively
As the central line will have been removed by this point, the final 10 ml of venous blood required for stress response analysis will be obtained via venepuncture of a peripheral vein in the patient s arm (at the same time as routine blood tests are being taken), performed by the anaesthetic clinical fellow on day 3. Patients will be assessed to ensure daily goals are met. From Day 4 onwards, two assessors blinded to patient group will individually assess whether discharge criteria have been met using a checklist of the following criteria: good pain control with oral analgesia, tolerance of solid food, independently mobile, normal or decreasing serum bilirubin and patient willing to be discharged

Control group (standard perioperative care)
1. Once randomised to the CG the patient will continue with normal pre-assessment. Starvation

times will be as normal.
2. On the morning of surgery, 10 ml venous blood taken for stress response analysis from newly inserted cannula in arm of patient (IV access is routinely required to administer anaesthesia)
3. After surgery, the patient will be fluid resuscitated (standard practice), using central venous pressure, central venous oxygen saturations and lactate levels as surrogate markers of perfusion. Post-operatively all patients will be admitted to (minimum) Level 2 critical care
4. In addition to the routine daily blood tests that the patients undergo, 10 ml of venous blood for stress response analysis will be sampled on four further occasions (immediately post-op and on the morning of days 1, 2 and 3 post-op) either from the central line in the patients neck, or peripheral venepuncture if this has been removed.
5. The epidural will continue to be reviewed by the pain team and will be discontinued on their advice. This is usually on day 3 or 4 currently. The urinary catheter will be removed 12 hours later as is current practice. Oral intake of fluids and diet is permitted immediately post-operatively but no specific dietary goals are set. On day one post-op, patients are mobilised from bed to chair by the physiotherapists, as their clinical condition allows, but are only seen once a day. On successive days mobilisation will be allowed as usual but with no specific daily goals.

In summary, both groups will have the same high-quality anaesthetic, surgery and post-operative care. The treatment group will have extra pre-operative education on what to expect during their operative course, pre-operative nutritional supplements, GDFT for 6 hours once the liver resection is completed, daily post-operative nutritional and mobilisation goals to lead to earlier oral intake and accelerated functional recovery

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Fortisip®

Primary outcome measure
The post-operative length of stay (in days): two independent assessors (who will be blinded to group allocation) will assess whether the patient is ready to be discharged home. The patient will only be discharged from hospital if both assessors agree to discharge.

Secondary outcome measures
1. Quality of Life (using EQ-5D)
2. Patient satisfaction
3. Incidence of post-operative morbidity (using Post-Operative Morbidity Survey [POMS])
4. Pain scores (Visual Analogue Score 0-10)
5. Stress response and cell-mediated immunity. The venous blood samples obtained from the patients will be analysed for the following:
5.1. Insulin, cortisol and glucose levels - to assess endocrine and metabolic response
5.2. C-reactive proteins (CRP) and cytokines (including interleukin [IL] 2, IL 4, IL 6, IL 8, IL 10, granulocyte-macrophage colony stimulating factor [GM-CSF], interferon gamma, tumour necrosis factor alpha) to assess the inflammatory response
5.3. T-cell markers (CD3, CD4, CD8, CD45RO, HLA-DR), natural killer (NK) cell markers (CD56, CD16) to assess the immune response

Overall study start date
22/03/2011

Completion date
22/07/2011

Eligibility

Key inclusion criteria
All adult open elective liver resections

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
90 patients, with 45 in each arm

Key exclusion criteria
1. Contraindications to epidural anaesthesia
2. Combined liver procedures e.g. with biliary surgery
3. Laparoscopic surgery
4. Adults unable to give informed consent

Date of first enrolment
22/03/2011

Date of final enrolment
22/07/2011

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Department of Anaesthesia and Intensive Care
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Sponsor information

Organisation
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Sponsor type
Hospital/treatment centre

ROR
https://ror.org/050bd8661

Funder(s)

Funder type
Government

Funder Name
Royal Surrey County Hospital NHS Foundation Trust (UK) - R&D Department

Funder Name
Guildford Undetected Tumour Screening Charity (G.U.T.S) (UK)

Funder Name
Liver Cancer Surgery Appeal Charity (LCSA) (UK)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/07/2013		Yes	No