PROTOCOL

Early recovery after preoperative high dose glucocorticoids for liver resection- a randomized double-blinded trial

EudraCT number: 2017-002652-81

Approved date: 06.09.2017

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Introduction

Liver resection is mainly performed for primary or secondary tumors (hepatocellular carcinoma, cholangiocellular carcinoma and colorectal cancer metastases). Advances in surgical techniques and perioperative optimization in fast track protocols have reduced morbidity and mortality with a subsequent reduced length of stay[1]. However, the existing pre-operative morbidity of most patients undergoing liver resection and the extent of the surgical procedure means that recovery still represents a challenge with postoperative complication rates in up to 40% depending on definitions and time frame[2–6]. Furthermore, postoperative complications are also related to the extent of surgery, type of anesthesia, any intraoperative complications, and in the immediate postoperative phase potentially also to the extent of the surgical stress response[7,8]. The surgical stress response can theoretically be reduced by the use of pre-operative glucocorticoids (GCs) by the downregulation of pro-inflammatory proteins and upregulation of anti-inflammatory proteins, resulting in an overall negative feedback on immunostimulation[9,10]. Several studies have reported the effect of preoperative GCs compared with control groups in reducing inflammatory cytokines and biomarkers of liver damage after liver resection surgery[6,11–13]. The GC effect on these surrogate outcomes has been shown to be statistically significant mostly on postoperative day one, but also evident immediately after surgery when measured within the first postoperative hours[12,13]. However, there is no evidence as to whether inflammatory control is related to a reduction in clinically relevant complications, as these have not been investigated as the primary outcomes in previous liver resection studies of preoperative GC administration. However, a lower overall morbidity rate[6] and reduced length of stay[6,11] in the GC intervention groups suggest that there might be an effect on these clinical outcomes in liver resection surgery as well as in other surgical procedures[14–19]. To investigate the preventive effects of GCs on adverse clinical outcomes, we chose to focus on the immediate postoperative phase (during post-anesthesia care unit (PACU) stay) where all patients are closely monitored, treated and discharged according to well-defined protocols.

Aim

The aim of this study therefore was to investigate whether a high dose of GCs (10 mg/kg methylprednisolone (MP)) given as a single pre-operative injection could reduce complications in the immediate post-operative phase compared to a standard low dose postoperative nausea and vomiting (PONV) prophylaxis of glucocorticoids (8 mg of dexamethasone) after liver resection. The primary outcome was number of patients with complications requiring treatment during observation in the PACU according to predefined criteria. We additionally hypothesized that high dose glucocorticoids would reduce length of stay in the PACU, lower pain scores and opioid consumption in the first 3-4 days after surgery without increasing 30-day morbidity.

Outcomes

Primary outcome

The primary endpoint was number of patients with a complication requiring treatment in the PACU, defined according to a standardized post-anesthesia discharge score (a modified version of the Aldrete discharge score[22] – supplemental digital content (SDC) 1). The score consists of six modalities (sedation, oxygen saturation, blood pressure (BP), heart rate (HR), pain (at rest) and nausea).

A PACU complication was defined as any score > 1 (except > 2 for saturation), on two consecutive measurements 30 minutes apart OR a score >1 at one timepoint accompanied by a relevant treatment (e.g. pain on a numeric rating scale (NRS)> 3, accompanied by a rescue opioid administration, brady- or tachycardia accompanied by frequency regulation/conversion for arrythmia, PONV accompanied by antiemetic treatment) OR relevant treatment for > 30 minutes regardless of score (continuous inotropic infusion for hypotension, >2L oxygen supply or other respiratory treatment).

Secondary outcomes

1. Mortality, all cause 30-day mortality.
2. Morbidity, 30 days (liver failure, ascites, intraabdominal fluid collection, bleeding, cholascos, bowel obstruction, perforated visceral organ, fascial disruption, other causes for reoperation, pleural effusion, pulmonary embolus, deep venous thrombosis, acute myocardial infarction, transitory cerebral ischemia, stroke, infections (pneumonia, UTI, sepsis, wound infection), other causes for prolonged hospitalization).
3. Number of patients with a complication requiring treatment during the first 24 postoperative hours. Any complication requiring treatment (procedural, medication, alterations in standard care).
4. Pain during movement (mobilization to sitting position or coughing). Pain scores (Numeric Rating Scale (NRS) 0-10), measured every hour during PACU stay (average).
5. Pain during admission. Reported once daily on a NRS scale (0-10), on postoperative day 0 to 4 (or day 3 if discharged).
6. Analgesic medication, rescue opioids during admission (postoperative day 0 to 4 (or day 3 if discharged). Converted to oral morphine equivalents (OMEQ) according to a standardized opioid conversion chart[23].
7. Nausea during admission. Reported once daily on a 4-NRS scale (no, light, moderate or severe nausea), postoperative day 0 to 4 (or day 3 if discharged).
8. Length of stay, PACU and hospital (measured from time of operation until time of discharge).
9. Changes in liver enzymes and function tests (alanine transferase (ALT), prothrombin time, total bilirubin) at baseline (preoperative evaluation) and on postoperative days 1 (all patients), 2 and 3 (major resections).

Methods

Study design

Randomized, double-blind, controlled intervention study. Superiority design.

Randomization and blinding

Patients were informed by trial personnel (KJS or HNA) in relation to the pre-operative appointment, usually 1-2 weeks prior to the operation and included in the trial on the day of surgery after written consent. Participants were stratified according to planned extent of surgery (major resections (≥ 3 liver segments) and minor resections (< 3 liver segments) and randomized 1:1 in parallel groups by block randomization. Block sizes varied (4,6,8) and were unknown to study personnel. The allocation sequence was generated by an independent physician using

Sealed Envelope Ltd 2017[20]. The allocation sequence with intervention details was concealed in consecutively numbered opaque envelopes by two other investigators not otherwise involved in the trial. Before sealing, 20% of the envelopes were randomly controlled, and the allocation sequence was stored by a physician not otherwise involved in the trial. After trial completion, the principal investigator received the allocation sequence without intervention revealed. The intervention allocation was revealed after performing statistical analysis and drafting the paper, including results, conclusion and comments from all authors. Throughout the trial, all participants, trial personnel, health care providers including surgeons, anesthetists and nurses, outcome assessors and data monitor were blinded. There were no code breaks during the trial.

Intervention

The high dose (HD) group received 10 mg/kg of MP (Solu-medrol®, Pfizer, Denmark) and the standard dose (SD) group received 8 mg of dexamethasone (Dexavit, Vital Pharma Nordic, Denmark). On the day of surgery, trial personnel (only assigned to prepare the intervention) received and opened the sealed envelope and prepared the trial drug. Both the HD and the SD were injected in a sterile (drip) bag containing 100 ml NaCl, covered in foil concealing content and amount. The bag was labelled with patient identification and handed to trial personnel together with the resealed and signed envelopes. Trial personnel administered the medication in 10 minutes immediately after anesthesia induction, around 30 minutes prior to surgery. The drip was flushed with NaCl at the end of administration of the trial drug.

Time schedule

Study expected to start: December 2017
Study expected to finish: August 2020

Location

Copenhagen University Hospital, Rigshospitalet, Denmark. Department of Orthopedic Surgery, and Department of Anesthesiology, Centre of Head and Orthopedics.

Participants

Number of participants: 174, 87 in each group.

Inclusion criteria

All patients scheduled for open liver surgery without biliary reconstruction were consecutively screened for inclusion. Patients considered were 18 years of age or older and able to provide informed oral and written consent. Exclusion criteria were planned simultaneous operation on other organs, simultaneous operation for herniation with insertion of mesh, planned two-stage or ALPPS procedure (Associating Liver Partition and Portal vein Ligation for staged hepatectomy), active Hepatitis C virus infection, daily/current use of glucocorticoids or immunosuppressant medication (within 10 days before the procedure), insulin-dependent diabetes, pregnancy or lactation.

Procedures

Inclusion and randomization

Eligible patients are informed about the trial in relation to the pre-operative appointment. Enrolled participants are randomized and assigned to consecutive numbers at the morning of surgery.

Standard care procedures

All patients were treated according to a well-implemented enhanced recovery after surgery (ERAS) protocol described previously [1,21]. Before surgery, all patients had an epidural analgesia catheter

inserted at Thoracic level 8-10, which was maintained with a continuous infusion of bupivacaine/morphine (2.5 mg + 50.0 µg ml^{-1}). After induction a 30 mg bolus of 0.5% bupivacaine was administered, and 15 mg 0.5% bupivacaine was repeated every hour during surgery. Anesthesia was induced with propofol (1.5-2.5 mg kg^{-1}), remifentanil (0.3-0.8 µg kg^{-1}) and cisatracurium (0.1 mg kg^{-1}) or suxamethonium (1 mg kg^{-1}). Anesthesia was maintained with propofol 0.05-0.15 mg kg^{-1} min^{-1}, remifentanil (0.3-0.8 µg kg^{-1} min^{-1}) and cisatracurium aiming at a train of four (TOF) response of 0%. In cases with impaired liver function in combination with major resection, sevoflurane could replace propofol. Norepinephrine infusion was administered to maintain a mean arterial pressure (MAP) > 60 mmHg. During resection, central venous pressure (CVP) was maintained around 4-5 mmHg. Ondansetron (4 mg) was administered 30-45 minutes before the end of surgery. Before extubation, a TOF ratio >90% was confirmed.

Monitoring included invasive arterial blood pressure, central venous pressure, ECG, pulse oximetry, nasopharyngeal temperature, nerve stimulator, urinary catheter and a nasogastric tube.

The surgical procedure was preferably performed through a curved subcostal incision extended in the midline to the xiphoid process (Th 7-10). In case of resections in the left lateral segment an upper midline incision was used. The resection was categorized as major if the resection equalized 3 or more segments, otherwise as minor. If hepatic clamping was performed, intermittent Pringle maneuver was applied for a maximum of 15 minutes at a time with 5 minutes intervals in between if repeated. Perioperative antibiotic was a single dose 2 grams of ceftriaxone. In case of bleeding exceeding 1000 ml it was continued as 1500 mg of cefuroxime 3 times daily and metronidazole 1500 mg once daily for three days. Drains were placed according to intraoperative bleeding and the surgeon´s evaluation of risk for bile leakage (typically major resections). It was planned removed on POD 1 in case there was no bleeding or bile leakage. Low molecular weight heparin was initiated on the morning of surgery and continued until full mobilization.

Nasogastric tubes were removed immediately after the procedure in the operating room. The radial artery cannula was removed on POD 0 before discharge from the PACU, the central venous catheter was removed on POD 1 in minor resections, and POD 3 in major resections. Urinary catheter was removed on POD 1.

Postoperative pain management consisted of epidural infusion of bupivacaine/morphine (2.5 mg + 50.0 $µg^{-1}$ ml^{-1}) infusion starting intraoperatively at 5 ml h^{-1} but titrated depending on effect/adverse effects and continued for a maximum of 3 postoperative days. Modified release acetaminophen 1330 mg every 8 h was started immediately after surgery (individual prescription in the major resection group). On the evening of POD 2 additional 200 mg celecoxib and gabapentin 600 mg was started (reduced dose if weight< 50 kg or age >65 years or in case of impaired renal function), and continued every 12 h (celecoxib 200 mg, gabapentin 300 mg in the morning and 600 mg in the evening) for one week.

In uneventful postoperative courses, discharge was expected and planned on POD 3 or 4.

Data management

Before patient enrolment, the trial is approved by the local ethics committee, the Danish data protection agency and the Danish Medicines Agency. The trial will be registered at

ClinicalTrials.gov and EudraCT and will be monitored by the Good Clinical Practice unit at a Copenhagen University Hospital.
Data belongs to sponsor.

Case Report Form

Every patient enrolled will have a case report form signed by investigator. REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Rigshospitalet will be used as case report form. Signed informed consent forms will be kept in a separate folder.

Clinical evaluations and outcome registration

Data are collected from the EPIC based electronic medical record and managed using REDCap electronic database hosted at Rigshospitalet[24] . Variables collected are:

Demographics (age, gender, weight, height, indication for surgery (disease), comorbidities, smoking and alcohol habits, medication, prior abdominal operative history, recent chemotherapy history) and intraoperative data (time of start and end of surgery, time of extubation, duration of hepatic clamping, insertion of drains, amount of anesthetics and fluids administered, bleeding, blood component therapy, level of epidural insertion, type of incision, procedures performed, including additional (unplanned) procedures). Postoperatively PACU data were collected (time of admission and discharge, vital values (BP, HR, oxygen saturation, respiratory rate) and pain, nausea and sedation every 30th minute, pain at mobilization every 60 minutes, and treatments administered (oxygen supply, analgesics, antiemetics, blood component therapy, fluid administered, vasopressors)) and the ward (vital values, pain, nausea and sedation at admission and any complications requiring treatment within 24 hours, analgesic and antiemetic treatment until POD 4 or discharge (whichever came first), discharge from hospital). All-cause mortality, readmissions (unplanned and related to surgery) and morbidity as described in secondary outcomes were assessed 30 days after surgery.

Biomarkers (hemoglobin (Hb), platelets, creatinine, potassium, sodium, prothrombin time (International Normalized Ratio (INR)), alanine aminotransferase (ALT), bilirubin) were collected for all patients at baseline and POD1, and for major resections also on POD 2-3.

Patients were requested to fill out a questionnaire every day on POD 0 to 4 (or discharge, whichever came first) containing following elements pertaining to the last 24 hours (except on POD 0, only time from after surgery until bedtime): Pain (NRS 0-10) in average and at worst, nausea (none, light, moderate, severe) in average and at worst, vomiting (yes/no), feelings of sadness (yes/no), restlessness (yes/no) or fatigue (yes/no), quality of sleep (good, trouble falling asleep, frequent awakenings, no sleep).

Sample size

The sample size calculation was based on internal audit and previous reports of a 40% complication rate in the PACU. An expected 50% reduction in the intervention group required 174 patients (87 in each group), with a 5% significance level and a power of 80%.

As patients were included and randomized at the time of operation, no dropout rate was expected.

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