Preoperative steroid in abdominal wall reconstruction: protocol for a randomised trial

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ABSTRACT

INTRODUCTION: Preoperative administration of high-dose glucocorticoid leads to improved recovery and decreased length of stay after abdominal surgery. Even so, studies on administration of glucocorticoids for patients undergoing abdominal wall reconstruction (AWR) for giant ventral hernia repair are lacking, perhaps due to a fear of impaired wound healing. We hypothesised that patients undergoing AWR would benefit from preoperative glucocorticoids and aimed at examining this in a randomised controlled trial.

METHODS: A total of 40 patients scheduled to undergo AWR for ventral hernias with a fascial defect exceeding 10 cm will be randomised for intravenous administration of either 125 mg methylprednisolone or saline at the induction of anaesthesia. The primary endpoint is pain at rest on the first post-operative day. Patients will be followed until 30 days postoperatively, and secondary outcomes include subjective measures, wound complications and analysis of blood and wound fluids.

CONCLUSIONS: This is the first trial on the effect of preoperative glucocorticoid administration in patients undergoing AWR. Due to long post-operative stays and a high rate of post-operative complications, this patient group can potentially benefit much from any post-operative optimisation. Furthermore, insight into any impact of glucocorticoids on wound healing in hernia patients may provide important information.

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TRIAL REGISTRATION: This study was registered with Clinicaltrials.gov (NCT02594241) and Eudra-CT (2015-004916-39).

Preoperative high-dose glucocorticoid has been shown to attenuate the post-operative inflammatory response [1] which leads to decreased morbidity and shorter length of stay (LOS) after colorectal and aortic surgery [1-3] as well as to a reduction of pain and improved subjective recovery after orthopaedic surgery [4, 5]. Methylprednisolone (MP, Solu-Medrol, methylprednisolonsuccinat) is one such glucocorticoid which has been shown to be safe for usage in surgery [6-9]. Abdominal wall reconstruction (AWR) for giant ventral hernia repair is associated with a high risk of post-operative morbidity and prolonged LOS compared with other hernia repair procedures requiring laparotomy [10-14]. Furthermore, the total costs of these procedures remain high [15]. Systemic administration of high-dose preoperative MP in ventral hernia repair has only been described anecdotally in the literature [3], and never with the aim of specifically improving the treatment for this patient group. At Bispebjerg Hospital, preoperative high-dose MP has been part of standard care for patients undergoing AWR since December 2014 [16]. It is, however, unknown to what extent benefits outweigh the potential drawbacks of using high-dose MP in AWR; patients are often at increased risk of post-operative wound morbidity [17]. Because a multimodal enhanced recovery pathway was implemented concurrently with the introduction of MP, any independent beneficial effect of MP warrants further investigation.

On this background we hypothesise that compared with placebo a preoperative high-dose MP results in improved recovery after AWR for giant ventral hernia repair.

METHODS

Study design and participants

This is a randomised double-blinded, placebo-controlled trial. Consecutive patients scheduled for elective repair of a giant (≥ 10 cm transverse fascial defect described on computed tomography) incisional hernia are screened and assessed for study eligibility when their operation is scheduled. The expected number of patients to be randomised and provide data for the primary outcome (that is, who are assessable for evaluation) is 40. In case of an unexpectedly high number of dropouts who do not provide data for the primary outcome, a protocol amendment seeking approval to include additional participants will be sent to the relevant authorities. Inclusion and exclusion criteria are shown in **Table 1**.

Randomisation

The study will be performed as a randomised, double-blinded, placebo-controlled trial with a 1:1 allocation ratio. Randomisation will be performed using a computer-generated sequence with varying block sizes. Based on this, a total of 40 randomisation envelopes and 40 sealed "code"-envelopes will be made. The randomisation and creation of the envelopes will be carried out by a physician who is not involved in the study.

PROTOCOL ARTICLE

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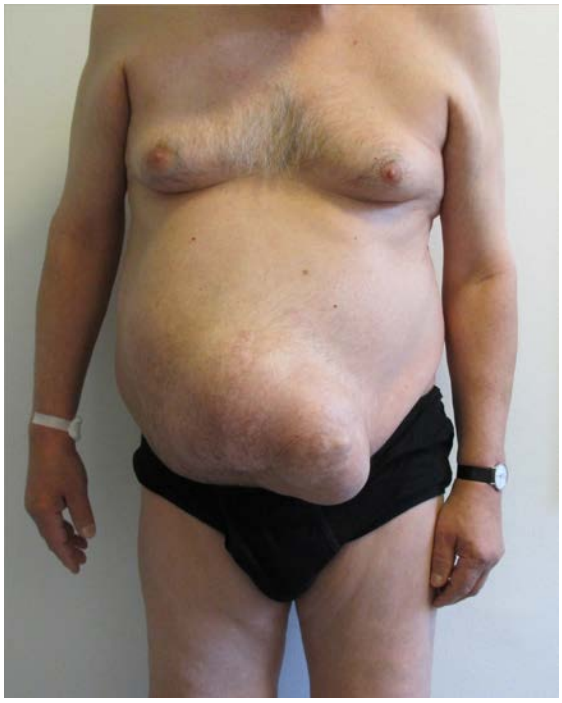

Patient with a giant incisional hernia.

Randomisation envelopes: Each envelope will contain information about whether the patient is to receive study medicine or placebo. In addition, a note with information on how to administer the drug will be placed in the envelope. Lastly, the envelope will contain a form where the nurse administering the drug can write the batch number of the drug and a label that will be used to re-seal the envelope.

Code envelopes: Each envelope will contain information on whether the patient was randomised to receive study medicine or placebo. The code envelopes are kept by the study sponsor and serve as backup in case of any adverse event necessitating repealing of the blinding.

The unmasked randomisation list will be kept by a doctor not involved in the study and will not be given to the principal investigator until the data analysis is complete. After randomisation, the drug (study medicine or placebo) will be prepared by a person not involved in the study. In order to uphold complete blinding, the syringe will be covered by a blank label and afterwards given to the anaesthesiologist in the operating room who will administer the drug. Thus, no persons in the operating room will know which drug is administered.

The person who prepares the drug notes the batch number of the drug on the paper found in the randomisation envelope and then re-seals the envelope and writes his/her initials and date on the label. All randomisation envelopes are kept in a locked room, but are accessible to the attending anaesthesiologist at all times.

TABLE 1

Inclusion criteria and exclusion criteria.

Inclusion criteria
Age ≥ 18 yrs
Ventral incisional hernia with a horizontal fascial defect ≥ 10 cm described at *either* clinical examination *or* computed tomography
Planned elective open hernia repair
Ability to speak and understand Danish
Ability to give written and oral informed consent
Exclusion criteria
Daily use of systemic glucocorticoid[a]
Heart disease: New York Heart Association class 3-4[a]
Chronic renal failure[a]: estimated glomerular filtration rate < 60 ml/min. per 1.73 m^2
Insulin-dependent diabetes[a]
Excessive abuse of alcohol, as per investigators estimate[a]
Known allergy to methylprednisolone or any substance in the study of medicine[a]
Planned pregnancy within 3 mo. post-operatively[a]
Pregnancy, evaluated by pregnancy test[b]
Breastfeeding[b]
Actively treated peptic ulcer disease within 1 mo. preoperatively[b]

a) Evaluated at planning of surgery.

b) Evaluated within 1 week preoperatively.

Standard treatment prior to intervention

An hour preoperatively, paracetamol 1 g, ibuprofen 600 mg and gabapentin 600 mg are administered orally and low-molecular-weight heparin 3,500 IE given subcutaneously. An epidural catheter is applied in the relevant vertebral interspace according to the location of the hernia. In case epidural access is contraindicated or impossible, a transversus abdominis plane block is applied. Anaesthesia is induced with remifentanil and subsequently maintained with sevoflurane. Muscle relaxation is achieved by rocuronium.

Study intervention

After induction of anaesthesia and prior to surgery, either methylprednisolone 125 mg or sodium chloride (placebo) is administered intravenously according to the randomised allocation.

Standard treatment after intervention

Post-operative analgesics consist of epidural analgesia (bupivacaine 0.25% and morphine 0.2 mg/ml, 4-6 ml/h) and orally administered ibuprofen 400 mg × 3 and paracetamol 1 g × 4. The epidural analgesia is discontinued on post-operative day two, at 9 p.m, and subsequently removed the morning after. One hour prior to the pausing of the epidural analgesia, morphine 10 mg is administered orally as analgesic bridging. Rescue analgesics consist of either orally or intravenously administered morphine or oxycodone.

Supplemental oxygen (2 l/min.) is administered when the patient is in supine position during the first two post-operative days. In addition, supplemental oxygen is given when the peripheral capillary oxygen saturation is below 0.92, aiming to keep saturation above 0.91. Drains are removed when the daily production is below 60 ml per drain. Early oral feeding is commenced immediately post-operatively. An enaema is administered at post-operative day 2 in the morning if bowel function is not present. Patients are mobilised from the bed post-operatively as soon as possible, preferably upon returning from the recovery ward. Pulmonary physiotherapy is initiated within 24 h after surgery. For prevention of post-operative ileus, chewing gum is administered four times a day and patients are encouraged to chew for at least 30 min. per administration.

Surgical procedure

Due to the heterogeneity of ventral hernias, the surgical procedure for hernia repair varies to some extent. However, the following steps are included in every procedure: Laparotomy and adhesiolysis, retromuscular prosthetic mesh placement ad modum Rives-Stoppa and closure of the fascia and skin. One to two drains are placed subcutaneously. If we anticipate that midline closure will be difficult, bilateral endoscopic anterior component separation is performed prior to laparotomy [18]. An abdominal binder is applied while the patient is still in the operating theatre, and patients are instructed to wear the binder until clinical follow-up 30 days post-operatively.

Outcome measures

The primary outcome of the study is self-reported pain at rest on a numerical rating scale (0-10) on the first post-operative day, at 8 a.m. (± 1 h). All study outcomes are shown in **Table 2**.

Ethics, monitoring and trial registration

Whether or not patients who undergo giant incisional hernia repair benefit from preoperative high-dose glucocorticoid has never been examined. Our hypothesis is that this treatment optimises the post-operative course for this patient group, and the results of this study will be of much importance to patients who are to undergo giant incisional hernia repair in the future. Thus, the expected benefits from the present study outweigh any potential drawbacks.

This study is monitored by the Good Clinical Practice unit (GCP) at Copenhagen University Hospital and will be conducted in accordance with the principles of GCP. The study has been approved by the Danish Data Protection Agency (ref. BFH-2015-076), the Research Ethics Committee of Copenhagen (Protocol No. H-2015-15017445) and the Danish Health Authority (2015-004916-39). Furthermore, the study is registered with clinicaltrials.gov (NCT no 02594241) and EudraCT (2015-004916-39).

Statistical considerations

Preliminary pilot studies have been carried out at the Digestive Disease Centre, Bispebjerg Hospital, in order to perform sample size calculations. Ten patients with giant incisional hernia undergoing incisional hernia repair were included. Mean self-reported pain on a visual analogue scale on the first post-operative day at 9 a.m. (± 1 h) was 3.64 (standard deviation 1.28). A 25% reduction in pain is considered clinically relevant and thus aimed for in the present study. For the sample size calculation, a two-sided, one-sample t-test was used: Considering a 0.05 significance level and a power of 0.80, a total of 36 patients is required for randomisation (18 in each group). Thus, taking dropouts into account, 40 patients are planned for inclusion in the present study. The study is completed when the last included patient has completed 30-day follow-up, and a minimum of 36 patients have provided data for the primary endpoint.

TABLE 2

Outcome measures.

Primary outcome
Self-reported pain at rest on a NRS: 0-10 on the 1st post-operative day, at 8 a.m. (± 1 h)
Secondary outcomes
Subjective:
Fatigue (NRS) on post-operative days 0-5 at 8.00 a.m. and 8.00 p.m.
Time to discharge (days): subjective assessment of discharge criteria at 8.00 a.m. & 8.00 p.m.
Pain (NRS) on post-operative days 0-5 at 8.00 a.m. and 8.00 p.m.: at rest, immediately after moving from supine to sitting position, when coughing
Nausea (NRS) on post-operative days 0-5 at 8.00 a.m. and 8.00 p.m.
Pain at 30-day post-operative control
Nausea at 30-day post-operative control
Fatigue at 30-day post-operative control
Objective:
Number of vomiting episodes on each post-operative day 0-5
Number of 30-day post-operative complications
30-day readmission
30-day surgical reintervention
Volume of drain output in each drain at post-operative day at 1.00 a.m. and 8.00 a.m. (± 1 h)
Concentrations of interleukin-6, interleukin-10 and tumour necrosis factor-α in drain fluid on post-operative days 1-3
Concentrations of interleukin-6, interleukin-10 and tumour necrosis factor-α in blood preoperatively and on post-operative days 1-3
Need for and required doses of rescue analgesics
Concentration of serum C-reactive protein preoperatively and on post-operative days 1-3, 8.00 a.m.

NRS = numerical rating scale.

Continuous measures will be reported as median (range) and compared across treatment groups with Wilcoxon's signed rank test, unless data are normally distributed. In this case, Student's t-test will be applied. Categorical parameters will be compared across groups by Fisher's exact test. p-values below 0.05 are considered statistically significant. In addition to the analysis of the primary outcome, fatigue, nausea and pain scores will each be analysed using repeated measurement mixed effect regression, maximum likelihood analysis. Thus, an overall p-value for the mean differences between the two groups will be presented. In case of deviations from the plan for statistical analysis, the information on clinicaltrials.gov and EudraCT will be updated. All statistical analyses will be undertaken using R 3.2 (Foundation for Statistical Computing, Vienna, Austria).

Trial registration: This trial was registered with clinicaltrials.gov (NCT02594241) and Eudra-CT (2015-004916-39).

DISCUSSION

The present study is designed with the overall aim of improving post-operative recovery after incisional hernia repair. Based on the pilot study and clinical experience, this patient group will likely benefit from improved post-operative recovery in the form of reduced nausea, pain and early mobilisation. Although not the aim of this trial, enhanced recovery protocols have been shown to reduce post-operative complications in general. This also offers a potential upside to the introduction of an ERAS protocol after AWR. Furthermore, patients who undergo incisional hernia repair are particularly vulnerable to wound infection due to the implanted mesh. Measures to potentially reduce post-operative complications are thus most relevant.

High-dose glucocorticoid for improvement of post-operative recovery has been examined in several different surgical disciplines [2]. The reason why glucocorticoids have never been introduced in hernia repair is likely a fear of impaired wound healing, which is a well-known side-effect to long-term glucocorticoid usage [19]. Previous studies have reported that a preoperative single-shot, high-dose glucocorticoid does not affect wound healing or morbidity, and we therefore find it ethically justifiable to administer glucocorticoid to patients with high-risk wounds [2, 20].

Extensive analyses of the systemic and local wound healing processes provide insight into any effect of a single-shot high dose of preoperative glucocorticoid. However, this study is not powered to examine any potential effect of glucocorticoid on the long-term incidence of hernia recurrence.

CONCLUSIONS

The current study aims at optimising the treatment of patients with giant incisional hernia, a patient group, which may benefit much from any improvement. Further, the results of the analyses of wound healing may generate novel results.

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