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Abstract

Title of Study	PILOT STUDY OF SINGLE DOSE INTRAOPERATIVE HIGH-DOSE STEROIDS AND OUTCOMES FROM PANCREATIC RESECTIONS
Abstract and methodological description	ABSTRACT Background: There is limited but significant evidence that intraoperative steroids can attenuate the inflammatory response from surgery which in turn, can result in decreased post-operative complications. Currently, only one randomised controlled trial has examined the impact of steroids following pancreatic resection. This study will examine the impact of high dose intraoperative steroids on a range of factors such length of stay, morbidity, inflammatory response (via circulating IL-6 and TNF-alpha levels), resumption of oral nutrition and visual analogue scores (VAS) for pain control, nausea and fatigue after pancreaticoduodenectomy. Methods:

Pilot double-blinded study. The treatment arm will receive 100mg of intraoperative dexamethasone 20mg on induction or normal saline placebo. Primary outcome measures include morbidity (assessed by the Clavien-Dindo system), 30 and 90 Day mortality, High Dependency Unit length of stay, overall length of stay, C reactive protein levels (days 0, 1, 3, 5 and 10 post-operatively), Visual analogue pain scores (VAS), (days 0, 1, 3, 5 and 10 post-operatively), (days 0, 1, 3, 5 and 10 post-operatively), anastomotic leak rates and grade (ISGPS grading), serum amylase (days 0, 1, 3, 5 and 10 post-operatively), drain amylase (days 1, 3, 5 and 10 post-operatively), patient controlled analgesia opiate consumption (converted to opiate equivalent units), oral opiate consumption (converted to opiate equivalent units), resumption of oral nutrition and evidence of delayed gastric emptying (ISGPS definition). Attenuation of an inflammatory response will be assessed with ELISA assays of IL-6 and TNF-alpha on days 0, 1, 3, 5 and 10.
Results:
All data entry will be verified by the main researcher. Statistical analyses planned will be ?² test and Fisher’s exact probability test for categorical data. Student's t-test will be used for comparisons between time points and for comparisons between groups at a particular time point; equal variances will not be assumed. Analysis of variance (ANOVA) will be used to analyse the effects of steroids on the overall results, effect of time factor (time points) on the overall results in both groups and to determine if there is any interaction between both groups. In all cases, a value of $P < 0.05$ will be taken to indicate statistical significance. Data will be presented as mean ± SEM.
BACKGROUND:
There is increasing evidence that intraoperative steroids can ameliorate the systemic response following major surgery. Benefits for gastrointestinal surgery include a reduction in post-operative nausea, shivering, improved recovery satisfaction scores (1). Other benefits include a reduction in post-operative pain scores, reduction in opiod usage (2), a reduction in post-operative delirium (3) improvement in mobility (4) and a reduced length of stay (Los) (5). These positive associations have been observed in a range of different surgeries from intra-abdominal procedures, thoracic surgery, cardiac surgery and orthopaedic surgery. No published study, thus far, has documented an increase in steroid-related post-operative complications (5,6).

In HPB surgery, there is a paucity of data regarding efficacy of intraoperative steroids. Evidence from the use of steroids during liver resection suggests that steroids may reduce the degree of liver dysfunction post-operatively (7) and that steroids in the post-operative period may encourage faster normalisation of liver function tests (8). In pancreatic resections, one single study has demonstrated that steroids reduced the risk of major complications in high-risk patients from 41 to 18% (9). Other work in pancreatic surgery has demonstrated that delayed gastric emptying (DGE) is an inflammatory associated consequence secondary to circulating IL-6 levels (10); making DGE a potential target for steroid administration.

These early results strong suggest that the use of high-dose intraoperative steroids requires further evaluation in pancreatic surgery. The potential beneficial effects include a reduced risk of major complications, reduced DGE, reduced nausea, reduce post-operative delirium, reduced LoS and improved patient satisfaction. There is currently no evidence that the single-use steroids significantly increases post-operative risk or increases cancer recurrence risk (11).

HYPOTHESIS:

Single shot high-dose steroids administered intra-operatively offer beneficial effects in patients undergoing pancreatic resections (due to attenuation of the inflammatory response associated with surgery) with no increase in morbidity or mortality.

OUTCOME MEASURES:

Primary outcome measures include-

• Morbidity (assessed by the Clavien-Dindo system)
• 30 and 90 Day mortality
• High Dependency Unit length of stay
• TNF-alpha and IL-6 serum levels on days 0, 1, 3, 5, and 10 post-operatively
• Overall length of stay
• C reactive protein levels days 0, 1, 3, 5 and 10 post-operatively
• Visual analogue pain scores (VAS) days 0, 1, 3, 5 and 10 post-operatively
• Nausea and vomiting scores (VAS) days 0, 1, 3, 5 and 10 post-operatively
• Anastomotic leak rates and grade, defined by Bassi et al (12)
• Serum amylase days 0, 1, 3, 5 and 10 post-operatively
• Drain amylase on days 1, 3, 5 and 10 post-operatively

• Patient controlled analgesia opiate consumption days 0, 1, 3, 5, and 10 (converted to opiate equivalent units)
• Oral opiate consumption, days 0, 1, 3, 5, and 10 (converted to opiate equivalent units)
• Resumption of oral nutrition and evidence of delayed gastric emptying as defined by the ISGPS (13)
Secondary outcome measures include-
• QOR-40 validated questionnaires for post-operative recovery day 1 and day
• Time to mobilise (days)
• Fatigue levels (VAS), days 0, 1, 3, 5 and 10 post-operatively
• 4-AT delirium score at days 0, 1 and 5 post-operatively
• Neutrophil to lymphocyte ratio on days 0, 1, 3, 5 and 10 post-operatively
• Platelet to lymphocyte ratio on days 0, 1, 3, 5, and 10 post-operatively
INCLUSION/EXCLUSION CRITERIA:
INCLUSION CRITERIA
• All patients with a radiological or histological diagnosis of periampullary cancer.
• Patients undergoing resection of their periampullary cancer
EXCLUSION CRITERIA
• Patients unable to consent to study due to capacity
• Patients already on steroids
• Patients with a history of steroid-related complications
METHODS AND PATIENT SELECTION:
Suitable patients will be identified from MDT discussions. Consent to enter the trial will be obtained in the out-patient consultation prior to surgery. Confirmation of consent will occur after 48 hours of the first consultation. Full demographic data will be collected on all patients including age, BMI, gender, ASA grade, performance status and relevant co-morbidities. All patients will under CPEX testing prior to surgery and receive Level II/III care post-operatively.
Baseline investigations will be collected following full recruitment to the study. These will consist of VAS charts for pain, nausea & vomiting and fatigue. Base-line bloods including CRP, amylase and serum samples of TNF-alpha and IL-6 will be collected at the pre-operative assessment clinic. Demographic data, intraoperative and post-operative data will be collected prospectively using an

existing database. The randomisation code will not be broken until after study completion and data analysis.
The treatment arm will receive 20mg of dexamethasone at induction; the non-treatment arm will receive an equivalent volume of placebo (normal saline). Post-operative bloods will be collected as per the collection timetable. Patients will be asked to complete VAS scores, QOR-40 and AT-4 scores assessing their nausea, pain, post-operative recovery, confusion, fatigue and delirium on days 1, 3, 5, and 10 post-operatively. Bloods will also be collected at these time-points. All patients will be part of an enhanced recovery protocolised pathway and will receive the same post-operative analgesia (intrathecal opiates via a spinal, wound infusion catheter and patient-controlled IV analgesia).
RANDOMISATION:
Patients will be allocated to a unique “kit number” decided by a randomisation spreadsheet, which will be developed and created by an independent third party (Welspring clinical services, Doncaster UK). Randomisation codes will only be broke once the study has been completed and following data analysis.
TIMELINE AND ETHICAL APPROVAL:
The study will be conducted from August 2021 to August 2022. Ethical approval is currently being applied for and the study will be conducted in accordance with the recommendations for Good Clinical Practice with support from the Leicestershire, Northhamptonshire and Rutland Research Ethics Committee UK. Indemnity will be provided by the University Hospitals of Leicester.
STATISTICAL ANALYSIS:
All data entry will be verified by the main researcher. Statistical analyses planned will $?^2$ test and Fisher’s exact probability test for categorical data. Student's t-test will be used for comparisons between time points and for comparisons between groups at a particular time point; equal variances will not be assumed. Analysis of variance (ANOVA) will be used to analyse the effects of steroids on the overall results, effect of time factor (time points) on the overall results in both groups and to determine if there is any interaction between both groups. In all cases, a value of $P < 0.05$ will be taken to indicate statistical significance. Data will be presented as mean ± SEM.
COSTS:

The funding applied for will be used to cover bench fees for ELISA assays to determine TNF-alpha and IL-6 levels.

STUDY PERSONNEL:

The lead investigators will be responsible for the clinical governance and trial design. Patient recruitment, data collection and bench work will be undertaken by a surgical trainee (ST5 or above) as part of his/her higher degree (MD). Salary will be provided by the UHL supporting the on-call emergency rota but with no regular elective commitments. The successful applicant will be registered with the University of Leicester.

DISSEMINATION OF RESULTS:

This body of work will form the basis of higher degree and the study design, methodology, conduct and results will be incorporated into their written thesis. Results from the study will be presented at national and international pancreatic meetings and submitted for publication in suitable peer-reviewed medical journals with a target audience of pancreatic specialists. Any additional support received from will be openly acknowledged as a potential conflict of interest.

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Timetable

Name	Completion of Ethics
Date	June 2021

Name	Recruitment Commencement
Date	August 2021

Name	Recruitment Finish
Date	December 2022

Name	Lab Work Completion
Date	April 2023

Name	Write-up and Analysis
Date	August 2023

Funding

Name	IL-6 96 well kit for both treatment arms
Amount	5000.0

Name	TNF-alpha 96 well kit for both treatment arms
Amount	7000.0

Details of ethical approval

Approval to be completed by 2021

Institutional approval information

Clinical Director for Cancer, Haematology, Urology, Gastroenterology, GI Surgery and Palliative Care
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Declaration

Confirm Declaration: Yes

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