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Randomized Control Trials

Metabolic and inflammatory responses and subsequent recovery in robotic versus abdominal hysterectomy: A randomised controlled study

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SUMMARY

Background & aims: Surgery causes inflammatory and metabolic responses in the body. The aim of the study was to investigate whether robotic-assisted total laparoscopic hysterectomy induces less insulin resistance than abdominal hysterectomy, and to compare inflammatory response and clinical recovery between the two techniques.
Methods: A randomised controlled study at the Department of Obstetrics and Gynaecology, Örebro University Hospital, Sweden. Twenty women scheduled for a planned total hysterectomy with or without salpingo-oophorectomy between October 2014 and May 2015, were randomly allocated to robotic-assisted total laparoscopic hysterectomy or abdominal hysterectomy. Insulin resistance after surgery was measured by the hyperinsulinemic normoglycaemic clamp method, inflammatory response measured in blood samples, and clinical recovery outcomes registered.
Results: There were no differences in development of insulin resistance between the robotic group and the abdominal group (mean ± SD: 39% ± 22 vs. 40% ± 19; $p = 0.948$). The robotic group had a significantly shorter hospital stay (median 1 vs. 2 days; $p = 0.005$). Inflammatory reaction differed; in comparison to the robotic group, the abdominal group showed significantly higher increases in serum interleukin 6 levels, white blood cell count and cortisol from preoperative values to postoperative peak values.
Conclusions: Robotic laparoscopic surgery reduced inflammatory responses and recovery time, but these changes were not accompanied by decreased insulin resistance.
Clinical trial registration: www.ClinicalTrials.gov Identifier no NCT02291406.

1. Introduction

All trauma, whether acute or planned as in surgery, causes a number of reactions in the body. The body enters a catabolic state via release of several inflammatory and neuroendocrine factors, creating a metabolic stress situation. This stress causes release of substrates such as fat, carbohydrates, and protein to be used for energy and as building blocks in the healing process. Insulin is the body's most powerful anabolic hormone. To achieve the mobilisation of substrates, insulin actions are reduced and insulin resistance develops. Insulin resistance after surgery places the otherwise healthy patient in a situation mimicking type 2 diabetes mellitus, with hyperglycaemia despite normal secretion of insulin [1,2].

Inflammatory responses have been studied previously in gynaecological surgery for the purpose of comparing reactions to different surgical techniques in hysterectomy. Studies comparing laparoscopic or vaginal hysterectomy to abdominal hysterectomy consistently show that the more minimally invasive techniques lead to a lesser increase in inflammatory parameters [3–7].

Abbreviations: ERAS, Enhanced Recovery After Surgery; RTLH, Robotic Total Laparoscopic Hysterectomy; AH, Abdominal Hysterectomy; 6MWT, Six minutes walk test; CRP, C-reactive protein; WBC, White blood cell count; BMI, Body Mass Index; VAS, Visual analogue scale; ADL, activities of daily living; WHO, World Health Organisation.

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However, no studies involving robotic-assisted hysterectomy have been performed in this field.

The degree of insulin resistance is believed to reflect the amount of metabolic stress related to the magnitude of the operation [8]. Insulin resistance is also one of the key mechanisms associated with postoperative complications, especially infections [1,9]. Reducing insulin resistance is now believed to be an important mechanism of action for modern perioperative care protocols, such as Enhanced Recovery After Surgery (ERAS) [1].

In one study, laparoscopic cholecystectomy produced less insulin resistance than open surgery, suggesting that minimally invasive techniques result in less metabolic stress [10]. Two early studies have compared glucose metabolism reaction after different kinds of hysterectomy, but no studies have yet investigated the development of insulin resistance in planned gynaecological surgery measured with a clamp technique [11,12].

Lesser invasive techniques like vaginal or laparoscopic/robotic hysterectomies are now recommended and are becoming more common when suitable, depending on indication and the size of the uterus, yet about 50% of hysterectomies in Sweden are still open surgery.

The hypothesis of this study was that robotic-assisted total laparoscopic hysterectomy (RTLH) would induce less insulin resistance than abdominal hysterectomy (AH). In addition, inflammatory response and clinical recovery were compared between the two techniques.

2. Material and methods

The study protocol was approved by the Regional Ethics Board (ref: Uppsala 2014/235), and written informed consent was obtained from each participant.

This was an open, randomised, controlled, single-center study comparing outcome after robotic-assisted hysterectomy with that after abdominal hysterectomy. All women scheduled for a planned total hysterectomy with or without salpingo-oophorectomy between October 2014 and May 2015 at the Department of Gynaecology and Obstetrics, Örebro University Hospital, Sweden were assessed for eligibility. Patients with benign and malignant disease were both included. Inclusion criteria were being over 18 years of age, having adequate knowledge of the Swedish language, and having been assessed as suitable for both techniques. In addition, it had to be possible for the uterus to be removed vaginally without morcellation. Exclusion criteria were metabolic disease including diabetes mellitus or medication causing insulin resistance, severe inflammatory disease, chronic pain and/or pain medication, known severe adhesions in the abdomen, allergy or contraindications to NSAID, mental disability, or severe psychiatric disease. HbA1c was analysed preoperatively.

A computerised randomisation sequence was produced by staff at the Statistical Department who did not otherwise participate in the study. The allocated mode of operation was sealed in opaque consecutively numbered envelopes. The envelopes were opened after inclusion, just before the preoperative clamp. The flowchart is presented in Fig. 1. Twenty women were randomised, and all completed the study.

All hysterectomies were total, and all operations, both open and robotic, were performed by experienced gynaecological surgeons, all as the first patient in the morning. In robotic hysterectomies, the da Vinci Surgery® system (Intuitive Surgical Inc, Sunnyvale, CA, USA) was used, with four ports, and dissection by bipolar and monopolar diathermia. The robotic technique is a minimally invasive surgical technique with similarities to laparoscopic surgery, the main differences being that the surgeon is situated in a separate console away from the operating table, has a three dimensional view of the operating field and also the instruments are more flexible moving like a human wrist. All open operations used Pfannenstiel incision and either LigaSure™ vessel sealer or traditional technique.

The anaesthetic technique was standardised and the same in both groups: general anaesthesia with endotracheal intubation, propofol for induction, remifentanil for analgesia, rocuronium bromide for neuromuscular blockade, and sevoflurane for maintenance. Morphine was given before awakening, and bupivacaine 0.25% 20 ml was injected in the wound edges. Postoperative pain was managed using paracetamol 1330 mg and diclofenac 50 mg three times daily, and an additional patient-controlled analgesia pump with morphine but with no basal infusion. The patient-controlled analgesia pump was removed on the day after surgery. All patients received the same perioperative care according to the principles of ERAS, including for example preoperative carbohydrate loading, early oral intake of fluids and food, and active mobilisation [13]. Only Ringer's acetate was given as intravenous fluid. Glucose infusion or betamethasone as prophylaxis against nausea was not allowed, to avoid any interference with insulin action during the clamps. Patients were discharged when mobilised, eating and drinking normally, managing pain by oral analgesics, voiding normally, and showing no sign of postoperative ileus. All received four weeks of sick leave to begin with, but were informed that they could return to work earlier if they felt they had recovered. Demographic and clinical data (length of stay, morphine consumption, mobilisation, oral fluids, eating a full meal, passage of gas, and visual analogue scale for pain) were systematically collected during the hospital stay, and registered in the case report form. At 30-days after operation data collection took place via a phone call, and also included activities of daily living, sick leave, days in need of pain medication, and World Health Organisation score.

2.1. Clamp and blood tests

During the hyperinsulinemic normoglycaemic clamp, insulin was infused intravenously to attain the elevation that would be seen after a normal meal [14]. At the same time, glucose was infused to balance the effect of insulin and to maintain a normal blood glucose level at 5.0 mmol/l. Insulin sensitivity was then measured as the amount of glucose infusion needed to achieve these goals at steady state for 45–60 min. The clamp procedure was performed twice: 1–13 days before surgery as a preoperative control measure, and on the morning after surgery to yield the relative change in insulin sensitivity following the operation (postoperative insulin resistance).

All clamps were performed after an overnight fast. Each clamp lasted approximately 150 min, and started at 08.00 h. Insulin (Actrapid; Novo Nordisk, Bagsvaerd, Denmark) was infused at 0.8 m-units $\times$ kg^{-1} $\times$ min^{-1}. Glucose (200 mg/ml) (Glucos; Fresenius Kabi, Uppsala, Sweden) was infused intravenously at a variable rate with the aim of maintaining the blood glucose level at 5.0 mmol $\times$ l^{-1}. Blood was drawn from an arterialised vein in the forearm using a heating pad, and blood glucose was analysed every 10 min immediately upon collection (2300 STAT PLUS Model 2300 D; YSI, Yellow Springs, Ohio, USA). Glucose levels and glucose infusion rate were at steady state approximately 60–70 min after insulin infusion began. During steady state, the amount of glucose served as a measure of insulin sensitivity: the M value, measured in mg glucose/(kg body weight $\times$ minutes). Insulin resistance was calculated as the relative change in M value before and after surgery for each participant (100−(M postoperative/M preoperative $\times$ 100)), and given as a percentage. Blood samples for determination of insulin levels were drawn before onset and after 30, 60, 90, and 120 min. All patients also had HbA1c analysed

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