Effect of 24 mg dexamethasone preoperatively on surgical stress, pain and recovery in robotic-assisted laparoscopic hysterectomy

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ABSTRACT

Background: Robotic-assisted hysterectomy is an alternative to laparoscopic surgery as part of a minimal invasive regimen. Several treatment strategies are followed to improve the overall outcome and minimize surgical stress. Glucocorticoids provide significant analgesic and antiemetic effects but their role in reducing inflammatory stress in a fast-track, multi-modal setting in patients undergoing minimally invasive surgery remains to be investigated in details.

Methods: This study will evaluate in a randomized trial the effect of a single dose of 24 mg dexamethasone on 100 women undergoing robotic-assisted hysterectomy with regard to surgical stress, measured by c-reactive protein as primary outcome and, further, other stress markers like white blood cell subtypes. The postoperative recovery will be registered in validated charts and questionnaires for pain and analgesic use, quality of recovery, inconvenience, sexual and work life. Furthermore, in a sub-analysis, transcriptional profiling will be performed to explore the mechanism of systemic innate and adaptive immune system perturbation induced by surgical stress.

Conclusion: The study will provide solid evidence on markers of immunomodulation biomarkers and in addition the subjective effects and underlying mechanisms of perioperative glucocorticoid in women undergoing robotic hysterectomy. These include important aspects of life quality like pain, fatigue, freedom of medications, resuming work and sexual activities.

1. Introduction

Robotic surgery in gynecology is one of the fastest growing fields as part of minimal invasive surgery in applied robotic technology. In Denmark, 4000 vaginal, conventional laparoscopic and lately robotic assisted hysterectomies are performed each year on benign indications and the use of minimal invasive techniques has risen from 35% in 2004 to 89% in 2022.

The use of robotic surgery on benign indications in gynecology is still disputed with regard to the cost - benefit due to the increased cost of the robotic platform and lack of evidence that suggests superiority in surgical outcomes compared to conventional laparoscopy. Robotic surgery is a part of multi-modal regimen as minimal invasive surgery, which reduces the duration of hospital stay without compromising patients' safety during surgery and postoperative recovery [1–8]. However, not all single elements are proven for efficacy, let alone the specific targets for effect [8].

To improve the overall outcome of surgery further, inflammatory biomarkers associated with postoperative pain and recovery are investigated [8–10]. Here amongst others, glucocorticoids have proven immunomodulatory effects and relieved pain in a number of procedures, i.e. colonic, gallbladder, breast and orthopedic surgery, as well as in patients undergoing minimally invasive hysterectomy [1–12]. The minimal dose of dexamethasone to provide a significant analgesic effect

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is 0.1–0.2 mg/kg or 15 mg of dexamethasone, which is substantiated by some reduction in the inflammatory response [7,8,12]. Glucocorticoids are known for immunomodulatory, analgesic, opioid-sparing and antiemetic effects but laparoscopic hysterectomy-specific mechanisms and outcomes are not well elucidated.

2. Aim and hypothesis

The study will evaluate the effects of a single dose of dexamethasone on 1) acute postoperative stress response and 2) pain following hysterectomy. We hypothesize that the surgical stress will be mediated via an inflammatory response measurable in c-reactive protein (CRP) and can be modified by glucocorticoids. While the positive effect of dexamethasone on PONV is non-controversial, the surgical stress amelioration is less well-established [6,13,14]. This accounts for the dose as well as the specific drug for the duration and size of effects. We will measure systemic surgical stress effects by quantification of CRP as well as expression of inflammatory biomarkers markers based on transcriptional profiling. Further, pain and medication needed is registered during hospital stay and after discharge, and when work and sexual function could be resumed. This treatment and the exploratory study may help identify biological pathways perturbations that can be targeted in the future to enhance women’s recovery after surgery. Our study can lay the foundation for further research to target these specific sites of the immune system.

3. Material and methods

A two-arm randomized controlled, double-blinded trial is performed. Participants are randomized to either receive a single intravenous dose of 24 mg dexamethasone, corresponding to 128 mg methyl prednisolone, or saline. The dose is given after the induction of anesthesia as the patient will not consciously sense the infusion and before the insertion of trocars and the pain associated with the operation. The robotic hysterectomy is performed with the Intuitive surgical Da Vinci Xi system. The randomization is generated by the random numbers in the Ciba-Geigy tables, read by a third person, who codes even or uneven numbers to saline or dexamethasone group, sealing the result in an envelope. Another third person will open the envelope before the operation and fill the patient number marked syringe with either saline or dexamethasone. The patient will then receive the fill of the syringe intravenously, blinded to the patient and operation team (gynecologist, operation ward and anesthesiologists). All patients in the department operated with a robotic assisted hysterectomy will be monitored and fill out a diary as the drop-out / omission analysis to evaluate the external validity of the trial.

Inclusion criteria are meno-metrorrhagia, dysmenorrhea, fibroma, dysplasia, and dysmenorrhoea. Exclusion criteria are current treatment with glucocorticoids, opioids and NSAID analgesics, diabetes, current treatment of malignant disease, renal or hepatic disease. The trial commenced in April 2022 and is expected to last until end of 2024.

3.1. Ethics

The project is registered at clinicaltrials.gov (NCT 04762381) and approved by the European Medical Agency (EUDRACT no. 2021-000874-28), the National Medical Agency, the National Scientific Committee, National Data Agency, and the unit of Good Clinical Practice. Considerations are that the glucocorticoid dose is comparable to the known side effects of glucocorticoids like hyperglycemia, potential peptic ulceration, transient dysphoria, which amongst others will be monitored and registered. Long-term effects after discharge are not expected due to the single dose and elimination kinetics of glucocorticoids (half time of 4-8h). The patient will a-priori need less analgesics and have questionnaires to fill in. Pre and postoperative blood sampling will collected, stored and some analyzed later in batch. In conclusion, no major disadvantage for the patients is expected.

3.2. Measures

The primary endpoint is a reduction of postoperative CRP levels after surgery as an objective measurement of the stress amelioration by dexamethasone. Levels of CRP will be ascertained at baseline 4 times after start of surgery (hour 0) until discharge (Fig. 1). As secondary outcome we register pain scores, cumulative analgesics, use of postoperative analgesic medication and quality of recovery (QoR-15D) [15]. Furthermore, following discharge, incontinence (ICIQ-UI), start of sexual life (PISQ-12/31), and resumption to recreational and work life will be ascertained in a diary. Inflammatory biomarkers will be measured with gene expression assay (Fig. 1).

3.3. Gene expression assay

Blood samples will be analyzed for whole blood transcriptional profiling using the NanoString nCounter platform [18,19]. Currently, more than 700 transcripts can be identified enabling to pinpoint the activation of genes responsible of inflammation and adaptive immune response. The technology is based on RNA hybridization with fluorescent molecular barcodes, which constitutes an mRNA profile of key gene targets and elucidate the biological profile specific to the sample [20].

Bioinformatics data analysis will be performed in Nanostring nSolver application [21] or scripting language R. Shortly, iterative quality control and data normalization will be performed. Downstream analysis will include dimensionality reduction based on principal component analysis [22], hierarchical clustering of genes, differential expression analysis, functional enrichment analysis [23] and immune cell deconvolution [24].

3.4. Statistics

Sample size was calculated to be 49 women included in each arm on the primary outcome of CRP rising to the level of 40 mg/l with an expected reduction of 10% with a standard deviation of 7 calculated by http://clinicalcalc.com/stats/samplesize.aspx [1,16,17]. This may seem a parsimonious reduction but in practical terms, it translates to more than halving the need of opioids early and late postoperatively [2]. The consumption of all analgesics will be registered over time at stay in hospital and later by diary with questionnaires over 4 weeks to substantiate this point. On the assumption of incomplete data in less than 10% of cases, 55 women will be included in each group with complete. Analysis will be performed based on the intention-to-treat principle with women with current use of analgesics as a subgroup analysis. Distribution will be analyzed by the Kolmogorov-Smirnov test. The statistics will be unpaired and paired analysis (Kruskal-Wallis, Mann-Whitney, Friedman’s 2-ways analysis of variance, and 2-ways ANOVA, when appropriate) including relevant co-variates. Regression analysis will be performed with the primary outcome as dependent variable and the secondary outcomes and anthropometrics as dependent variables. A two-tailed p-value of 0.05 is the level of significance. A full statistics plan is implemented with the statisticians at Research Department of Sygehus Sønderjylland.

4. Discussion

The study will provide solid evidence on the subjective effects and underlying mechanisms of perioperative glucocorticoid in women undergoing robotic hysterectomy in a multimodal, fast-track regimen [10]. These include important life qualities like pain, fatigue, freedom of medications as well as resuming work and sexual activities. Further, future adjuvant eliminative medical regimens may be able to target the stress response specific biomarkers.

The evaluation is on clinically relevant outcomes that directly benefit the patients. The randomized design will evaluate the effects of the single dose of dexamethasone on the highest level of evidence. The anti-
Hours are measured after first skin incision for application of trocars.

Crp: c-reactive protein, VAS: Visual analogue score

post-surgical complications. Surgical recovery showed strong correlation with signaling responses in multiple cells, most predominantly in CD14+ monocytes [27]. Other temporal studies demonstrated mRNA expression in perioperative and postoperative blood samples associated with development of chronic pain after surgery [28].

To our knowledge, this study is the first of its kind by thorough characterization and coupling of clinical outcomes will allow for enhanced and more personalized treatment in a robotic assisted hysterectomy set-up. This improvement targets post-surgical recovery, pain, fatigue, freedom of medications as well as resuming work and sexual activities associated with patients’ systemic transcriptional profile.

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**Declaration of competing interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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