Göteborg, 2020

The effect of intra-abdominal local anaesthetics following major gynaecological surgery

Clinical and experimental studies

Akademisk avhandling
Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras på Hälsovetarbacken, hus 2, sal 2119, Göteborgs universitet, den 12 juni, klockan 13.00

Av Jane Hayden

Fakultetsopponent:
Professor Johan Raeder
Institute of Clinical Medicine, University of Oslo, Norge

Avhandlingen baseras på följande delarbeten

I. Hayden J, Oras J, Karlsson O, Olausson K, Thörn SE, Gupta A. *Post-operative pain relief using local infiltration analgesia during open abdominal hysterectomy: a randomized, double-blind study*. Acta Anaesthesiol Scand. 2017;61(5):539-548

II. Hayden J, Gupta A, Thörn SE, Thulin P, Block L, Oras J. *Does intraperitoneal ropivacaine reduce postoperative inflammation? A prospective, double-blind, placebo-controlled pilot study*. Acta Anaesthesiol Scand. 2019;63(8):1048-1054

III. Hayden J, Oras J, Block L, Thörn S-E, Palmqvist C, Salehi S, Nordstrom J, Gupta A. *Intraperitoneal ropivacaine reduces time interval to initiation of chemotherapy after surgery for advanced ovarian cancer. A randomized controlled double-blind pilot study*. BJA 2020;124(5):563-570

IV. Hayden J, Tinnert A, Oras J, Block L, Gupta A, Thörn S-E, Oredsson S. *The effect of local anaesthetics on ovarian cancer cell lines.* 2020. Manuscript

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER

GÖTEBORGS UNIVERSITET

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Abstract

Background: Local anaesthetics (LA), in addition to inhibition of pain signalling, also have anti-inflammatory properties. In vitro studies have demonstrated anti-proliferative and cytotoxic effect of LAs on cancer cells. Intraperitoneal administrated LA is shown to improve surgical recovery. Retrospective studies have indicated beneficial oncological outcome of regional anaesthesia on cancer recurrence when used in cancer surgery. New therapeutic approaches to enhanced recovery with reduced postoperative pain and inflammation is of great interest.

Methods and aim: The thesis aimed to evaluate the efficacy of intrabdominal local anaesthetics on pain, inflammatory response, serum concentration of LA and patient recovery after gynaecological surgery (study I, II and III) and additionally the effects on proliferation and migration in ovarian cancer cell lines, exposed to LA in concentrations corresponding to doses used in the clinical studies (study IV). The clinical studies were prospective, double blind, randomized and placebo-controlled. Study I included women scheduled for abdominal hysterectomy and study II and III women undergoing cytoreductive surgery for advanced ovarian cancer. Patients were randomised to receive either intraperitoneal LA or saline.

Results: The median supplemental requirements of morphine during 0–24 hours after abdominal hysterectomy was significantly lower compared to control (18 mg vs. 27 mg, $p = 0.028$). Perioperative intraperitoneal LA resulted in significantly decreased serum cortisol levels. Serum concentrations of ropivacaine were well below toxic concentrations (study II). Time to initiation of chemotherapy was significantly shorter in group intervention group (Median 21, IQR 19-29 vs. 29 days, IQR 21-40, $p = 0.021$). No differences in standardized recovery endpoints were found between the groups (Study III). The laboratory study showed a significantly reduced cell number and an inhibited cell migration. Cell size were significantly increased and cells with cancer stem cell phenotypes showed a reduction in all cells by up to 50% (Study IV).

Conclusion: Intra-abdominal LA offers a potential to have beneficial effects on pain, recovery and circulating tumour cells after gynaecological surgery.

Keywords: Local anaesthetics, postoperative pain, hysterectomy, inflammation, ropivacaine, toxicity, recovery, ovarian cancer, ovarian cancer cells

ISBN 978-91-7833-840-5 (PRINT) http://hdl.handle.net/2077/63620
ISBN 978-91-7833-841-2 (PDF)