Midline laparotomy is used in abdominal surgery. Peripheral neural blocks are part of the modern multimodal analgesia postoperatively and the rectus sheath block focus in the midline. This block can be administered once, in repeated doses or continuous infiltration. This study compares these three methods with a control group for 48 hours postoperatively. Long-lasting blocks via catheters enhance patient satisfaction and concentrations of anti-inflammatory cytokine IL-10.
Rectus sheath block after midline laparotomy
MARTIN PURDY

Rectus Sheath Block After Midline Laparotomy

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ABSTRACT
Midline laparotomies are needed in gastroenterological and gynaecologic operations and these patients need effective analgesia after surgery. Multimodal analgesia combines paracetamol, non-steroidal anti-inflammatory drugs, opioids, regional analgesia techniques and adjuvants as needed with the intent of minimizing the adverse effects (AE) of exclusively opioid based analgesia techniques. Thoracic epidural analgesia has been the most popular block applied in midline laparotomies. Anticoagulant medications and degenerative changes in the backs of an ageing population have become more common in the western world; both are contraindications to some extent and increase technical failures of epidural blocks. The nerves to the skin and muscle fascia of the midline pass through the rectus muscle sheath facilitating a local nerve block. Previously, this rectus sheath block (RSB) has been investigated with respect to continuous infusions or repeated blocks administered through catheters or as single dose blocks. The relative effectiveness of these types of RSB on pain management are far from clear. This prospective, randomised study compared these three different methods of RSB. A total of 57 patients with midline laparotomy were investigated, 17 of them were treated with continuous infusion RSB, 12 with repeated dose RSB and 16 with single dose RSB. Twelve patients without any block served as a control group. The postoperative RSB did not significantly affect the oxidative cell stress marker 8-OHdG or the cytoprotective GPX1 concentrations in blood compared to those measured in the control group. Concerning the inflammatory response, CRP or interleukins, when compared to the control group, only the concentrations of the anti-inflammatory cytokine IL-10 were elevated after the RSB, especially with the continuous infusion RSB. Oxycodon consumption and oxycodone plasma concentrations were similar in all four groups. Statistically significant differences were found in the pain assessments during the first 24 hours after surgery in favour of the repeated doses RSB. Patient satisfaction with analgesia was high in all four study groups. The median of satisfaction was highest in the repeated doses group (10/10) and the infusion group (10/10), when compared to the single dose group (9/10) and the control group (8/10). All plasma concentrations of levobupivacaine were below toxic concentrations. In conclusion, the continuous infusion- and repeated doses-techniques seem to be most effective method for ensuring RSB and is recommended for minimum 24 h postoperatively as an alternative to epidural block.

Medical Subject Headings:
Laparotomy; Pain Management; Nerve Block; Opioid; Interleukin-10; Patient Satisfaction; Prospective Studies; Randomized Controlled Trial.
ABSTRACT

Midline laparotomies are needed in gastroenterological and gynaecologic operations and these patients need effective analgesia after surgery. Multimodal analgesia combines paracetamol, non-steroidal anti-inflammatory drugs, opioids, regional analgesia techniques and adjuvants as needed with the intent of minimizing the adverse effects (AE) of exclusively opioid based analgesia-techniques.

Thoracic epidural analgesia has been the most popular block applied in midline laparotomies. Anticoagulant medications and degenerative changes in the backs of an ageing population have become more common in the western world; both are contraindications to some extent and increase technical failures of epidural blocks. The nerves to the skin and muscle fascia of the midline pass through the rectus muscle sheath facilitating a local nerve block. Previously, this rectus sheath block (RSB) has been investigated with respect to continuous infusions or repeated blocks administered through catheters or as single dose blocks. The relative effectiveness of these types of RSB on pain management are far from clear.

This prospective, randomised study compared these three different methods of RSB. A total of 57 patients with midline laparotomy were investigated, 17 of them were treated with continuous infusion RSB, 12 with repeated dose RSB and 16 with single dose RSB. Twelve patients without any block served as a control group.

The postoperative RSB did not significantly affect the oxidative cell stress marker 8-OHdG or the cytoprotective GPX1 concentrations in blood compared to those measured in the control group. Concerning the inflammatory response, CRP or interleukins, when compared to the control group, only the concentrations of the anti-inflammatory cytokine IL-10 were elevated after the RSB, especially with the continuous infusion RSB. Oxycodone consumption and oxycodone plasma concentrations were similar in all four groups. Statistically significant differences were found in the pain assessments during the first 24 hours after surgery in favour of the repeated doses RSB. Patient satisfaction with analgesia was high in all four study groups. The median of satisfaction was highest in the repeated doses group (10/10) and the infusion group (10/10), when compared to the single dose group (9/10) and the control group (8/10). All plasma concentrations of levobupivacaine were below toxic concentrations.

In conclusion, the continuous infusion- and repeated doses techniques seem to be most effective method for ensuring RSB and is recommended for minimum 24 h postoperatively as an alternative to epidural block.

Keski-linjan vatsaleikkauksissa suosituin puudutusmenetelmä on torakaalinen epiduraalipuudutus. Selkärangan rappeutumismuutokset ja verenhyytymistä estävä lääkitys yleistyvät väestön ikääntyessä, mistä johtuen epiduraalipisto voi olla vasta-aiheinen ja epäonnistuu harkemmin.


Ainoastaan IL-10 nousi suhteellisesti enemmän puudutetuilla ja erityisesti jatkuvan puudutuksen saaneilla potilailla. Emme voineet osoittaa merkittävää eroa kipulääkikulutuksessa. Oxycodonin kulutus ja pitoisuudet plasmassa eivät eronneet merkittävästi ryhmien välillä.

Kipuarvioinneissa saimme tilastollista merkittävyyttä toistopuudutuksen eduksi ensimmäisen leikkauksen jälkeisen vuorokauden ajalta. Potilaiden tyytyväisyys leikkauksen jälkeiseen kivunhoitoon oli hyvä kaikissa tutkimusryhmissä. Tyytyväisyyden mediaaniarvo oli korkein toistopuudutettujen ryhmässä 10/10) ja jatkuvan puudutuksen saaneilla (10/10) verrattuna kertapuudutusryhmään (9/10) ja kontrolliryhmään (8/10). Kaikki plasman levobupivakainipitoisuudet olivat turvallisia tutkimuksen aikana.

Jatkuvana infuusiona tai toistuvasti annosteltuna rektustuppipuudutus vaikuttaa tehokkaimmin, ja suositellaan vähintään 24 tunnin kestoiseksi ja vaihtoehdoksi epiduraalipuudutukselle.
TIIIVISTELMÄ

Keskilinja-avausta eli laparotomiaa käytetään suoliston ja synnytyselinten sairauksia leikattaessa. Tehokas monimuotoinen kivunhoito on tarpeen. Siinä yhdistetään parasetamoli, tulehduskipulääkitys, opioidit ja puudutukset kivunhoidon sivuvaikutusten minimoimiseksi.


Randomisoidussa, prospektilisessa tutkimuksessa vertailimme näitä puudutusmuotoja. Tutkimuspotilaita oli 57, joista 17 sai jatkuvan puudutuksen, 16 kertapuudutuksen, 12 potilasta toistuvan puudutuksen ja 12 potilasta kuuluivat ilman puudutusta vertailuryhmään.


Jatkuvaa infuusioa tai toistuvasti annosteltuna rektustupippuudutus vaikuttaa tehokkaammin, ja suositellaan vähintään 24 tunnin kestoiseksi ja vaihtoehdoksi epiduraalipuudutukselle.
To my Families and Kin
Acknowledgements

The present study and thesis were carried out in the Departments of Surgery, Urology and Gynaecology in Kuopio University Hospital and University of Eastern Finland.

First, I am immensely grateful to my principal supervisor, Professor Matti Eskelinen whose guidance and support were essential in carrying me through every phase of this work. He has inspired me and clarified the link between basic and clinical sciences.

I am deeply grateful to my supervisor, Professor Hannu Kokki, who suggested and helped design this interesting study combining surgery and anaesthesia. His experience and knowledge of medical research were essential also when conducting the statistical analysis and in solving many practical problems throughout the study.

I must warmly thank Professor Kari Pulkki, PhD Marko Lehtonen, and PhD Juho Hokkanen for their excellent work in the chemical analyses of these studies.

I thank cordially Professor Tuomo Rantanen, Docent Merja Kokki and Docent Petri Juvonen. Their support gave me perseverance, especially during the last years.

I express my warmest thanks to Docent Maarit Anttila and the other oncological gynaecologists of Kuopio University Hospital for their devotion. They made this work possible.

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Hämeenlinna 26.08 2017
Martin Purdy
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Hämeenlinna 26.08 2017

Martin Purdy
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II. Purdy M, Kokki M, Anttila M, Aspinen S, Juvonen P, Korhonen R, Selander T, Kokki H and Eskelinen M. Does the Rectus Sheath Block Analgesia Reduce the Inflammatory Response Biomarkers' IL-1ra, IL-6, IL-8, IL-10 and IL-1β Concentrations Following Surgery? A Randomized Clinical Trial of Patients with Cancer and Benign Disease. Anticancer Res. 2016 Jun;36(6):3005-11.


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List of the original publications

This dissertation is based on the following publications:


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## Abbreviations

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<th>Description</th>
<th>Abbreviation</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse effects/adverse events</td>
<td>ROS</td>
<td>Reactive oxygen species</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximal concentration</td>
<td>RSB</td>
<td>Rectus sheath block</td>
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<tr>
<td>CMI</td>
<td>Cell-mediated-immunity</td>
<td>SIR</td>
<td>Systemic inflammatory reaction</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
<td>TAP</td>
<td>Transversus abdominis plane</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
<td>TEA</td>
<td>Thoracic epidural analgesia</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Time to maximal concentration</td>
</tr>
<tr>
<td>GPX</td>
<td>Glutathione peroxidase enzyme</td>
<td>WI</td>
<td>Wound infiltration</td>
</tr>
<tr>
<td>Hs-CRP</td>
<td>High sensitivity C-reactive protein</td>
<td>8-OHdG</td>
<td>8-Hydroxy-2′-deoxyguanosine</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
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<tr>
<td>LA</td>
<td>Local anaesthetic</td>
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<td>NRS</td>
<td>Numeric rating scale</td>
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<td>NSAID</td>
<td>Nonsteroidal anti-inflammatory drug</td>
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<td>OCS</td>
<td>Oxidative cell stress</td>
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<td>OIH</td>
<td>Opioid induced hyperalgesia</td>
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<td>OS</td>
<td>Open surgery</td>
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<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>p</td>
<td>Probability value</td>
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<tr>
<td>PACU</td>
<td>Post anaesthesia care unit</td>
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<tr>
<td>PCA</td>
<td>Patient controlled analgesia</td>
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<td>PMN</td>
<td>Polymorphonuclear granulocytes</td>
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<tr>
<td>PONV</td>
<td>Postoperative nausea and vomiting</td>
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<tr>
<td>POP</td>
<td>Postoperative</td>
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<td>POP1</td>
<td>Immediately postoperatively</td>
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<tr>
<td>POP2</td>
<td>24 hours after operation</td>
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<tr>
<td>PS</td>
<td>Patient satisfaction</td>
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<tr>
<td>PRE</td>
<td>Immediately before operation</td>
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<tr>
<td>RNS</td>
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Postoperative pain is the principal adverse effect associated with midline incision. Pain after laparotomy derives from multiple origins; e.g. the abdominal wall, abdominal viscera and peritoneal irritation. It is evident that appropriate pain control is necessary as laparotomy decreases pulmonary function by as much as 30 % even when effective pain treatment is administered (Hendolin et al. 2000). The multimodal treatment of postoperative pain includes paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), regional blocks, opioids and adjuvants as needed. Enhanced recovery after surgery (ERAS) are increasingly used in surgical patients and these protocols warrant effective pain management that promote early mobilization of the patient (Aarts et al. 2012, Feldheiser et al. 2016).

Thoracic epidural analgesia (TEA) has gained a position as the golden standard for postoperative pain control but lately its benefits have been questioned (Rawal 2012). TEA may evoke hypotension or nausea and it has been reported to lead to longer hospital stays and urine tract infections may also be more common (Halabi et al. 2016, Liu & Wu 2007).

The opioids are needed to control pain and have to be administered for at least one to three days after a midline laparotomy. These compounds are especially effective in controlling visceral pain but their AE, i.e. gastrointestinal tract dysfunction, ileus and constipation are major problems and may delay recovery after midline laparotomy (Beard et al. 2011).

Nerves enter the rectus abdominis muscle from both sides of the spinal cord roots following the dermatomes Th6-L1 (Rozen et al. 2008). These nerves travel transversal to the rectus sheath in the posterior fascial layer from where they penetrate obliquely the muscle, aiming to the midline of the skin and innervating most of the skin above the rectus sheath. The placing of a catheter in a vertical position laterally behind the muscle enables blocking of the nerves coming to the midline.

The local anesthetics (LAs) possess anti-inflammatory (Ballou et al. 2013, Fares et al. 2014, Chen et al. 2015) and cytoprotective properties. In the present study, the possible anti-inflammatory and cytoprotective influence of RSB were evaluated by defining possible changes in the concentrations of cytokines as well as the oxidative cell stress (OCS) product 8-hydroxy-2'-deoxyguanosine (8-OHdG) and concentrations of the anti-oxidant, glutathione peroxidase (GPX). The first RSB was described 1899 to achieve analgesia and muscle relaxation (Schleich 1899). There is an unresolved debate about whether RSB diminishes the need for opioids.
1. **Introduction**

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The local anaesthetics (LAs) possess anti-inflammatory (Ballou et al. 2013, Fares et al. 2014, Chen et al. 2015) and cytoprotective properties. In the present study, the possible anti-inflammatory and cytoprotective influences of RSB were evaluated by defining possible changes in the concentrations of cytokines as well as the oxidative cell stress (OCS) product 8-hydroxy-2'-deoxyguanosine (8-OHdG) and concentrations of the anti-oxidant, glutathione peroxidase (GPX).

The first RSB was described 1899 to achieve analgesia and muscle relaxation (Schleich 1899). There is an unresolved debate about whether RSB diminishes the need for opioids
(Charlton et al. 2010, Shido et al. 2010). The effects of this procedure on patient satisfaction (PS) are not known. The concentration of LA in blood should be a concern if the patient is receiving continuous or repeated high volume block, but reports so far have mainly focused on the concentration of LA after single dose blocks (Steward et al. 2003, Flack et al. 2014, Hamada et al. 2016, Kitayama et al. 2014).

In this study, RSB was evaluated after a midline laparotomy. The specific aim was to determine whether there would be differences between single dose, repeated doses and continuous infusion techniques in effectiveness and safety and to compare these three modes of RSB with a control group. The primary endpoints were the consumption of opioids after surgery, concentrations of CRP, interleukins (ILs), 8-OHdG, and GPX, pain evaluation and final patient satisfaction (PS) for the postoperative analgesia. Consumption of oxycodone with an iv. patient controlled analgesia (PCA) pump for rescue analgesia was registered for the first 48 postoperative hours. Pain scores and PS were assessed by a numerical rating scale (NRS,0-10). Plasma concentrations of levobupivacaine and oxycodone were analysed. All complications during the hospital stay were recorded.
2 Review of the Literature

2.1 RECTUS SHEATH INNERVATION

The nerves of spinal cord roots Th6-L1 enter the abdomen wall from both sides. These nerves pass between the internal oblique and transversus abdominis muscles. They branch and communicate widely in the intercostal plexus, within the transversus abdominis plane and around the deep inferior epigastric artery. Nerves from dermatomes Th 7-11 enter the rectus sheath’s posterior fascia, then reach its anterior sheath via the muscle and then they innervate the fascia in the midline and the skin around about the area of the rectus sheath. Possible nerve damage in rectus sheath does not cause any major effects because of the rich communications between the nerves (Rozen et al. 2008). The local anaesthetic (LA) must be deposited behind the muscle to allow the LA to spread easily. There, the nerves transit in the lateral half from posterior fascia to the muscle (Seidel et al. 2017). The anterior fascia is tied to the muscle with arcuate ligaments preventing its use for effective analgesia. The umbilical region is always innervated by the root Th10, the branches of which may also innervate the dermatomes Th9 and 11 (Rozen et al. 2008). The iliohypogastricus nerve (dermatome Th12) does not penetrate the rectus sheath but innervates the fascia and skin above the pubis over an area of approximately five centimetres. It is blocked most easily near the anterior iliac spine above the transversus aponeurosis (Benz-Wörner & Jöhr 2013). In Rozen’s study, the iliohypogastric nerve was found to be a branch of L1.

In contrast to other reports, Courreges found that in up to 30% of the population, the anterior cutaneous branch of the intercostal nerves is formed before the rectus sheath and therefore it does not penetrate through it but instead runs anterior to the sheath in the subcutaneous tissue (Courreges et al. 1997). An ultra sound (US)-guided single dose RSB may be sufficient for intraoperative analgesia in adult umbilical hernia operation in 53% of cases. The remaining patients need local wound infiltration (WI) prior to skin incision (Manassero et al. 2015). This supports Courreges’ finding although it has been questioned in other studies of the anatomy of this region.
Figure 1. Transverse section of the abdominal wall showing the path of nerves T7-T12 as they travel from the spine to the anterior abdomen. (Figure 1 is published with the kind permission of Katrina Webster)

Figure 2. Cutaneous sensory nerve distribution and dermatomes on the abdominal wall. (Figure 2 is published with the kind permission of Katrina Webster)
2.2 OPIOIDS IN ABDOMINAL SURGERY AND LOCAL ANESTHETICS

2.2.1 Opioids

Opioids are very effective pain controllers especially for visceral pain. However, patients’ sensitivity to opioids varies extensively. Some patients who use opioids frequently or metabolize them quickly need large doses which increases the risk of AE such as postoperative nausea and vomiting (PONV), dizziness, somnolence and mental disturbances (Kokki et al. 2012). Larger doses may also induce opioid-induced hyperalgesia (OIH) (Raffa & Pergolizzi 2012). Some patients are slow metabolizers of opioids and may develop AE with lower doses than needed for analgesia and are at a higher risk to suffer postoperative distress and mental disturbances (Boom et al. 2013).

Opioid receptors are present also in the gastrointestinal tract where opioids slow the motion of the intestine and may cause obstipation (Beard et al. 2011, Webster 2015). Opioid induced bowel dysfunction may delay recovery after midline laparotomy.

2.2.2 Local anaesthetics

Bupivacaine is an amino-amide local anaesthetic (LA) and belongs to the family of the n-alkyl substituted pipelaconylides which were first synthesized in 1957 by Ekenstam (Ekenstam et al. 1957). It has two optically active stereoisomers and is highly lipid-soluble. The solution of bupivacaine contains equal amounts of dextrorotatory (R+) and levorotatory (S-) enantiomers, and is called a racemic solution. Enantiomers have different affinity for the different ion channels i.e. the S- enantiomer is less cardio- and central nervous system (CNS)- toxic (Aberg 1972). Ropivacaine belongs to the same pipelaconylide group, but is much less lipophilic. Levobupivacaine and ropivacaine are optically pure (S-) solutions. The values of elimination half-life ($T_{1/2}$) are 111 min. for ropivacaine, 157 min. for levobupivacaine and 210 min. for bupivacaine (Adams et al. 2002). The relative potency of levobupivacaine and bupivacaine to produce adequate pain control are equal, and 15-50% more when compared with ropivacaine (Polley et al. 1999, Capogna et al. 1999, Sia et al. 2005).

The recommended highest daily deliveries are as follows: bupivacaine 400 mg, levobupivacaine 695 mg, lidocaine 300 mg, lidocaine with epinephrine 500 mg and ropivacaine 770 mg. The recommended values have been made in part by extrapolations from animal experiments, clinical experiences from the use of various doses and measurement of blood concentrations, case reports of LA toxicity, and pharmacokinetic results. The reduced clearance of LA associated with renal, hepatic, and cardiac diseases is the most important reason for a need to reduce the dose with repeated or continuous administration (Rosenberg et al. 2004).

The LAs may cause both local and systemic AE. The most common AE in clinical trials have been hypotension (31%), nausea (21%), postoperative pain (18%), fever (17%), vomiting (14%), anaemia (12%), pruritus (9%), headache (7%), constipation (7%), dizziness (6%), and foetal distress (5%) (Purdue Pharma L.P. 1999).
Excessively high concentrations in blood may cause serious AE on cardiovascular or CNS. The signs of CNS intoxication are usually evident before the appearance of cardiovascular toxicity. Initial signs are usually shivering, muscle twiching and tremors, which are produced by a block of inhibitory central pathways. Subsequently, with increasing LA plasma concentrations, a generalized CNS depression with hypoventilation and respiratory arrest and finally generalized convulsions occur. The CNS excitatory phase with sympathetic activation can mask the direct myocardial depression which is followed by arrhythmias and cardiac depression (Gristwood 2002). Although the CNS symptoms emerge with lower plasma concentration than cardiovascular AE, the latter may occur without any CNS symptoms, when the plasma concentrations are excessively high or increase rapidly (Albright 1979, Heath 1982).

Levobupivacaine produces significantly less effects on cardiovascular function than bupivacaine (Bardsley et al. 1998). In animal studies, bupivacaine has a 1.5-2.5 lower convulsive threshold compared to the two S-isomers, levobupivacaine and ropivacaine (Groban 2003, Marganella et al. 2005). The cardiovascular toxicity concentrations of levobupivacaine has been reported to be 3000-4000 ng/ml (Scott et al. 1989). These values were similar to those of ropivacaine (Wada, 2012). Ropivacaine appears to be less potent but to have a lower risk of toxicity than bupivacaine. The CNS symptoms appear with a 25% higher intravenous dose of ropivacaine compared to that of bupivacaine (Scott et al. 1989). In a comparison between ropivacaine with levobupivacaine, no difference was reported in CNS and cardiovascular effects at equal concentrations, milligram doses and i.v.-infusion rates (Steward et al. 2003).

The placement of local analgesia is significant: the time to peak plasma concentration (Tmax) of LA after RSB was like ilioinguinal/iliohypogastric blocks reported previously, but longer than those reported with paravertebral or intercostal or transversus abdominal plane (TAP) blocks (Murouchi et al. 2015). Bupivacaine is absorbed more effectively following RSB than after WI in children (Flack et al. 2014). The duration of analgesia varies from 6 to 20 hours, depending of the location (Albright 1979).

Levobupivacaine at concentrations of 2.5mg/ml or less has greater vasoconstrictive effects than bupivacaine (Aps, 1987), and at higher concentrations, the vasodilator activity is less than that of bupivacaine (Burke, 1998). The vasoconstriction may enhance the elimination time of LA leading to a longer duration of analgesia. The duration of sensory block seems to depend on the LA concentration (Bardsley et al. 1997).

Adding dextran to levobupivacaine provides better analgesia and decreases the risk of toxicity in TAP block plus RSB in patients undergoing laparoscopic colectomy (Hamada et al. 2016). In that study, a volume of 80 ml 2.0mg/ml levobupivacaine was injected once in normal saline or 8 mg/ml dextran mixture; the mean maximal plasma concentrations (Cmax) of LA were correspondingly 1410 ng/ml and 1140 ng/ml and were reached earlier in the saline group (Tmax 50 min. vs 73 min.).Adding 1mg/ml lidocaine plus epinephrine to ropivacaine did not have any significant difference in plasma concentrations of ropivacaine in RSB, although in TAP, it lowered Cmax and postponed Tmax (Kitayama et al. 2014). Both lidocaine and ropivacaine are known to be vasoconstrictive at low concentrations. Levobupivacaine is safer than bupivacaine (Foster & Markham, 2000) and achieves more sensory block and less motor block. Compared with ropivacaine, there are no clear differences except that it seems that levobupivacaine exerts a marginally longer sensory block (Casati et al. 2002, Maheshwari et al. 2016).
The safety of analgesic agents depends on both their local and systemic concentrations and their toxicity. Blood concentration have been investigated for both ropivacaine (Murouchi et al. 2015) and levobupivacaine (Yasumura et al. 2016). In both reports, the treatment was a single dose block and the concentrations were analysed for two hours after drug administration. In both studies, the absorption from RSB was slower than from TAP and the C_max were reached in about one hour. The absorption of bupivacaine in children’s umbilical operations has been studied with the C_max being achieved in 30-60 min. after a single block RSB (Flack et al. 2014).

In summary, levobupivacaine and ropivacaine are particularly recommended for local analgesia such as in epidural and intravenous blocks in which there is a risk of accidental intravascular administration or higher doses are needed.

2.3 RECTUS SHEATH BLOCK

2.3.1 Single dose rectus sheath block

The RSB has been developed and investigated for gynaecologic surgery using single dose LA into the rectus sheath with“ a needle-scratching-fascia technique” (Yentis et al. 1999). All pain scores during the first 48 postoperative hours were moderate or even less in 86% of patients although the LA was injected only in two or four points in the rectus sheath; for ilioinguinal blocks, it was administered near to anterior iliac spines. Epidural analgesia and iv.PCA-opioids became virtually obsolete after the appearance of this kind of technique.

Bashandy&Elkholy reported of ultra sound (US)- guided preoperative single dose RSB being delivered in abdominal cancer surgery of 56 patients (Bashandy&Elkholy 2014). A Tuohy needle and levobupivacaine 2.5 mg/ml in doses 20 plus 20 ml were used. The incisions were extensive, extending from xiphosternum to the symphysis pubis. It was found that perioperative fentanyl use, the need for opioids during two POP days and the postoperative pain in the post-anaesthesia care unit (PACU) were all diminished. Husain&Ravalia (2006) reported that they had applied perioperative US-guided RSB with ilioinguinal blocks for postoperative analgesia in gynaecologic operations involving a Pfannenstiel incision, which allowed them to abandon iv.morphine-PCA. The total dose of 40 ml of bupivacaine (2.5 mg/ml) was mixed with 200 μg epinephrine and 60 μg of clonidine to prevent toxic dosage.

A retrospective analysis in another study compared subcutaneous WI (n= 51) with a surgical RSB (n= 47) in a consecutive series of gynaecologic infraumbilical laparotomies with a volume of 40 ml of 2.5 mg/ml bupivacaine being used in both groups. The RSB was achieved by injecting LA in the superior (umbilical) pole of the rectus sheath before closure of the wound. The results were statistically significant in favour of RSB concerning pain in the recovery room, cumulative postoperative morphine consumption, timing of the discontinuation of iv.PCA-opioids and discharge from hospital (Crosbie et al. 2012). Recently a single dose RSB was studied in upper abdomen surgery with subcostal or transverse incisions in patients undergoing liver resections and Whipple procedures.
(Abdelsalam & Mohamdin 2016). The combination of pre-incisional US-guided RSB plus TAP-block were significantly better than WI at the end of the operation as measured by pain scores, intraoperative fentanyl and postoperative opioid consumptions. Liver operations carry a risk of coagulopathy which is a contraindication to epidural blocks. Both the preoperative infiltration and the TAP-block may have improved these results. In a review (Charlton et al. 2010), only one (Smith et al. 1988) of the three prospective and randomised studies that were included showed a reduction in postoperative analgesic requirements. This study was made with 60 gynaecologic diagnostic laparoscopies. RSB was achieved by bilateral infiltrations before incisions. More patients were pain-free for 10 hours in the RSB group.

Umbilical hernia operations in children are perhaps the best documented area of single dose RSB (Table 1.2). The block may be achieved in general anaesthesia preoperatively with US-guidance (Alsaeed et al. 2013) or after hernia repair and then compared with WI performed by the surgeon at the end of the surgical procedure. Only 1 of 22 children who received RSB prior to the operation required morphine postoperatively. In another study, in the WI - group, 11/25 children required opioids in the post anaesthesia care unit (PACU) compared with 5/27 children who received RSB at the end of the operation (Dingeman et al. 2013). A comparison has been made between WI at the end of the procedure vs RSB prior to the incision: in the RSB group, there was a longer time before the first morphine dose was needed (median 65.5 vs 47.5 min.). A doubled risk of requiring morphine was found in the WI - group (Flack et al. 2014). Plasma concentrations of bupivacaine were also investigated. The $C_{\text{max}}$ was higher in the US-guided RSB group (median 632 ng/ml) compared with the WI - group (390 ng/ml). The $T_{\text{max}}$ was 45 min. in the RSB- group vs 20 min. in the WI - group.

In an umbilical hernia operation in adults, an US-guided single dose RSB was reported to achieve excellent postoperative analgesia in 97% of patients (Manassero et al. 2015). Single-port trans-umbilical laparoscopic appendectomies for children with non-perforated appendicitis (275 patients) with preincisional US-guided RSB or WI were compared: total opioid administration was significantly reduced in the RSB - group compared to the WI - group, with a mean of 0.112 mg/kg of morphine vs 0.290 mg/kg morphine. Patients undergoing RSB reported lower initial (0.4 vs 2.4) and mean pain scores (1.3 vs 1.8). The time to rescue analgesia was prolonged in patients undergoing RSB compared to WI (59 min. vs 42 min) (Maloney et al. 2017). Litz et al. (2017) studied whether percutaneous US-guided RSB would achieve better pain relief postoperatively than intraoperative RSB but they found no differences in need of opioids or in the length of stay.

There are also contradictory results concerning the efficacy of RSB. A pilot study with 14 children aged 1-8 years detected no significant differences in pain scores or morphine consumption when comparing RSB with WI, both administered at completion of umbilical hernia surgery (Isaac et al. 2006). There may have been a technical error as the LA was infused under the front sheath of the rectus abdominis and not on the posterior sheath. That could explain their contradictory results.
That could explain their hernia consumption when comparing RSB with children aged 1. They found no differences in need of undergoing RSB reported lower initial (0.2 mg/kg) opioid administration was significantly reduced in the RSB group. The block may be achieved in the RSB group. The combination of pre and intraoperative RSB provided significant pain relief in the postoperative period compared with the WI group. This study was made with 60 gynaecologic diagnostic laparoscopies. RSB operations carry risk of requiring morphine postoperatively. In another study, the risk of requiring morphine was higher in the US group.

Table 1.1 Single dose block studies. Adult patients. All local anesthetic concentrations are 2.5 mg/ml. Add = additives; Bupivac.= bupivacaine; Dimin. = diminished; Epineph. = epinephrine; Lap. = laparoscopy; LA = local anaesthetic; Levobup. = levobupivacaine; Preop. = preoperatively; Prospect = prospective; Pts = number of patients; Random. = randomized; Rertosp. = retrospective; Ropivac. = ropivacaine; TAP = transversus abdominis plane block; US = ultrasound guidance.

<table>
<thead>
<tr>
<th>Writer /year</th>
<th>Type</th>
<th>US</th>
<th>LA &amp; Adds</th>
<th>Type of surgery</th>
<th>Pts</th>
<th>Opioid need</th>
<th>Pain</th>
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Table 1.2 Single block studies. Child patients. All local anesthetic concentrations are 2.5mg/ml. 

<table>
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<tr>
<th>Writer/year</th>
<th>Type</th>
<th>US</th>
<th>LA &amp; Adds</th>
<th>Type of surgery</th>
<th>of pts</th>
<th>Opioid need</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isaac et al. 2006</td>
<td>Prospect. Random.</td>
<td>-----</td>
<td>Bupivac. 2.5mg/ml + epineph.</td>
<td>Umbilical hernia</td>
<td>14</td>
<td>Equal</td>
<td>Equal</td>
</tr>
<tr>
<td>Dingeman et al. 2013</td>
<td>Prospect. Postop.</td>
<td>Ropivac.</td>
<td>Umbilical hernia</td>
<td>52</td>
<td>Halved</td>
<td>Dimin. P&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Alsaeed et al. 2013</td>
<td>Prospect. Non-random.</td>
<td>Preop.</td>
<td>Bupivac. 2.5mg/ml</td>
<td>Umbilical hernia</td>
<td>22</td>
<td>21/22 pts.: no need.</td>
<td></td>
</tr>
<tr>
<td>Flack et al. 2014</td>
<td>Prospect. Random.</td>
<td>Preop.</td>
<td>Bupivac. 2.5mg/ml</td>
<td>Umbilical hernia</td>
<td>40</td>
<td>Halved</td>
<td>Equal</td>
</tr>
<tr>
<td>Maloney et al. 2017</td>
<td>Retros. Pre-incision</td>
<td>Single-port Lap. App.</td>
<td></td>
<td></td>
<td>275</td>
<td>Dimin. P=0.001</td>
<td>Dimin. P=0.015</td>
</tr>
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</table>

2.3.2 Repeated doses rectus sheath block

A catheter placed on both sides in the vertical direction under the rectus abdominis muscle on the posterior rectus sheath enables repeating the scheduled LA- dosage. Webster (2010) mentions that 2.5 mg/ml bupivacaine or 3.75 mg/ml ropivacaine as a 20-ml bolus every 6 h will provide effective continuous analgesia for 5-7 h, but lower doses or lower concentrations will reduce the duration of the block.

A study with 74 gynaecological oncology midline laparotomies used intermittent doses every 6-hour delivered through intraoperatively placed catheters. Patients received 20 ml of either LA (bupivacaine 2.5 mg/ml) or normal saline. The pain scores decreased significantly in the LA- group compared with the saline- group both at rest and with movement. The morphine consumption of iv.PCA was reduced significantly at 24 hours and 48 hours postoperatively in the LA- group compared with the saline- group. (Bakshi et al. 2016). Bimanual palpation and Tuohy needle were used for placement of catheters with the placement being confirmed by US.
A retrospective work studied US-guided RSB in 200 patients undergoing open radical cystectomy or radical retropubic prostatectomy. The catheters and first dose of 20 ml (levobupivacaine 2.5 mg/ml) on both sides were administered prior to incision. Afterwards, the same dose was given every 6 hours. The mean (range) duration of postoperative use was 3.6 (2-7) days in the cystectomy group and 2.1 (1-5) days in the prostatectomy group. Early removals of catheters occurred in 6% of cases. It was found that cystectomy patients needed more often iv.PCA-opioids than prostatectomy patients to achieve adequate postoperative analgesia. This was explained by the difference in visceral pain as the prostatectomy had been performed retroperitoneally. The opioid requirements were observed to decline sharply after the first 24 postoperative hours (Dutton et al. 2014).

Adding morphine to bupivacaine compared to plain bupivacaine was studied in 50 adults receiving repeated RSB. The bupivacaine dose 20 ml (2.5 mg/ml) was administered with 2 mg of morphine in the study group. LAs were administered at every 6 hours. Catheters were removed on the 5th postoperative morning. PCA-morphine consumption during the first 18 hours and total consumption in the first 24 postoperative hours were significantly lower in the study group compared to plain LA group. Total iv.PCA-opioid consumption in 24 h was 0.7 mg (SD 2.0) in the morphine group, much less than in the control group (6.3 mg, SD 8.3). Pain scores were also significantly reduced at rest and mobilisation was improved in the 6th, 12th and 18th postoperative hours. The authors speculated on whether the positive effect of the adjuvant opioid in RSB was mediated through a systemic effect or locally in the block area and that the measurement of plasma concentrations of opioids might have provided the answer to that question (Shabana et al. 2013, Stein 2016).

Padmanabhan et al. (2007) found no difference between LA- or normal saline-infusions in postoperative pain, consumption of iv.PCA-opioid or postoperative pulmonary function. Their method was an intermittent administration via catheters every 8 hours for the first 48 h after operation. 19 patients were administered 20 ml bupivacaine (2.5 mg/ml) on both sides and 21 had normal saline as a placebo. Catheters were placed through a separate incision into the rectus sheath under the naked eye at the end of the procedure without the assistance of US. The wounds were all 20-23 cm long. Unfortunately, the placement of catheters may have been too medial as indicated by the figure in the article.

**Table 2.** Studies of repeated rectus sheath block. Adds=additives; Bupivac.=bupivacaine; LA=local anaesthetic; Levobup.=levobupivacaine; Morph.=morphine; Prospect.=prospective; Pts=Number of patients; Random.=randomized; Retrop.=retroperpective; US=Ultrasound sound; VAS=Visual analogue scale (0-10).

<table>
<thead>
<tr>
<th>Writer /year</th>
<th>Type</th>
<th>US</th>
<th>LA + Adds</th>
<th>Type of surgery</th>
<th>Pts</th>
<th>Opioid need</th>
<th>Pain</th>
</tr>
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<tbody>
<tr>
<td>Dutton et al. 2014</td>
<td>Pre-oper.</td>
<td>Levobup. 2.5 mg/ml</td>
<td>Pelvic urologic</td>
<td>200</td>
<td>Dropped after 24h.</td>
<td>VAS &lt; 3 in all pts.</td>
<td></td>
</tr>
<tr>
<td>Shabana et al. 2013</td>
<td>-----</td>
<td>Bupivac. 2.5 mg/ml +/− morphine</td>
<td>Extended midline laparotomy</td>
<td>50</td>
<td>Less with morphine 18 h: P&lt;0.04</td>
<td>Better with Morph. P&lt;0.04</td>
<td></td>
</tr>
<tr>
<td>Bakshi et al. 2016</td>
<td>Prospect. Random.</td>
<td>-----</td>
<td>Levobup.</td>
<td>Gynaecologic oncology</td>
<td>74</td>
<td>Reduced P&lt;0.001</td>
<td>Decreased P&lt;0.001</td>
</tr>
</tbody>
</table>
2.3.3 Continuous infusion rectus sheath block

In RSB, the continuous infusion occurs through catheters tunnelled behind the rectus abdominis muscle delivered via commercial disposable or electric driven infusion pumps although with disposable pumps, the patient is more free to move about. Good prospective studies concerning continuous infusion- RSB are lacking. Ropivacaine infusion into the lower abdomen rectus sheath and a retroperitoneal infusion with catheters was evaluated for postoperative analgesia (Biglamia et al. 2011). The RSB was used only on the operated kidney’s side. The live donor nephrectomy was conducted retroperitoneoscopy and hand assisted through a 7 cm Pfannenstiel incision. A total of 40 patients were administered ropivacaine infusion with the case control group consisting of 40 donors. All patients were maintained on standardized multimodal analgesia and postoperatively received a nurse-controlled opioid delivery. Although some patients lost their catheters in the first POP- day, the results were statistically significant in terms of reducing postoperative pain and the need for opioids in the infusion group vs standardized multimodal postoperative analgesia without LAs. In addition, the time spent in the PACU (160 vs 243 min.) and the total hospital stay (4 days vs 6 days) were shorter in the infusion- group. Thus, the retroperitoneal infusion that blocked visceral pain in the operative field, may have contributed to the good results.

Some case reports have described positive results of continuous RSB in clinical practice (Shido et al. 2010, Malchow et al. 2011).

2.4 THORACIC EPIDURAL ANALGESIA

After laparotomies, TEA is considered as the gold standard for postoperative analgesia, even after laparoscopic operations (Sjövall et al. 2015). If the patient has sepsis or is receiving antithrombotic medication, then this procedure is contra-indicated (Gogarten et al. 2010, Nightingale et al. 2011). As the western population is aging, this means that the use of anti-clotting agents is on the increase. The aging thoracic spines with osteoarthritic changes also will lessen the number of successful TEA procedures and technical difficulties can lead easily to multiple punctures (Pöpping et al. 2008). Mild AE as hypotension, respiratory depression, bladder dysfunction and muscle weakness may occur in a few percent of cases. Mobilization is delayed by 0.6 days and catheterization of bladder increases the risk of urinary tract infection (odds ratio, OR 1.8) (Halabi et al. 2014). TEA does not affect the incidence of respiratory failure, pneumonia, anastomotic leak, ileus or urinary retention (Halabi et al. 2014). Serious complications such as epidural abscesses, haemorrhages and paraparesis are fortunately rare (Pöpping et al. 2008, Pitkänä et al. 2013). Nonetheless, this procedure may add costs and nursing workload compared to less invasive pain management techniques.

In the postoperative period, there may be technical problems being responsible for insufficient analgesia in 25 - 50% of TEAs (Pöpping et al. 2008, de Leon-Casasola et al. 1994). TEA has been estimated to lead to higher hospital charges by 317€ (Halabi et al. 2007). In radical prostatectomy, WI combined with oral oxycodone was found to be...
superior to TEA in one trial (Hohwü et al. 2006). Thus, whether TEA should be viewed as a gold standard has been questioned by Rawal in 2012.

2.5 OPIOID CONSUMPTION WITH RSB

In elective diagnostic gynaecologic laparoscopies, RSB achieved a significant reduction of opioid use one, 6 and 10 hours postoperatively when compared with WI at the end of the operation (Abdelsalam & Mohamdin 2016). The same conclusion was found in two trials in paediatric umbilical hernia surgery (Dingeman et al. 2013, Flack et al. 2014). The US-guided single dose RSB halved and postponed morphine consumption after umbilical hernia surgery in children (Flack et al. 2014).

A US-guided single dose RSB before the incision was found to reduce morphine need in extensive midline cancer operations when compared to general anaesthesia alone (Bashandy & Elkholey 2014). A significant reduction was also found with repeated RSB compared to placebo boluses for 48 hours after gynaecologic cancer surgery (Bakshi et al. 2016) and after major gynaecological operations when compared to standard WI (Crosbie et al. 2012). Some case reports have also described a reduction in opioid needs (Bakshi et al. 2015, Shido et al. 2010, Alsaeed et al. 2013). After gynaecologic midline incisions, a reduction was found in mean opioid consumption when a single dose RSB and ilioinguinal block were added to a multimodal pain treatment schema (Yentis et al. 1999). Before the RSB was introduced, the mean 48 h morphine consumption was 1.0 mg/kg, which fell to 0.34 mg/kg after the introduction of the new procedure. When a mixture of morphine added to bupivacaine was compared against bupivacaine alone, the total consumption of morphine showed a marked sparing effect during the first 24 hours postoperatively. Bupivacaine 2.5 mg/ml 20 ml on each side was mixed with 2 mg morphine with the treatment being repeated every 6 hours (Shabana et al. 2013).

Most of the studies have not found significant reduction in postoperative opioid consumption with RSB. Bupivacaine vs normal saline in repeated dose RSB caused no difference in the postoperative opioid requirement in one study (Padmanabhan et al. 2007), but the placement of the catheters may not have been optimal (too much on the medial location). A single dose RSB in 130 paediatric laparoscopic appendectomies with bupivacaine plus epinephrine compared with normal saline control observed a significant difference in global pain score only for the first 3 hours in favour of bupivacaine but no difference in opioid requirements (Hamill et al. 2015). One year later, the same author detected an opioid saving effect 6-8 hour after paediatric surgery (Hamill et al. 2016). In paediatric umbilical hernia operations, no difference could be found when comparing WI with a single dose RSB in one pilot study (Isaac et al. 2006), but the technique described did not reach the posterior compartment behind the muscle. A retrospective study comparing preincisional US-guided RSB with TEA found no difference in opioid sparing properties (Godden et al. 2013). Another study comparing RSB and TEA found that significantly more patients with RSB had received iv.PCA-opioids than TEA, but the RSB patients mobilized earlier (2.4 vs 3.5 days). There was no difference in postoperative pain scores or length of stay (Tudor et al. 2015).

The cost effectiveness review comparing epidural analgesia, iv.PCA-morphine and continuous preperitoneal wound infusion (CWI) with catheters concluded that CWI was
more effective than PCA and less costly (Brassier et al. 2007). CWI was also found to be equivalently effective but less costly than TEA. The relatively high costs of the CWI devices were counterbalanced by a reduction in the time needed for nursing care postoperatively (Tilleul et al. 2012). RSB uses the same devices as CWI and therefore the costs should be about the same with these two approaches.

As a summary: RSB diminishes the opioid consumption in umbilical hernia, gynaecologic and minor midline laparoscopic operations. Other results are conflicting.

2.6 COMPARING RECTUS SHEATH BLOCK WITH THORACIC EPIDURAL ANALGESIA

Rectus sheath block has been compared with TEA in two studies. One study reviewed 120 open colorectal cancer surgeries with data being collected prospectively. During 33 months, a total of 120 patients were operated with 109 being included in the study. Exclusions were technical failure of TEA in four patients and of RSB in three patients and insufficient data concerning four patients. At the beginning of the 33 months, 85 patients received TEA and then following the introduction of the new RSB technique, 24 patients were administered RSB, which became a new standard. In the TEA- group, the treatment commenced in the PACU as an infusion of 1.25 mg/ml bupivacaine with 4 µg/ml fentanyl. In the RSB –group, levobupivacaine (2.5 mg/ml) 10 - 20 ml was repeated at 6 hour intervals for 3 days, then 10 - 20 ml when needed and after 5 days, if pain persisted, at 6 hour intervals for a further 48 hours. The RSB catheters were inserted following induction of anaesthesia. The TEA- group experienced significantly more often hypotension on the first POP. There were no differences in pain scores, consumption of opioids or complications. Their conclusion was that RSB with US-guidance appeared to provide an equivalent level of postoperative analgesia as TEA (Godden et al. 2013). In that publication, the authors stated that they planned to start a prospective trial to compare TEA and RSB in open abdominal and pelvic surgery, but no results have been published so far.

An observational study compared RSB-catheters to epidural infusion analgesia after open or converted to open colorectal operations (Tudor et al. 2015). In RSB, a dose of 20 ml levobupivacaine 2.5 mg/ml through each catheter was given at 6 hour intervals and later more sparsely as pain eased. Regional analgesia was used for up to 1- 5 days. There were no differences in postoperative pain scores or length of stay, but mobilisation occurred significantly earlier in the RSB group. This study was not randomised, the anaesthetist made the decision about the use of TEA, which may have introduced some bias in the trial’s outcomes. The conclusion was that RSB provided equivalent analgesia to TEA and should be adopted more widely. In conclusion, there are increasing doubts whether epidural analgesia should be considered as a gold standard for routine postoperative analgesia (Rawal 2012) because of the increasing evidence that less invasive regional analgesic techniques are equally effective as epidural blockade and the risks for serious AE are less.
2.7 INFLAMMATORY RESPONSE

2.7.1 Inflammatory response and cytokines

Inflammation is a reaction of the host tissue against trauma or pathogens. For example, it is well known that surgical trauma triggers an acute inflammatory response. First, the vasoactive mediators, histamine and leukotrienes (from mast cells and platelets) and bradykinin cause vasodilation. Leukotrienes (LT), particularly LTB4, are potent stimulators of the activity of polymorphonuclear granulocytes (PMN) (Samuelsson et al. 1987). These inflammatory mediators evoke pain in the sensory nervous system.

This first phase is followed by activation of cytokines, which are predominantly produced by helper T-cells and macrophages. Cytokines activate neutrophils and macrophages and regulate the inflammatory response (Marik & Flemmer 2012). The production of cytokines is considered to reflect the degree of surgical stress (Aosasa et al. 2000).

Proinflammatory cytokines alter the concentrations of CRP, albumin, ferritin, transferrin and fibrinogen (Gabay & Kushner 1999). Interleukins-1 (IL-1α and IL-1β), IL-8 and tumour necrotizing factor (TNF)-α coordinate the local inflammatory response. TNF-α induces the release of IL-1 and stimulates the synthesis of IL-6. These two cytokines, IL-6 and TNF-α, activate lymphocytes and mediate the systemic inflammatory response (SIR). IL-1α and IL-1β are pyrogenic and activate leucocytes, epithelial and endothelial cells (Shaikh 2011). IL-12 and IL-18 intensify the inflammatory response.

The anti-inflammatory cytokines are intended to control excessive inflammation. The most important of these agents are IL-4, IL-10, IL-11 and IL-13. IL-4 and IL-10 inhibit the production of proinflammatory cytokines. IL-10 is very potent, since it both up-regulates anti-inflammatory and down-regulates proinflammatory cytokines, such as IL-1, IL-6 and TNF-α. A specific IL-1 receptor antagonist (IL-1ra), binds to the same receptor as IL-1, blocking it without producing IL-1β mediated cellular changes (Maier et al. 1993, Sweitzer et al. 2001). Specific cytokine receptor antagonists for IL-1, TNF-α and IL-18 act as inhibitors for pro-inflammatory cytokines (Shaikh 2011). IL-18 binding protein prevents action of IL-18. Some agents i.e. leukaemia inhibitory factor, interferon-α, IL-6 and transforming growth factor (TGF)-β can be either anti- or pro-inflammatory under different circumstances.

TGF-β has multiple functions, i.e. it prevents the actions of cell growth factor. TGF-β counteracts IL-1, IL-2, IL-6 and TNF and inhibits cytokine production in macrophages (Roberts & Sporn 1993). TGF-β can convert an active site of inflammation into one dominated by resolution and repair. TGF-β often exhibits effects mediated through the immune activity in local tissues and immune suppressive activity in the systemic circulation (Shaikh 2011).

IL-6 and CRP display the strongest association with the magnitude of surgical trauma (Ohzato et al. 1992, Watt et al. 2015). IL-6 regulates cellular metabolic activity and stimulates the production of CRP. The concentrations of IL-6 will increase a few hours after surgery and remain elevated for 72 hours (Baigrie, 1992). CRP activates the complement cascade and stimulates phagocytosis by macrophages and neutrophils. The concentrations of CRP increase from 12 to 72 h postoperatively only returning to baseline
after two weeks (Ohzato et al. 1992). A significant local inflammation causes a systemic response, termed the acute phase reaction, which increases CRP.

Cytokines can be classified according to the cells that produce these agents: lymphokine by lymphocytes, monokine by monocytes and interleukin made by and acting on other leucocytes. Chemokines induce chemotaxis functioning primarily in the activation and migration of leukocytes; IL-8 belongs to this subgroup. Cytokines may act on cells in which they are produced in (an autocrine effect), on nearby cells (a paracrine effect), or on distant cells (an endocrine effect) (Zhang & Jianxiong 2007).

2.7.2 Cytokines and pain mechanisms

IL-1β is expressed in nociceptive dorsal root ganglion (DRG) neurons (Copray et al. 2001). Crush injuries to peripheral nerve and trauma lead to enhancement of IL-1β’s effects in CNS cells (Yan et al. 1992). IL-1β increases the release of substance P and prostaglandins in neuronal and glial cells. The intraperitoneal or intrathecal injection of IL-1β has been reported to produce hyperalgesia (Watkins et al. 1994).

IL-6 contributes to the development of neuropathic pain behaviour following a peripheral nerve injury (DeLeo et al. 1996, Ramer et al. 1998). Nonetheless, not all of its effects are negative; a suppression of IL-6’s effects by antibodies led to reduced regenerative effects after nerve trauma.

TNF-α, also known as cachectin, plays a significant role in both inflammatory and neuropathic hyperalgesia (Woolf et al. 1997, Cunha et al. 1992). TNF-α receptors are present in both neurons and glia (Boka et al. 1994).

Chemokines are up-regulated in neuroinflammatory models, demyelinating diseases (White et al. 2005), CNS trauma (Berman et al. 1996) and in injured peripheral nerves (Taskinen & Roytta 2000). Receptors of chemokines are expressed in DRG neurons.

IL-10 has been reported to suppress the development of spinally-mediated pain in animal studies (Wieseler-Frank et al. 2004). On the other hand, low concentrations of IL-10 and IL-4 have been detected in patients with chronic widespread pain (Uceyler et al. 2006).

TGF-β1 is present in meninges, choroid plexus, peripheral ganglia and nerves. TGF-β1 counteracts the actions of IL-1, IL-2, IL-6 and TNF-α and inhibits cytokine production in macrophages and Type 1 T helper (Th1) cells. It also prevents the production of nitric oxide which is involved in the final pathway of neuropathic pain (Ding et al. 1990). One may speculate that either TGF-β1 or agents inducing its activity may be effective therapy for neuropathic pain in future.

The spinal glial activation is necessary for induction of neuropathic pain. Spinal administration of fractalkine induced cutaneous hyperalgesia whereas its receptor antagonist had pain-relieving properties. The traditional tetracycline antibiotic, minocycline has recently been demonstrated to act also as a glia-specific inhibitor, inhibiting IL-1β and inducible nitric oxide synthesis and thus blocking the development of neuropathic pain (Watkins et al. 2003).
There is a possible correlation between the inflammatory responses and sympathetic nerve sprouting, both of which are present in various chronic pain states. Proinflammatory cytokines and chemokines may directly modulate neuronal activity in the peripheral and CNS. IL-6 has been found to promote sympathetic nerve sprouting in nerve injury, an effect mediated in DRG (Ramer et al. 1998).

It is possible that in the future, specific cytokines or antagonists will be developed to act as disrupters of the hyperexcitability in the sensory neurons, providing a non-opioid treatment of pathological pain due to inflammation or peripheral nerve injury (Stein & Machelska 2011).

### 2.7.3 Effects of type of surgery on inflammatory response

Open gastric surgery is invasive and causes an excessive surgical trauma and release of inflammatory cytokines such as CRP, TNF-α, IL -1, -6, -12 and -18 (Servis et al. 2008). The adoption of a laparoscopic technique compared to open laparotomy for distal gastrectomy in gastric cancer seems to attenuate the extent of the inflammatory reaction. The concentrations of IL-6 (Hayashi et al. 2005, Adachi et al. 2000) and CRP (Hayashi et al. 2005, Sakuramoto, 2013) in blood were significantly reduced in two randomized, controlled studies as well as in five retrospective studies. Most studies have reported also lower numbers of white blood cells (WBC) in laparoscopy. The CRP response differs also between minimally invasive or laparoscopic vs open procedures such as cholecystectomy (27 vs 80 mg), colorectal cancer resection (97 vs 133 mg) and aortic aneurysm repair (132 vs 180 mg) (Watt et al. 2015). Similar inflammatory responses based on the concentrations of IL-8, IL-10 and IL-1β were detected in minilaparotomy cholecystectomy and laparoscopic cholecystectomy, although the laparoscopic technique was associated with lower relative elevations in IL-1ra and IL-6 concentrations (Aspinen et al. 2016).

In a study of paediatric Nissen-fundoplication with 29 patients, only plasma concentrations of the anti-inflammatory marker IL-10 in the open laparotomy group were higher compared with the corresponding values in the laparoscopic group. No significant differences were found between the groups in the concentrations of proinflammatory markers TNF-α, IL-6, IL-8, WBC-count, CRP or monocyte chemoattractant protein-1 (Knatten et al. 2014).

ERAS protocol is promoted as reducing SIR to surgery. The different components have been analysed and only the laparoscopy technique was found to reduce SIR. The duration of surgical procedure was not associated with postoperative SIR (McSorley et al. 2016).

### 2.7.4 Effects of type of analgesia on inflammatory response

The effect of spinal anaesthesia on inflammatory response was recently studied by Day et al. (2015). There are no significant differences in median concentrations of insulin or ILs, TNF-α, interferon-γ or vascular endothelial growth factor if spinal analgesia is the primary form of postoperative analgesia when compared to morphine PCA, after a laparoscopic
colorectal surgery. Only at the time point of three hours after surgery were the median concentrations of cortisol and glucose lower in the spinal analgesia-group.

In 1984, the effect of TEA on the endocrine response was examined in 24 female patients undergoing a cholecystectomy. The administration of epidural morphine and bupivacaine attenuated the rise of plasma cortisol concentration (although not immediately) after cholecystectomy. The plasma epinephrine concentration was lower immediately after the operation only in the TEA combined with LA-group whereas the plasma norepinephrine concentrations remained unchanged. There was an intermediate increase in the plasma norepinephrine concentration in the TEA-with morphine-group while the plasma norepinephrine concentrations were higher in the control-group (Rutberg et al. 1984). In 1988, in another study with 24 cholecystectomy patients only a minor and clinically unimportant modulation of perioperative and postoperative plasma concentrations of cortisol, glucose as well as WBC and differential counts were found when comparing TEA with a conventional pain treatment (Schulze et al. 1988). The TEA-group were given bupivacaine for 48 hours and epidural morphine for 96 hours which eliminated postoperative pain during rest and coughing. TEA was found to be effective after Ivor Lewis-oesophagectomy compared with the only-iv.PCA-opioid group: mean resting and dynamic pain, PCA morphine consumption in the first three POP days and blood concentrations of IL-6 and IL-8 declined significantly in the TEA-group. Interleukins were measured at 1 h and 20 h after the end of the surgical procedure (Fares et al. 2014). Epidural analgesia has been reported to decrease CRP concentrations also after colorectal surgery (Chen et al. 2015). Inflammatory mediators (TNF-α, IL-6, and IL-8) were significantly lower after the surgical operation with continuous epidural anaesthesia compared with only general anaesthesia in radical gastric carcinoma surgery (Zhao & Mo 2015).

LAs are known to attenuate the inflammatory response, inhibiting sequestration and activation of PMNs and macrophages and monocytes (Sinclair et al. 1993). LAs block LT, which may explain some of their anti-inflammatory properties (Samuelsson et al. 1987). The vasoconstrictive properties of LAs may also diminish the swelling induced by inflammatory cytokines (Gamse et al. 1980). The concentrations of LA needed for local and regional anaesthesia or antiarrhythmic effects are many times greater than those needed to achieve many other pharmacologic effects such as those that attenuate PMNs, macrophages and monocytes (Hollmann et al. 2000, Hollmann & Durieux 2000). Although LAs can modulate excessive inflammation, they do not impair significantly the host defences. The antibacterial (Sakuragi et al. 1996) and antiviral effects (De Amici et al. 1996) of LAs become evident only at high concentrations. A gross bacterial contamination may therefore carry the risk of infection in theory but this has not been evident in clinical studies (Peck et al. 1985).

Many of the mechanisms which are involved in the anti-inflammatory properties of LAs have been examined in in-vitro and animal studies. In clinical use, there are only few applications such as an antiarrhythmic lidocaine infusion which also attenuates the inflammatory reaction and the myocardial injury associated with the reperfusion of the ischemic heart. IL-6 and IL-8 are important regulators of the inflammatory response in myocardial infarction (Neumann et al. 1997).

It has been reported that iv. lidocaine (first as an iv. lidocaine bolus (1.5 mg/kg) and then infusion (3 mg/min., unless weight <70 kg, then 2 mg/min. aiming at with plasma
concentration of 1.3-3.7μg/ml) accelerated the return of bowel function in patients undergoing radical prostatectomy, resulting in a significant shortening of hospital stay (Groudine et al. 1998). Lidocaine (100 mg bolus iv. plus 3 mg/min. continuous iv. infusion, or bupivacaine 2 mg/kg intra-abdominal installation) also shortened the duration of postoperative ileus in patients undergoing major abdominal surgery (Rimback et al. 1986, Rimback et al. 1990). Ropivacaine has been found to exert an anti-inflammatory effect by acting on different aspects of the inflammatory response in vitro and in animal studies. In ulcerative colitis or proctitis, rectally administered ropivacaine (200 mg twice daily) reduced clinical symptoms for two weeks (Arlander et al. 1996). The treatment with a rectal ropivacaine gel in all volumes between 20 and 80 ml was found to spread up to the descending colon (Arlander et al. 2003).

In conclusion, the antiarrhythmic use of lidocaine seems to be at present the only one widely accepted in clinical use besides analgesia.

2.8 OXIDATIVE CELL STRESS

2.8.1 8-Hydroxy-2’-deoxyguanosine

Oxidative cell stress is defined as an imbalance between the production of oxidants and their elimination by protective antioxidants (Reuter et al 2010). OCS can activate a variety of transcription factors i.e. p53, beta-catenin, activator protein (AP)-1, peroxisome proliferator-activated receptor (PPAR)-γ, and nuclear factor like (Nrf) 2. Activation of these factors has been found to lead to the expression of over 500 genes of chemokines, inflammatory cytokines, growth factors, and anti-inflammatory molecules.

Oxidative stress can cause a permanent damage to lipids in cellular membranes as well as to proteins and deoxyribonucleic acid (DNA) (Valavanidis et al. 2009). Carcinogens and mutagens react with nucleic acid bases, particularly guanine (Kasai et al. 1984). 8-Hydroxy-2’-deoxyguanosine is one of the predominant forms of free radical-induced oxidative lesions detectable in nuclear and mitochondrial DNA. It has been widely exploited as a surrogate for measuring the extent of endogenous oxidative damage to DNA and as a factor involved in the initiation and promotion of carcinogenesis (Kasai 1997). The OH• molecule is the most important oxygen free radicals and 8-OHdG is its most abundant DNA lesion (Valko et al. 2004). It is relatively easily formed and promutagenic, a potential biomarker of carcinogenesis (Kasai 1997). 8-OHdG has been studied since 1984.

Reactive oxygen species (ROS) are formed continuously in living cells during normal metabolic processes. These ROS and oxygen-free radicals have physiologic functions, but they may also cause oxidative damage. There are also exogenous factors such as asbestos (Unfried et al. 2002), tobacco smoking (Pryor 1997), ultraviolet (UV)-radiation (Dröge 2002), diesel exhaust particles (Harri et al. 2005) and chemicals which can produce ROS. When the balance between oxidative damage and defensive antioxidant mechanisms fails, the resulting damage to DNA contributes to aging (Beckman & Ames 1998), degenerative diseases (Harman 1956, Harman 1986) and carcinogenesis.
The importance of exogenous carcinogens in carcinogenesis may be evaluated by the high incidence of sporadic cancer, which is unlikely to be caused by environmental exposure (Ames & Gold 2000). It has estimated that in each human cell, approximately 20,000 nucleobases in DNA are damaged each day (Beckman & Ames 1997). The most important DNA repair mechanism of 8-OHdG damage is a specific 8-oxoguanine glycosylase (OGG1) protein which initiates the base repair pathway (Chung et al. 1991, Yamamoto et al. 1992).

In abdominal surgery, the laparoscopic approach seems to attenuate OCS (Arsalani-Zadeh et al. 2011, Aspinen et al. 2016). Serum concentrations of isoprostane 8-epi prostaglandin F2α (epiPGF2α), free radical catalyzed product of arachidonic acid, were found to be a more suitable marker than 8-OHdG8 for defining the oxidative status after colectomy operations for cancer (Pappas-Gogos et al. 2013). Although no signs of decreased splanchic tissue oxygenation were found during laparoscopic carbon dioxide pneumoperitoneum (Thaler et al. 1996), the effect of pneumoperitoneum on local OCS requires further investigations (Arsalani-Zadeh et al. 2011).

The results of meta-analysis of 29 studies with 2477 patients with depression showed that OCS plays a role even in major depressive disorders. The activity of antidepressants may be mediated via improvements in OCS / antioxidant function (Jimenez-Fernandez et al. 2015). Chronic inflammation, for instance as is present in chronic pancreatitis, ulcerative colitis and Crohn’s disease, induces persistent OCS and nitrosative cell stress and excess lipid peroxidation (Bartsch & Nair 2006), and continuing OCS can lead to chronic inflammation (Reuter et al. 2010).

Surgical trauma is associated with the generation of ROS. 8-Hydroxy-2’-deoxyguanosine - is frequently used as a biomarker of OCS (Kasai 1997). In a recent study concerning the effects on OCS of either minilaparotomy or laparoscopic cholecystectomy, the 8-OHdG concentrations were rather similar, but the individual plasma values correlated with concentrations of the anti-inflammatory cytokine, IL-10 and the proinflammatory cytokine, IL-1β, suggesting that inflammation is related to OCS (Aspinen et al. 2016).

2.8.2 Glutathione peroxidase

Glutathione peroxidase is the general name of an enzyme family with peroxidase activity whose main biological role is to protect organisms from oxidative damage by free oxygen radicals and the generation of ROS (Bartsch & Nair 2006, Muller et al. 2007, Reuter et al. 2010). GPX reduces lipid hydroperoxides to their corresponding alcohols and converts free hydrogen peroxide into water.

It has been shown that a low plasma GPX concentration in patients with type-2 diabetes correlates with macroalbuminuria and the stage of diabetic nephropathy (Sedighi et al. 2016). In one study, the activity of GPX was lower in patients with relapsing–remitting multiple sclerosis (Socha et al. 2014), and in celiac disease suggesting that GPX plays a role in the development of celiac disease (Kumar et al. 2017).

2.8.3 Oxidative cell stress, pain and analgesia
Opioid analgesics have potential antioxidant properties i.e. morphine’s antioxidative effect has been demonstrated (Gülçin et al. 2004). Even the use of epidural analgesia for labour was found to effect both the level of OCS and the anti-oxidant defence of the neonates: the extent of lipid peroxidation and the antioxidant catalase and glutathione diminished in the cord blood (Gyurkovits et al. 2013). In addition, superoxide dismutases (SODs) and GPX diminished. In rats, the effect of ageing was found to increase the oxidative stress in brain, with a negative correlation with antinociceptive effect of opioids and lowering the nociceptive threshold (Raut & Ratka 2009). A similar negative correlation was found between OCS markers and fentanyl’s antinociceptive effect.

One could argue that appropriately administered antioxidants may decrease the sensation of pain and protect CNS against free radicals. The administration of simultaneous injection of antioxidants and analgesics (acetylsalicylic acid or morphine) normalized OCS and functional indicators of pain in rats after a painful stimulation but did not change the level of OCS if analgesics were given without antioxidants. Normally the lipid peroxidation persisted for up to 15 days after painful stimuli (Rokyta et al. 2013). One novel active analgesic agent, 3-[4-(3-triofluoromethyl-phenyl)-piperazin-1-yl]-dihydrofuran-2-one, has been studied in vitro and in ex vivo assays. A single dose caused an increase in antioxidant glutathione concentration in brain tissue homogenates of mice by 34% vs control group, p<0.05 (Salat et al. 2014). Human immuno-deficiency virus (HIV)-proteins enhances the efficiency of viral transcription. Trans-Activator of Transcription (TAT)1-72 -proteins are known to be neurotoxic and induce dose dependent OCS and this could be attenuated by both peptide and non-peptide opioid agonists and furthermore, this beneficial effect was partially reversed by the δ-opioid antagonist naltrindole in neuroblastoma cell cultures, evidence that δ-opioid agonists possess antioxidative effects (Wallace et al. 2006).

2.9 ANALGESIA AND CANCER

The possible connection of analgesia with the results of cancer surgery has aroused substantial interest. The systemic inflammatory response (SIR) as measured by CRP after colorectal and oesophagogastric surgery has been associated negatively not only with postoperative complications but also with long term survival independent of complications (McSorley et al. 2016). There are hints emerging from retrospective analyses and animal models that regional anaesthesia may play a protective role in cancer surgery. Regional anaesthesia protects cell-mediated-immunity (CMI) and diminishes the surgical neuroendocrine stress response by blocking afferent neural transmission and decreasing the requirement for opioids and volatile anaesthetics. LAs inhibit proliferation and migration of cancer cells (Yoon et al. 2011) and induce apoptosis of cancer cells (Perez-Castro et al. 2009, Chang, Liu et al. 2014, Chang, Hau et al. 2014) in vitro studies.

In 2006, Exadaktylos et al. published a retrospective analysis of 129 breast cancer operations suggesting that paravertebral block (50 patients) vs iv.PCA-morphine (79 patients) may reduce the risk for tumour progression after primary breast cancer operation (p=0.012).

The effects of opioids on cancer cells are still being debated. Opioids have been claimed to promote cancer growth (e.g. by Gupta et al. 2002, Mathew et al. 2011) but these were only
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in vitro studies. The dose of opioids may be important because higher doses are more effective in terms of pain relief and attenuating the stress response to surgery (Page 2005). NSAIDs are a component of multimodal pain management. They reduce the resistance of cancer cells to apoptosis and inhibit the activity of the enzyme cyclooxygenase-2 (COX-2) responsible for the production of prostaglandin (PG)E2 (Cha & DuBois 2007). NSAIDs appear to reverse the cancer-promoting effects of opioids and surgery in experimental animals (Melamed et al. 2005, Farooqui et al. 2007). A retrospective analysis of 327 breast cancer patients, ketorolac was associated with a lower recurrence of the malignancy (Forget et al. 2010).

Many volatile anaesthetics suppress CMI but iv. anaesthetic propofol has been claimed to possess properties protecting the body from the tumour (Tavare et al. 2012, Melamed et al. 2003). Nitrous oxide does not appear to exert any effect on cancer recurrence (Fleischmann et al. 2009).

2.10 PAIN RATING SCALES

There are several different methods to measure the intensity of pain. The three most commonly used are the visual analogue scale (VAS), the verbal rating scale (VRS), and the numerical rating scale (NRS). VAS uses a 10-cm line, where the ends are marked by verbal descriptors, usually ‘no pain’ and ‘worst imaginable pain’. The patient marks with a line to indicate the level of pain and the measure from point 0 in centimetres is the numerical value. Repeated measures using the VAS produces errors of approximately 20 mm (DeLoach et al. 1998) or 20% (Rosier et al. 2002). VRS uses a list of adjectives to describe increasing pain intensities. The most common words are: no pain; mild pain; moderate pain; and severe or intense pain. NRS is an 11-point scale where the end points are the of no pain and pain as bad as it could be, or alternatively most possible pain. The NRS can be graphically or verbally delivered, even by telephone enquiry (Jensen et al. 1986).

The lack of sensitivity of the VRS can lead over- or under-estimation of pain changes (Jensen et al. 1994). The VAS and the NRS are superior in this respect because they have greater sensitivities at detecting changes (Ohnhaus & Adler 1975, Jensen et al. 1986, Jamison et al. 2002). The NRS and the VAS give almost identical values in the same patient at various times after surgery, whereas VRS seems to underestimate the most intense pain compared with the VAS (Brejvik et al. 2000).

The Brief Pain Inventory (BPI) assesses pain severity using 0–10 NRS and the degree of interference with function (general activity, walking, normal work, relations with other people, mood, sleep, and enjoyment of life). It enquires about the least, the average and the worst pain experienced right now and during last 24 h representing a good base level on which to compare the response to treatments (Wang & Cleeland 2008). (Appendices)

2.11 PATIENT SATISFACTION

Patient surveys can help to identify novel ways of improving practice. Conductance of a survey reveals to health care staff and the community that the institution is interested in quality (White 1999). As stated above, NRS is more sensitive than VRS as a way of rating
pain and is used in PS questionnaires. To better understand possible divergences, an open-ended question is connected to the questionnaire. There are Patient Satisfaction Questionnaires, which are adaptable, reliable, and validated tools for use in various settings (Thayaparan & Mahdi 2013).

In a large survey, 10 811 in-patients were interviewed on the first POP day after their surgical procedure. The major subjective outcome measure was PS. Other predetermined outcomes, such as PONV, pain and complications were also measured. The overall satisfaction was high (97%), only 246 (2.3%) patients were ‘somewhat dissatisfied’ and even fewer, 97 (0.9%), were ‘dissatisfied’ with their anesthetic care. There was a clear relationship between patient dissatisfaction and moderate or severe postoperative pain (OR 3.9), PONV (OR 4.1) and any other postoperative complications (OR 2.0). (Myles et al. 2000).

In the United States of America, a letter questionnaire was sent to clinical trial patients who had consented to participate and/or completed a clinical trial in the research institute in the previous year. Ninety surveys were returned in the 6 months following the mailing i.e. a 41 % response rate. The questions with the highest-ranking responses were related to interactions with staff. Fifty-one percent of patients strongly agreed that they would seek future care in the same system (Pflugeisen et al. 2016). Pflugeisen strongly recommends that clinicians should make more use of PS questionnaires.
Aims of the study

The general aim of this study was to evaluate the efficiency and safety of postoperative RSB and to compare three different LA administering modalities in patients after a midline laparotomy.

The specific aims were:

1. To evaluate the effect on the oxidative cell response: whether it could be altered by the post-surgery placement of RSB. The working hypothesis of the study was that patients' pain experience in NRS would correlate with the concentration of the oxidative stress marker, 8-OHdG in patients with benign disease and cancer (Publication 1).

2. With respect to the SIR, it was decided to evaluate whether the post-surgery placement of the RSB would reduce the inflammatory response following surgery. The main hypothesis of the study was that patients' pain experience in NRS postoperatively would correlate with the concentrations of inflammatory response biomarkers, such as IL-1ra, IL-6, IL-8, IL-10, IL-1β, in patients with benign disease and cancer (Publication 2).

3. The possible cytoprotective effect was evaluated to determine whether the overall satisfaction as measured by NRS regarding analgesia would be associated with the plasma GPX1 concentrations and secondly, to evaluate the differences in GPX1 concentrations in patients with and without RSB analgesia, with special emphasis on benign or malign antdisease status (Publication 3).

4. The main object of the study was to find if RSB could diminish the need for opioids in postoperative pain control. Patients' satisfaction of postoperative analgesia was evaluated as a secondary outcome (Publication 4).
3 Aims of the study

The general aim of this study was to evaluate the efficiency and safety of postoperative RSB and to compare three different LA administering modalities in patients after a midline laparotomy.

The specific aims were:

1. To evaluate the effect on the oxidative cell response: whether it could be altered by the post-surgery placement of RSB: the working hypothesis of the study was that patients’ pain experience in NRS would correlate with the concentration of the oxidative stress marker, 8-OHdG in patients with benign disease and cancer (Publication 1).

2. With respect to the SIR, it was decided to evaluate whether the post-surgery placement of the RSB would reduce the inflammatory response following surgery. The main hypothesis of the study was that patients’ pain experience in NRS postoperatively would correlate with the concentrations of inflammatory response biomarkers, such as IL-1ra, IL-6, IL-8, IL-10, IL-1β, in patients with benign disease and cancer (Publication 2).

3. The possible cytoprotective effect was evaluated to determine whether the overall satisfaction as measured by NRS regarding analgesia would be associated with the plasma GPX1 concentrations and secondly, to evaluate the differences in GPX1 concentrations in patients with and without RSB analgesia, with special emphasis on benign or malignant disease status (Publication 3).

4. The main object of the study was to find if RSB could diminish the need for opioids in postoperative pain control. Patients’ satisfaction of postoperative analgesia was evaluated as a secondary outcome (Publication 4).
Patients and study design

4.1 Patients and flowcharts

All operations were performed in Kuopio University Hospital. The inclusion criteria were: age between 18-80 years, midline laparotomy, elective or emergency operation, mental capability to use the PCA-pump. Exclusion criteria were: pregnancy or nursing, chronic pain medication, abuses of opioids or alcohol, incapability to use PCA-pump, body mass index (BMI) > 35 kg.m\(^{-2}\), contraindications to LA or opioid analgesics or their excipients and a second operation during the same hospital stay.

A sample size calculation was performed indicating that 15 patients would be needed in each group to show a 30% decrease of assumed opioid need of 20 mg (SD 5) of oxycodone during the first 24 postoperative hours with a desired power of 0.9 and at a significance level of 0.05.
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Enrolment and randomisation to laparotomy with the rectus-sheath block
n = 46

Placebo n = 11
Single-dose n = 12
Repeated-dose n = 12
Continuous-infusion n = 11

Baseline before and immediately after operation
hs-CRP, IL-1ra, IL-6, IL-8, IL-10, IL-1β and 8-OHdG

Placebo Analysed n = 8
Single-dose Analysed n = 8
Repeated-dose Analysed n = 11
Continuous-infusion Analysed n = 9

At 24 hours after operation
hs-CRP, IL-1ra, IL-6, IL-8, IL-10, IL-1β and 8-OHdG

Placebo Analysed n = 8
Single-dose Analysed n = 8
Repeated-dose Analysed n = 11
Continuous-infusion Analysed n = 9

No blood samples
n = 3

No blood samples
n = 4
No blood samples
n = 1
No blood samples
n = 2

No blood samples
n = 3
No blood samples
n = 4
No blood samples
n = 1
No blood samples
n = 2

No blood samples
n = 3
No blood samples
n = 4
No blood samples
n = 1
No blood samples
n = 2

Place 3. Flowchart of the cytokine and 8-OHdG studies.
Enrolment and randomisation to laparotomy with the rectus-sheath block n=56

Placebo n=12
Single-dose n=16
Repeated-dose n=12
Continuous-infusion n=16

Baseline before and immediately after operation
Baseline: Hs-CRP and GPX1

At 24 hours after operation
Hs-CRP and GPX1

Figure 4. Flowchart of the GPX1 and CRP study.
80 patients scheduled for elective midline laparotomy

Excluded 3 patients
- Change to mini-invasive surgery n=2
- Change to epidural analgesia without patient consent (n=1)

Declined 20 patients
- Want nothing extra (n=2)
- Fear of the control group randomization (n=2)
- Hope to have epidural analgesia (n=1)
- Patient thought not to be able to use iv-PCA-pump (n=1)
- Declined cognition (n=1)
- General health poor (n=1)
- No specific reason (n=12)

Randomisation n=57

The initial bolus at the end of surgery
Levobupivacaine 25 mg/20 ml to both catheters

Control (n=12)
No local anaesthetic

Single dose (n=16)
Catheters removed after the initial bolus

Repeated doses (n=12)
Levobupivacaine 12.5 +12.5 mg at every 4 hours for 48 h

Infusion (n=17)
Levobupivacaine 12.5 mg/h for 48 h

Figure 5. Flowchart of the oxycodone, levobupivacaine and patient satisfaction study.

4.2 STUDY DESIGN AND METHODS

The study was designed as a prospective, randomised, controlled, open label clinical trial with four parallel groups. The study protocol was approved by the Research Ethics Committee of the University Hospital District of Northern Savo, Kuopio, Finland and registered with EudraCT and Clinical Trials database. The Finnish Medicines Agency was notified and the study received institutional approval. The study was conducted in accordance with principles presented in the Declaration of Helsinki (WMA, 2013) between June 2012 and December 2015. Patients were enrolled after receiving written consent after verbal and written information given by an anaesthesiologist or the operating surgeon. Patients were informed about the different analgesic methods and that they had the possibility to quit the study whenever without any reason was emphasized.
4.2.1 Randomisation in four groups

Randomisation was computer generated (www.randomization.com). The randomisation was done concealed with an opaque envelope method until the end of the operations.

4.2.2 Anaesthesia, analgesia and rectus sheath block

The premedication and anaesthesia were standardized and all deviations were noted. Midazolam 1-2 mg i.v. and thiopental i.v. were used for induction of anaesthesia. Endotracheal intubation was facilitated with rocuronium 0.5 mg i.v. To ensure that there was an adequate level of anaesthesia, response entropy indexes were kept between 40 and 60 through the anaesthesia by adjusting the inhaled desflurane concentration accordingly. Remifentanil infusion 0.5–2.0 μg/kg/min. was used for intraoperative analgesia. Lungs were ventilated with oxygen 35% in air with positive pressure ventilation. At the end of anaesthesia, muscle relaxation was reversed by administration of sugammadex. Remifentanil infusion 0.1 mg/h was continued for the first postoperative hour in the recovery room. Patients’ vital parameters, blood pressure, heart rate, peripheral oxygen saturation, central temperature, neuromuscular block, anesthetic gases, oxygen and end-tidal carbon dioxide (CO2) partial pressure were monitored continuously throughout the anaesthesia.

In all groups, except for the control-group, two rectus sheath catheters (InfiltraLong, Pajunk, Geisingen, Germany) were inserted before skin closure through separate skin punctures four or five centimetres cephalad to the incision using disposable blunt rods with sheaths. The surgeon guided manually the rod’s insertion into the abdomen to prevent gut perforations and aiming at the lateral half behind the muscle where the nerves enter the sheath. The catheter’s length was chosen to contain all the radicular nerves coming to the wound. The length of a catheter was not to be registered. All patients, except for those in the control-group, received 25 mg/20ml levobupivacaine (Chirocaine 1.25 mg/ml, AbbVie, Espoo, Finland) in both catheters, a total dose of 50 mg. In the single bolus-group, rectus sheath catheters were removed after the first doses and the incisions were covered with wound dressings. After the initial dose in the repeated boluses-group, levobupivacaine doses, 12.5 mg/10ml in both catheters, a total dose of 25 mg, were administered at every four hours for the first 24-48 postoperative hours. In the infusion-group, an infusion of levobupivacaine 12.5 mg/h via both catheters, was achieved with Autofuser pumps (ACE Medical, Seoul, Korea) immediately after the initial boluses, and this was continued for 48 hours or until discharge if earlier than 48 hours. In the control-group, no punctures were made but the wound dressings were used as if they had a single block puncture to ensure blinding. Patients in the control-group did not receive any WI. Patient controlled analgesia-pump with an iv. bolus dose of 2 mg of oxycodone and a lock-out interval of 10 min. and a maximum dose of 12 mg/h was used for rescue analgesia. For background analgesia patients were given i.v. paracetamol 4 g/24 h or 3 g/24 h if the patient weighed less than 50 kg.

4.2.3 Pain inventories

The pain assessment was conducted by a NRS where “0” represents no pain at all and “10” was the worst possible pain. The same scale was used for patient’s satisfaction of
postoperative analgesia with “0” meaning very dissatisfied and “10” nothing to complain about and totally satisfied. The pain at rest and dynamic pain, when pressing the wound with 20 N force and pain when coughing, were measured in the PACU and surgical wards at 15 and 30 min. and at 1, 2, 4, 12 and 24 hours after the first LA bolus or the end of operation (the control-group) when the blood samples were taken. In addition, patient status and pain inventory were scheduled three times a day for the first two postoperative days – in the morning, afternoon and evening.

4.2.4 Quality of life

A questionnaire (Brief pain inventory, short form [Cleeland Cs 1991]) was filled by each patient before the operation, when leaving the hospital and at one month and a year afterwards. At the same time, patients were asked to fill in another questionnaire about intestinal symptoms and defecation.

4.2.5 Blood samples

The first blood sample was collected before the induction of the anaesthesia, and then 15 min., 30 min., 60 min., 2 h, 4 h, 12 h, 24 h and 48 h after the first LA dose. In the infusion group, samples were also taken 15 min., 30 min., 60 min., 2 h and 4 h after the termination of the infusion to study the elimination of levobupivacaine. In the repeated dose group, this sample was taken once at two hours after the last bolus. The blood was centrifuged at 20-25 °C, 5 ml samples at 2500 x g for 10 min. and 10 ml samples at 1000 x g for 15 min. and then stored at -70 °C.

The plasma 8-OHdG assays were performed using the HT 8-oxo-Dg ELISA Kit II (Trevigen, Gaithersburg, MD, USA). Plasma high sensitive (Hs) -CRP was analysed with a Cobas 6000-analyzer (Hitachi, Tokyo, Japan). The inflammatory and cell stress markers were analysed from the samples taken preoperatively, immediately after (POP1) and 24 hours after the operation (POP2). The plasma interleukins IL-1β, IL-1ra, IL-6, IL-8 and IL-10 assays were performed using enzyme-linked immunosorbert assay (ELISA) methods from R&D Systems (Minneapolis, MN, USA). The plasma GPX1 assays were performed using sandwich-type ELISA from BioVendor GPX1 ELISA Kit (Brno, Czech Republic). The method for analysing the oxycodone plasma concentration has been described earlier (Kokki et al. 2014). Plasma oxycodone and its main metabolites concentrations were analysed from the blood samples taken at 12, 24 and 48 hours after surgery. The cumulative oxycodone consumption was recorded at the same time points.

All samples were analysed for plasma levobupivacaine concentrations. Levobupivacaine concentrations were measured by quantitative liquid chromatography with triple quadrupole mass spectrometric detection (LC/MS/MS). The LC/MS/MS method was based on a method previously published by Hoizey (2005). The lower limit of quantification (LLOQ) in plasma samples for levobupivacaine was 12.5 ng/ml. This LC/MS/MS method was selective, accurate, and precise for concentrations within a calibration range of 12.5 – 5000 ng/ml for plasma.
4.2.6 Adverse effects

All AE were to be recorded whether they were related or not by the RSB.

4.2.7 Statistical analysis

The data were entered and analysed using IBM SPSS 23.0 (International Business Machine Corp., Armonk, NY, USA). To analyse differences between groups Mann-Whitney U-test was used and for continuous variables analysis of variance (one-way ANOVA, Bonferroni correction) was performed. Group differences at different time points were tested by Mann-Whitney U-test and Kruskall-Wallis-test as appropriate. The results are mainly presented as median with the range because distributions were skewed. A two-sided p-value of less than 0.05 was considered as the limit of statistical significance.
RESULTS

5.1 PATIENT SAMPLE

A total of 80 patients undergoing midline laparotomy were asked to participate and 60 of them agreed to take part in the trial. Reasons to decline were not wanting anything extra (n=2), not wanting to be randomized into the control group (n=2), a desire to receive epidural analgesia (n=1), patient thought not to be able to use i.v.-PCA-pump (n=1), memory loss (n=1), general condition at a low level (n=1) and no specific reason (n=12).

Three patients were lost after they had given consent: two operations were converted to laparoscopies and one operator decided to use TEA. Thus ultimately, 57 patients were in the final study population. Unfortunately, it was not possible to obtain more patients undergoing colorectal surgery. The flowcharts are presented in the Methods section.

5.2 CHARACTERISTICS

5.2.1 Characteristics of patients

The patient characteristics and type of surgery are presented in Table 1. Body mass index was higher in the single bolus group when compared to other groups (p=0.049). The study groups were similar in other terms of variables.

5.2.2 Characteristics of surgery

Diseases were benign in 16 patients whereas 41 patients were subjected to surgery for cancer. A total of 25 gynecologic patients had a cancer operation, most of them a time-consuming gynaecological debulking with a xiphosternum-pubis incision (Table 3).
5 RESULTS

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Table 3. Patient demographics and the type of surgery (n=57). Data are median [range] or number of cases. ASA = American Society of Anesthesiologists Physical Status Classification. BMI = Body Mass Index. * p=0.04 between single dose and repeated dose (one-way ANOVA, Bonferroni correction)/p=0.049 Kruskall-Wallis.
**Because there was unreliable data about when some of the anaesthesia ended, especially after long operations, the durations of anaesthesia can only be approximated.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control n=12</th>
<th>Single dose n=16</th>
<th>Repeated doses n=12</th>
<th>Infusion n=17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>4/8</td>
<td>5/11</td>
<td>3/9</td>
<td>2/15</td>
</tr>
<tr>
<td>ASA I/II/III/IV</td>
<td>1/8/3/-</td>
<td>-/9/6/1</td>
<td>-/7/5/-</td>
<td>2/9/5/-</td>
</tr>
<tr>
<td>Duration of anaesthesia (min.)</td>
<td>245 [45-462]</td>
<td>221 [86-503]</td>
<td>223 [80-441]</td>
<td>290 [131-606]</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>700 [20-2600]</td>
<td>300 [0-3000]</td>
<td>500 [0-3400]</td>
<td>850 [100-2750]</td>
</tr>
<tr>
<td>Type of surgery</td>
<td>Gastrointestinal;</td>
<td>4</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>benign/cancer</td>
<td>1/3</td>
<td>4/4</td>
<td>2/3</td>
</tr>
<tr>
<td></td>
<td>Gynaecological</td>
<td>7</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>benign/cancer</td>
<td>0/7</td>
<td>2/4</td>
<td>2/5</td>
</tr>
<tr>
<td></td>
<td>Urological</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>benign/cancer</td>
<td>0/1</td>
<td>0/2</td>
<td>0/0</td>
</tr>
</tbody>
</table>
5.3 INFLAMMATORY MARKERS

Table 4. The inflammatory marker concentrations for the placebo and rectus sheath block (RSB) groups; three active groups, single-dose, repeated-dose and continuous infusion groups combined. Data are given as median (interquartile range). Plasma concentrations of CRP and five interleukins (IL-1ra, IL-6, IL-8, IL-10, IL-1β) were measured at three time points; before the operation (PRE), immediately after the operation (POP1) and 24 h after the operation (POP2).

<table>
<thead>
<tr>
<th>Marker</th>
<th>Placebo n=8</th>
<th>RSB n=28</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>3.4 (1.2-13)</td>
<td>3.3 (0.8-48)</td>
<td>0.7</td>
</tr>
<tr>
<td>POP1</td>
<td>6.6 (1.0-13)</td>
<td>4.4 (0.8-60)</td>
<td>0.9</td>
</tr>
<tr>
<td>POP2</td>
<td>246 (82-469)</td>
<td>190 (93-303)</td>
<td>0.5</td>
</tr>
<tr>
<td>IL-1ra (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>220 (186-316)</td>
<td>294 (218-450)</td>
<td>0.12</td>
</tr>
<tr>
<td>POP1</td>
<td>1671 (351-2000)</td>
<td>1314 (624-4836)</td>
<td>0.6</td>
</tr>
<tr>
<td>POP2</td>
<td>701 (496-902)</td>
<td>621 (375-879)</td>
<td>0.6</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>3.3 (3.1-4.3)</td>
<td>4.4 (3.1-11)</td>
<td>0.3</td>
</tr>
<tr>
<td>POP1</td>
<td>85 (38-165)</td>
<td>112 (64-300)</td>
<td>0.3</td>
</tr>
<tr>
<td>POP2</td>
<td>67 (51-129)</td>
<td>64 (39-139)</td>
<td>0.8</td>
</tr>
<tr>
<td>IL-8 (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>6.96 (4.8-12)</td>
<td>7.9 (5.5-20)</td>
<td>0.6</td>
</tr>
<tr>
<td>POP1</td>
<td>26 (7.9-42)</td>
<td>17 (8.5-55)</td>
<td>0.9</td>
</tr>
<tr>
<td>POP2</td>
<td>11 (7.5-24)</td>
<td>16 (7.6-27)</td>
<td>0.5</td>
</tr>
<tr>
<td>IL-10 (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>0.8 (0.8-0.8)</td>
<td>0.8 (0.8-1.2)</td>
<td>0.2</td>
</tr>
<tr>
<td>POP1</td>
<td>0.8 (0.8-3.5)</td>
<td>5.8 (1.8-14)</td>
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</tr>
<tr>
<td>POP2</td>
<td>0.8 (0.8-3.2)</td>
<td>0.8 (0.8-2.0)</td>
<td>0.9</td>
</tr>
<tr>
<td>IL-1β (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>0.2 (0.1-0.4)</td>
<td>0.3 (0.1-1.2)</td>
<td>0.3</td>
</tr>
<tr>
<td>POP1</td>
<td>0.3 (0.2-0.7)</td>
<td>0.9 (0.1-1.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>POP2</td>
<td>0.1 (0.1-0.2)</td>
<td>0.4 (0.4-2.0)</td>
<td>0.053</td>
</tr>
</tbody>
</table>
Table 5. The inflammatory marker concentrations for the placebo group and the three active groups; single-dose, repeated-dose and continuous infusion RSB analgesia groups. Data are median and interquartile range. Values are median (interquartile range). Plasma concentrations of hs-CRP and five interleukins (IL-1ra, IL-6, IL-8, IL-10, IL-1β) were measured at three time points; before the operation (PRE), immediately after the operation (POP1) and 24 after the operation (POP2).

<table>
<thead>
<tr>
<th>Marker</th>
<th>Placebo n=8</th>
<th>Single n=8</th>
<th>Repeated n=11</th>
<th>Continuous n=9</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-CRP (mg/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>3.5 (1.1-13)</td>
<td>4.7 (0.9-48)</td>
<td>1.2 (0.6-4.0)</td>
<td>9.6 (1.5-74)</td>
<td>0.5</td>
</tr>
<tr>
<td>POP1</td>
<td>6.6 (1.0-13.2)</td>
<td>9.2 (2.9-83)</td>
<td>2.3 (0.6-5.1)</td>
<td>26 (1.0-232)</td>
<td>0.3</td>
</tr>
<tr>
<td>POP2</td>
<td>246 (82-469)</td>
<td>190 (96-349)</td>
<td>207 (82-284)</td>
<td>159 (79-479)</td>
<td>0.9</td>
</tr>
<tr>
<td>IL-1ra (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>220 (186-316)</td>
<td>346 (237-829)</td>
<td>259 (207-310)</td>
<td>294 (231-658)</td>
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<tr>
<td>POP1</td>
<td>1671 (351-2000)</td>
<td>944 (595-2058)</td>
<td>946 (570-13829)</td>
<td>2000 (703-15500)</td>
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</tr>
<tr>
<td>POP2</td>
<td>701 (496-902)</td>
<td>565 (410-1450)</td>
<td>661 (318-753)</td>
<td>617 (398-957)</td>
<td>0.9</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>3.3 (3.1-4.3)</td>
<td>7.0 (3.3-20)</td>
<td>3.1 (3.1-4.5)</td>
<td>6.2 (3.7-22)</td>
<td>0.051</td>
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<tr>
<td>POP1</td>
<td>85 (37-165)</td>
<td>88 (64-171)</td>
<td>112 (69-300)</td>
<td>218 (63-745)</td>
<td>0.6</td>
</tr>
<tr>
<td>POP2</td>
<td>67 (51-129)</td>
<td>83 (44-176)</td>
<td>55 (27-111)</td>
<td>57 (50-147)</td>
<td>0.7</td>
</tr>
<tr>
<td>IL-8 (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>7.0 (4.8-12)</td>
<td>9.5 (5.7-24)</td>
<td>6.0 (4.8-8.8)</td>
<td>8.8 (6.7-20)</td>
<td>0.6</td>
</tr>
<tr>
<td>POP1</td>
<td>26 (7.9-42)</td>
<td>12 (8.1-41)</td>
<td>17 (8.5-55)</td>
<td>31 (7.7-64)</td>
<td>0.9</td>
</tr>
<tr>
<td>POP2</td>
<td>11 (7.5-24)</td>
<td>13 (7.0-27)</td>
<td>14 (7.0-22)</td>
<td>26 (13-52)</td>
<td>0.3</td>
</tr>
<tr>
<td>IL-10 (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>0.8 (0.8-0.8)</td>
<td>0.8 (0.8-1.1)</td>
<td>0.8 (0.8-0.8)</td>
<td>0.94 (0.8-1.9)</td>
<td>0.010</td>
</tr>
<tr>
<td>POP1</td>
<td>0.8 (0.8-3.5)</td>
<td>4.8 (2.0-14)</td>
<td>3.7 (0.8-8.8)</td>
<td>13 (5.4-23)</td>
<td>0.029</td>
</tr>
<tr>
<td>POP2</td>
<td>0.8 (0.8-3.2)</td>
<td>0.8 (0.8-1.4)</td>
<td>0.8 (0.8-0.9)</td>
<td>1.23 (0.8-3.7)</td>
<td>0.4</td>
</tr>
<tr>
<td>IL-1β (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>0.2 (0.1-0.4)</td>
<td>0.3 (0.1-2.5)</td>
<td>0.3 (0.1-0.9)</td>
<td>0.2 (0.1-1.1)</td>
<td>0.7</td>
</tr>
<tr>
<td>POP1</td>
<td>0.3 (0.2-0.7)</td>
<td>0.4 (0.1-1.4)</td>
<td>0.9 (0.5-1.2)</td>
<td>1.7 (0.12-6.8)</td>
<td>0.3</td>
</tr>
<tr>
<td>POP2</td>
<td>0.1 (0.1-0.2)</td>
<td>0.4 (0.1-0.5)</td>
<td>0.4 (0.2-0.7)</td>
<td>0.4 (0.2-0.9)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Patients’ pain experiences in NRS postoperatively and the concentrations of inflammatory response biomarkers, such as IL-1ra, IL-6, IL-8, IL-10 and IL-1β, were studied in patients with benign disease and cancer.

With respect to the anti-inflammatory cytokines, patients in the continuous infusion-group had significantly higher anti-inflammatory IL-10 median values postoperatively than the three other study groups (p=0.029). In addition, the three active treatment groups combined had significantly higher IL-10 median values immediately after the operation than the control group (p=0.028). The catheter with LA was administered before closing
the wound and the first POP blood sample was taken before the anaesthesia was completed.

A difference was seen also in subgroups of benign and malignant disease. There was a positive correlation between the PS and IL-10 values postoperatively in the placebo group and in the three active treatment groups separately (r=0.40, p=0.03) and a positive correlation between the PS and pro-inflammatory IL-1β values postoperatively in the placebo group and the three active treatment groups separately (r=0.38, p=0.04).

The use of RSB was not reflected in the plasma concentrations of CRP, IL-1ra, IL-6, IL-8, IL-10 and IL-1β and there were no statistically significant differences between patients with benign and malignant disease in these parameters.

5.4 OXIDATIVE CELL STRESS

5.4.1 8-Hydroxy-2′-deoxyguanosine

Patients in the continuous infusion group showed a trend towards lower median 8-OHdG values than in the other groups (p=0.15). The difference was seen also in subgroups of benign and malignant diseases. The elevation of the CRP median values 24 h postoperatively was less in the patients in three active groups combined than the CRP in the placebo group. There was a significant inverse correlation between the individual values of the plasma CRP and 8-OHdG concentrations in patients in both subgroups with malignant and benign disease (r=–0.40, p=0.02). However, there was no significant correlation between the individual PS levels and concentrations of 8-OHdG.

![Figure 6. The scatter plots of the individual CRP (C-reactive protein) values vs 8-OHdG (8-hydroxy-2′-deoxyguanosine) values post-surgery for the placebo group and three study groups (r=−0.4, p=0.02).](image1)

![Figure 7. The scatter plots of the post-operative NRS (11-point numeric rating scale) values vs 8-OHdG (8-hydroxy-2′-deoxyguanosine) values post-surgery for the groups (r=−0.01, p=ns).](image2)
Table 6. The plasma 8-OHdG (8-hydroxy-2'-deoxyguanosine) and CRP concentrations for the placebo group and the three active treatment groups; single-dose, repeated-dose and continuous infusion RSB analgesia groups. Data are median and interquartile range.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Placebo n=8</th>
<th>Single n=8</th>
<th>Repeated n=11</th>
<th>Continuous n=9</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hs-CRP (mg/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>3.5 (1.2-13)</td>
<td>4.7 (0.9-48)</td>
<td>1.2 (0.6-4.0)</td>
<td>9.6 (1.4-73)</td>
<td>0.5</td>
</tr>
<tr>
<td>POP1</td>
<td>6.6 (1.0-13)</td>
<td>9.2 (2.9-83)</td>
<td>2.3 (0.6-5.1)</td>
<td>26 (1.0-231)</td>
<td>0.3</td>
</tr>
<tr>
<td>POP2</td>
<td>246 (82-469)</td>
<td>190 (96-349)</td>
<td>207 (82-284)</td>
<td>159 (79-479)</td>
<td>0.9</td>
</tr>
<tr>
<td>8-OHdG (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>17 (5.3-60)</td>
<td>47 (6.9-297)</td>
<td>24 (8.0-211)</td>
<td>10 (6.2-19)</td>
<td>0.4</td>
</tr>
<tr>
<td>POP1</td>
<td>15 (7.6-34)</td>
<td>29 (6.5-50)</td>
<td>21 (7.7-261)</td>
<td>8.0 (4.7-8.8)</td>
<td>0.15</td>
</tr>
<tr>
<td>POP2</td>
<td>12 (9.7-30)</td>
<td>15 (5.7-31)</td>
<td>11 (5.5-68)</td>
<td>7.4 (5.4-69)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

5.4.2 Glutathione peroxidase

No differences were detected in the GPX1 concentrations between the placebo and the three active treatment groups combined preoperatively and immediately after operation. However, the patients in the single-dose group had a significantly lower median GPX1 values at 24 hours after surgery compared to the three other groups separately (p=0.032). The plasma concentrations of GPX1 differed significantly between patients with benign disease and those with cancer preoperatively (p=0.006).

Table 7. The plasma hs-CRP and GPX1 (glutathione peroxidase) concentrations in the placebo group and the three active treatment groups; single-dose, repeated-dose and continuous infusion RSB groups. Plasma concentrations of hs-CRP and GPX1 were measured at three time points; before the operation (PRE), immediately after the operation (POP1) and 24 hours after the operation (POP2). Median (interquartile range) values are shown.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Placebo n=8</th>
<th>Single n=11</th>
<th>Repeated n=11</th>
<th>Continuous n=14</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hs-CRP (mg/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>3.5 (1.2-13)</td>
<td>4.7 (0.9-48)</td>
<td>1.2 (0.6-4.0)</td>
<td>6.5 (0.6-74)</td>
<td>0.8</td>
</tr>
<tr>
<td>POP1</td>
<td>8.2 (1.6-15)</td>
<td>9.2 (2.9-83)</td>
<td>2.3 (0.6-5.1)</td>
<td>4.80 (0.7-63)</td>
<td>0.3</td>
</tr>
<tr>
<td>POP2</td>
<td>312 (112-499)</td>
<td>190 (96-349)</td>
<td>207 (82-284)</td>
<td>159 (79-479)</td>
<td>0.9</td>
</tr>
<tr>
<td>GPX1 (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>12 (8.8-19)</td>
<td>11 (5.4-17)</td>
<td>19 (6.7-22)</td>
<td>17 (9.5-19)</td>
<td>0.6</td>
</tr>
<tr>
<td>POP1</td>
<td>12 (8.2-36)</td>
<td>9.4 (6.1-23)</td>
<td>15 (6.5-30)</td>
<td>15 (10-21)</td>
<td>0.8</td>
</tr>
<tr>
<td>POP2</td>
<td>11 (5.8-16)</td>
<td>5.1 (3.2-9.2)</td>
<td>8.6 (5.3-19)</td>
<td>12 (6.7-20)</td>
<td>0.032</td>
</tr>
</tbody>
</table>
Table 8. The plasma hs-CRP and GPX1 (glutathione peroxidase) marker concentrations in the placebo group and in the RSB group; three active treatment groups, single-dose, repeated-dose and continuous infusion groups combined.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Placebo n=8</th>
<th>RSB n=28</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hs-CRP (mg/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>3.5 (1.2-13)</td>
<td>3.3 (0.8-36)</td>
<td>0.7</td>
</tr>
<tr>
<td>POP1</td>
<td>8.2 (1.6-15)</td>
<td>3.9 (0.8-53)</td>
<td>0.9</td>
</tr>
<tr>
<td>POP2</td>
<td>312 (112-499)</td>
<td>190 (94-303)</td>
<td>0.4</td>
</tr>
<tr>
<td>GPX1(pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>12 (8.8-19)</td>
<td>16 (7.7-20)</td>
<td>0.9</td>
</tr>
<tr>
<td>POP1</td>
<td>12 (8.2-36)</td>
<td>12 (6.9-23)</td>
<td>0.5</td>
</tr>
<tr>
<td>POP2</td>
<td>11 (5.8-16)</td>
<td>8.7 (5.2-15)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Table 9. The plasma hs-CRP and GPX1 (glutathione peroxidase) concentrations in the benign and in the cancer patients. Plasma concentrations of hs-CRP and GPX1 were measured at three time points; before the operation (PRE), immediately after the operation (POP1) and 24 hours after the operation (POP2). Median (interquartile range) values are shown.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Benign n=15</th>
<th>Cancer n=29</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hs-CRP (mg/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>2.2 (0.6-3.8)</td>
<td>5.5 (1.0-63)</td>
<td>0.099</td>
</tr>
<tr>
<td>POP1</td>
<td>2.5 (0.6-6.1)</td>
<td>8.6 (0.8-59)</td>
<td>0.2</td>
</tr>
<tr>
<td>POP2</td>
<td>136 (62-254)</td>
<td>210 (101-375)</td>
<td>0.3</td>
</tr>
<tr>
<td>GPX1(pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>18 (13-22)</td>
<td>10 (6.3-19)</td>
<td>0.006</td>
</tr>
<tr>
<td>POP1</td>
<td>17 (8.7-23)</td>
<td>11 (7.4-22)</td>
<td>0.3</td>
</tr>
<tr>
<td>POP2</td>
<td>12 (6.7-25)</td>
<td>8.1 (5.2-12)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

5.5 OPIOIDS

5.5.1 Opioid consumption

The median oxycodone consumption was similar during the first 48 postoperative hours in all groups. (Tables 2.-4.). However, during the first 12h postoperatively, the oxycodone consumption was less in the infusion group and in the repeated doses group than the corresponding consumption in the single dose group and in the control group (p = 0.07). The interindivdual variation in the oxycodone consumption was high in all four groups, the lowest amount being 12 mg/48h (patient in the infusion group) and the highest being 286 mg/48h (patient in the single dose group). The mean opioid consumption of all patients was 49 mg/24h, (range 6-173 mg, SD 33mg) and 90 mg/48h (range 12-286mg, SD 61 mg).
Table 10. Cumulative oxycodone consumption (mg). Data are median [minimum-maximum].

<table>
<thead>
<tr>
<th></th>
<th>Control n = 12</th>
<th>Single dose n = 16</th>
<th>Repeated doses n = 12</th>
<th>Infusion n = 17</th>
<th>p-value</th>
</tr>
</thead>
</table>

5.5.2 Opioid concentrations

The plasma concentrations of oxycodone and its main metabolite noroxycodone did not differ markedly between the four groups. Plasma concentrations of oxymorphone and noroxymorphone were so low in all four study groups that they exerted no analgesic effect.

Table 11. Plasma concentrations of oxycodone (ng/ml). Data are median [minimum-maximum].

<table>
<thead>
<tr>
<th></th>
<th>Control n = 12</th>
<th>Single-dose n = 16</th>
<th>Repeated doses n = 12</th>
<th>Infusion n = 17</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 h after surgery</td>
<td>n=0</td>
<td>20 [13-33]</td>
<td>24 [7.8-70]</td>
<td>13 [4.2-50]</td>
<td>0.16</td>
</tr>
<tr>
<td>48 h after surgery</td>
<td>n=0</td>
<td>11 [3.8-85]</td>
<td>19 [0.1-43]</td>
<td>n=7</td>
<td>0.7</td>
</tr>
</tbody>
</table>

5.5.3 Opioids’ adverse effects

One patient in the single dose group and one in the control group terminated the iv-PCA-oxycodone because of nausea in the second postoperative afternoon after the surgery. One patient in the control group perhaps experienced opioid induced hyperalgesia (OIH) (Silverman 2009).

5.6 LEVOBUPIVACAINE

5.6.1 Concentrations of levobupivacaine in plasma

Even after 24 h, the plasma concentrations of levobupivacaine were still elevating especially with continuous infusion (Figure 8). All plasma concentrations of levobupivacaine remained safe during the 48 hours. The highest concentration in the present study was 1865 ng/ml in this study when 2620 ng/ml is considered toxic levobupivacaine concentration (Bardsley et al. 1998).
5.6 LEVOBUPIVACAINE

5.6.1 Concentrations of levobupivacaine in plasma

Even after 24 h, the plasma concentrations of levobupivacaine were still elevating especially with continuous infusion (Figure 8). All plasma concentrations of levobupivacaine remained safe during the 48 hours. The highest concentration in the present study was 1865 ng/ml in this study when 2620 ng/ml is considered toxic levobupivacaine concentration (Bardsley et al. 1998).

5.7 OVERALL PATIENT SATISFACTION

Patient satisfaction with postoperative analgesia was high in all four study groups (Figure 9). On a scale of 0-10, the PS was higher in the repeated doses group, median 10 [minimum-maximum 8-10], and in the infusion group, 10 [4-10], compared with the single dose group, 9 [4-10], and the control group, 8 [3-10]. Experienced surgeons (with 30 patients) inserting the RSB-catheters had a mean PS value of 9.0 vs 8.6 of the first timers (12 patients), but the median 10 and range [4-10] were similar.
The mean PS (52 patients) was 8.6. The best values were given when the incision was 30 cm or longer (19 patients; mean 9.2 [8.5] vs shorter incisions (32 patients; mean 7.2 [8.0]). When the incision crossed the umbilical region (17 patients), the mean was 8.8 [9.0], and with xiphosternum-pubic wounds (14 patients) the mean was 8.5 [9.5].

5.7.1 Effect of incision length or location

Patients (n=48), who had a definitive diagnosis in the end of the surgery and the PS value at 48-hours, were analysed: The mean PS was 8.4, with benign disease 8.5 and 8.3 with malignance. The mean PS in females was 8.3 (n=37) being lower in patients with malignant disease 8.2 (n=24) compared to 8.5 with a benign disease (n=13). In men, the mean PS was 8.8 (n=11), with benign disease 8.75 (n=4) and with malignant disease 8.9 (n=7).

5.7.2 Effects of gender and disease

5.8 ADVERSE EFFECTS AND EVENTS

There were no severe or unexpected AE observed during the study (Table 13). One patient in the infusion-group developed pleural effusion after protracted oncologic surgery with debulking of cancer deposits in the diaphragmatic peritoneum. One patient in the repeated doses group experienced a substantial bleeding (3400 ml) during surgery, and she was given 2 units of packed red blood cells. Both incidents were considered unrelated to the study compounds. One peripheral paraesthesia in the lower extremity was noted.
During the hospital stay after a long gynaecological cancer operation caused probably by local nerve compression. During the first 30 postoperative days, two superficial (one in the single dose- group, one in the infusion-group) and one deep (in the control-group) wound infections were noted.

After a prolonged cancer operation, in control-group, one patient’s opioid consumption in the PACU was 52 mg vs mean 24.6 mg (SD 17.6). During the first 24 h, this individual’s consumption was highest of all patients, 167 mg vs mean 48.9 (SD 33.2) and at 48 h 260 mg vs mean 85.8 mg (SD 56.0). The 24-hour plasma oxycodone concentration was 48.5 ng/ml, noroxycodone 40.7 ng/ml, noroxymorphone 20.6 ng/ml and oxymorphone 0.77 ng/ml. This patient was not satisfied before she was administered ketamine analgesia after which she gave PS of 8. This form of ketamine analgesia was needed for three postoperative days.

Two patients, one in the single-dose group and one in the control-group stopped the iv.PCA-oxycodone at the second postoperative afternoon due to protracted nausea.

The patient giving a PS of “4” in the infusion-group was probably a slow opioid metabolizer. After 124mg of oxycodone in 48 hours, her oxycodone plasma concentration was 48 ng/ml (median 19 ng/ml in the infusion-group). In the PACU and later in the ward, she was observed to fall asleep every time she was administered i.v. oxycodone (2 mg), and her iv.PCA-oxycodone could not be started before the first morning after surgery.

There were problems with rectus sheath catheters in six patients and seven catheters. One catheter with patient in the infusion-group and one with patient in the repeated-doses group were leaking but although this was marked in the data it did not require any measures. Three patients’ catheters in the infusion-group became accidentally detached; one patient’s first catheter on the first POP morning and the other catheter at 36 hours, in one patient the catheter became detached on the first postoperative evening and in one patient on the second postoperative morning. One catheter in a patient in the infusion group became constricted with sutures leading to uneven dosing during the 48 hours postoperatively.

There were no local or severe systemic AE attributable to LA. Mild AE regardless of causality to the drug are common (Purdue 1999). Although one patient’s starting dose was accidentally 40 ml of 5 mg/ml (200mg) of levobupivacaine, she reported no toxic signs during the following 9 h.
Table 13. Adverse events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control n = 12</th>
<th>Single-dose n = 16</th>
<th>Repeated-doses n = 12</th>
<th>Infusion n = 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects with at least one of AE</td>
<td>5 (42%)</td>
<td>14 (88%)</td>
<td>7 (58%)</td>
<td>11 (65%)</td>
</tr>
<tr>
<td>Total number of AE</td>
<td>14</td>
<td>22</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>8</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Pain</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Oxygen saturation &lt; 94%</td>
<td>4</td>
<td>7</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal vision</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bloating</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
5.9 OTHER CONSIDERATIONS

5.9.1 Protocol violations

One patient was lost from the study when the operator and the anaesthetist together decided to use TEA despite the written consent of the patient.

One patient needed ketamine analgesia postoperatively. She was receiving the antiepileptic drug, carbamazepine, which is known to induce CYP3A4. Oxycodone is mainly metabolized via CYP3A4, and induction of this metabolizing enzyme may have increased the clearance of oxycodone and thus decreased the analgesic efficiency.

One patient randomised for the continuous infusion was administered accidentally 5 mg/ml, not 1.25 mg/ml levobupivacaine as the starting dose (40 ml, a total dose of 200 mg) thus exceeding the safety limit (150 mg) for a single dose. Nonetheless, this dose did not evoke any local or systemic toxic reactions. The infusion was postponed for 9 hours. Her data was then handled as intended to treat (ITT) -basis. Her PS was 10/10.

5.9.2 Outliers of patient satisfaction

Five patients estimated the postoperative analgesia as less than 7/10. The patient giving a very low score i.e. 4/10 in the infusion group was probably a slow opioid metabolizer. In the PACU and subsequently in the ward, she was observed to fall asleep every time after being administered iv. oxycodone (2 mg) and her iv.PCA-oxycodone could not be started before the first morning after surgery. In the single dose-group, one patient gave a PS of 4/10. She had a short incision (12 cm) and half an hour’s exploratory laparotomy which revealed abdominal carcinosis. Two patients with a 6/10 were also in the single dose-group. The only score of 3/10 was awarded by a patient from the control-group.
6.1 PATIENTS AND STUDY DESIGN

The inclusion and exclusion criteria were similar as in many other this kind of clinical studies. Mental status was an exclusion criterion reflecting uncertainty about the ability to use PCA-pump especially in the aged population; this is normal in this kind of study.

The technique of the surgeon inserting the catheters for RSB is easily taught and learned and no significant difference was found in the values of PS between first-time administrators and more experienced physicians. The first-time administrators were supervised by a surgeon with sound experience of the method.

Levobupivacaine 1.25 mg/ml was used in the study. Although 2.5 mg/ml concentration could have been expected to give a more prolonged effect, the 1.25mg/ml gives at least as fast an onset of effect with less motor block (Casati et al. 2004). Moreover, with levobupivacaine 1.25mg/ml solution, large volume could be used. That could provide more extensive spread of LA in dose administration.

To a best knowledge, this is the first study where plasma concentrations of oxycodone and levobupivacaine have been assayed after a RSB for 48 h.

6.2 STUDY SAMPLE

A sample of 60 patients was calculated to provide sufficient power to detect statistical difference in the opioid consumption calculation if any. Only 57 patients were collected, which makes the statistical analysis more uncertain and leads to somewhat larger than desirable confidence intervals.

RSB is effective only in midline laparotomies. The patient material became heterogenic, but this reflects the normal clinical practice (Sundbo, 2017), where RSB may be a part of multimodal postoperative analgesia. Other studies of RSB have been done with smaller samples of 14-56 patients (Smith et al. 1988, Yentis et al. 1999, Bashandy & Elkholy 2014, Abdelsalam & Mohamdin 2016, Isaac et al. 2006, Dinge man et al. 2013, Alsa seed et al. 2013). There are few studies investigating larger samples up to 74 patients (Biglamia et al. 2011, Bakshi et al. 2016, Lit et al. 2017, Crosbie et al. 2012). In three studies the samples were 98, 200 and 275 patients (Crosbie et al., Dutton et al. 2014 and Maloney et al. 2017), but these studies were all retrospective.
6 Discussion

6.1 PATIENTS AND STUDY DESIGN

The inclusion and exclusion criteria were similar as in many other this kind of clinical studies. Mental status was an exclusion criterion reflecting uncertainty about the ability to use PCA-pump especially in the aged population; this is normal in this kind of study.

The technique of the surgeon inserting the catheters for RSB is easily taught and learned and no significant difference was found in the values of PS between first-time administrators and more experienced physicians. The first-time administrators were supervised by a surgeon with sound experience of the method.

Levobupivacaine 1.25 mg/ml was used in the study. Although 2.5 mg/ml concentration could have been expected to give a more prolonged effect, the 1.25mg/ml gives at least as fast an onset of effect with less motor block (Casati et al. 2004). Moreover, with levobupivacaine 1.25mg/ml solution, larger volume could be used. That could provide more extensive spread of LA in dose administration.

To a best knowledge, this is the first study where plasma concentrations of oxycodone and levobupivacaine have been assayed after a RSB for 48 h.

6.2 STUDY SAMPLE

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6.3 INFLAMMATION AND OXIDATIVE CELL STRESS

6.3.1 Inflammatory markers

One of the main findings was that there were higher concentrations of the anti-inflammatory cytokine, IL-10 in all active treatment groups in comparison with the control group. In the control group, the concentration was 0.77 [median] pg/ml, in the single dose group it was more than six times higher i.e. 4.8 pg/ml, in repeated-group it was 3.7 pg/ml but in continuous infusion group, the concentration was much higher - 13 pg/ml (p=0.029). This may be explained by the anti-inflammatory properties of LAs consequently increasing the concentrations of the anti-inflammatory cytokines. One new finding in the present work was the revelation of a positive correlation between the patients’ pain experience and plasma concentrations of anti-inflammatory cytokine IL-10 and the pro-inflammatory cytokine IL-1β postoperatively, suggesting that inflammation and pain are related, as has been noted in earlier ex vivo and animal studies (Watkins et al. 1994, Perkins & Kelly 1994, Jeanjean et al. 1995, Wieseler-Frank et al. 2004).

The timing of the assessment of the cytokines needs to be considered, since the T1/2 of cytokines in blood is usually less than one hour. A time point under 6-hour after the surgical procedure would appear to be the optimal time for measuring the kinetics of the proinflammatory cytokine IL-1β and the anti-inflammatory cytokines IL-1ra and IL-10. Therefore, the samples taken at 24 hours postoperatively will miss the early postoperative peak values and may not allow a fair comparison of the individual NRS values vs these inflammatory marker values.

6.3.2 8-Hydroxy-2'-deoxyguanosine

The continuous infusion method showed a trend to lower median 8-OHdG concentrations which may indicate that the LAs possess cytoprotective features. Interestingly, although the plasma concentrations of 8-OHdG decreased after surgery, the plasma concentration of hs-CRP, the inflammatory response marker, did increase post-operatively, i.e. OCS diminished although inflammation increased at the same time.

6.3.3 Glutathione peroxidase enzyme

GPX1 concentrations were higher in the continuous infusion-group as compared with the single dose or repeated dose-groups. This may have been caused by the higher plasma concentrations of levobupivacaine in the continuous infusion-group (Fig 8) and the cytoprotective properties of LAs.

The single dose RSB produced lowest median GPX1 concentration (5.1 pg/ml) when assessed at 24 hours after surgery. Cancer diagnosis was correlated with lower individual plasma GPX1 values.
**6.4 OPIOID CONSUMPTION**

We could not detect any significant opioid sparing effect of RSB. But as in many earlier studies, some positive effect was found during the first POP.

One patient who was unable to tolerate oxycodone and fell asleep after its administration suffered detrimental utility function (Boom et al. 2013), which means that the opioid’s negative effects came unusually early compared with the opioid’s positive effects.

A patient using carbamazepine as a continuous medication had high concentration of oxycodone metabolites reflecting the induced metabolism of this opioid which accounts for her tolerance towards opioids and the consequent dissatisfaction with the degree of postoperative analgesia. Carbamazepine is an inducer of CYP3A4, a member of cytochrome P450 family and oxycodone is metabolized mainly in the liver by this enzyme. However, carbamazepine has also been reported to potentiate the effects of morphine (Due et al. 2014). The opioid induced hyperalgesia is known to be possible even in such low doses as 30 mg per 24 h (Berland & Rodgers 2012).

**6.5 PATIENT SATISFACTION**

In the present study, the PS for pain treatment was best in those receiving repeated doses. The reservoir where the nerves are bathed with LA may shrink somewhat with the continuous infusion which could explain why the repeated doses deliver better analgesia in the first hours after operation and better overall PS.

High satisfaction was reported even though pain ratings were relatively high in some patients also in the repeated doses-group. An earlier study assessing PS in pain treatment after various surgical procedures indicated that even though 62% experienced severe postoperative pain, 87% were satisfied with pain management (Sauaia et al. 2005). Other studies have also reported this paradoxical finding (Owen et al. 1990, Svensson et al. 2001). In the present study, females were marginally unhappier with postoperative analgesia in all groups. This agrees well with the earlier study of postoperative pain conducted in Finland, where females experienced more pain after surgery than males. Furthermore, the duration of operation correlated positively with the amount of postoperative pain (Mattila et al. 2005).

Interestingly, in the present study, patients with longer incisions as needed in extensive oncologic surgery were more satisfied with the POP analgesia. This may reflect the difference in the mental status with a serious disease receiving treatment and hope compared to patients with a more benign disease when a treatment is simply a necessary evil. Only 2/19 patients were males in this subgroup. Only those in the control-group gave PS < 9/10. This strongly supports the multimodal postoperative analgesia with RSB in longer wounds and more prolonged operations.

Patient satisfaction depends on many factors. A nurse taking care of pain treatment at every four hours might have a positive effect on patient satisfaction in the repeated doses-group.

Four patients estimated the postoperative analgesia worth of less than 7/10 (NRS: 0-10).
In the single dose group, one patient gave a PS value of 4/10. She had a short incision (12 cm) and half an hour’s exploratory laparotomy which revealed abdominal carcinosis. On the first POP morning, she suffered shortness of breath. Her oxycodone consumption was modest (40 mg) during 48 h and the plasma oxycodone concentration was modest 26.7 ng/ml at 24 h postoperatively (median 23 ng/ml in the single dose-group). The psychologic distress of the revelation that she had a serious malignant disease may have contributed to her dissatisfaction with analgesia.

One patient in the infusion group gave 4/10 in PS. Her anaesthesia lasted ten hours and the extensive oncologic operation took seven hours. The infusion catheters were placed by a first timer under the senior physician’s supervision. The infusion pump containers emptied 43 h after the operation instead of the expected 56 hours. The pain queries (NRS) were uneven i.e. they were eight in the mornings but ranged between 2/10 and 4/10 in the afternoons and evening. Her oxycodone consumption was relative high 124 mg vs 90 mg (all patients) over 48 h but the plasma concentrations of oxycodone at 12 and 24 h after the operation were similar (12 ng/ml and 33 ng/ml vs median 13 ng/ml and 27 ng/ml of the infusion-group). The main oxycodone metabolite noroxycodone concentration in plasma was high at 12 h, 24 h and 48 h after the operation (13 ng/ml, 41 ng/ml and 52 ng/ml) suggesting rapid first phase metabolism. She was using thyroxine, which like opioids, is metabolized by CYP3A4. Nonetheless, the other five patients being administered thyroxine as a continuous medicine were among the most satisfied patients.

A patient in the control group reported PS 3/10. Her 24h iv.PCA- oxycodone consumption was 47 mg (e.g. mean of one PCA-dose per hour) and plasma concentration of oxycodone 45 ng/ml and noroxycodone 30 ng/ml. She experienced PONV during the first day. The total PCA- oxycodone in 48 h was only 79 mg as her venous cannula did not work properly on the second day. The PONV may have been a result of a detrimental utility function.

In the single dose group, one patient awarded PS value of 6/10 because of the intolerable pain in the PACU.

Since there are possible individual differences of opioid metabolism, drug interactions and the possibility of OIH, it is essential that the postoperative analgesia is individually planned, multimodal and flexible to remodelling when needed (Kokki et al 2012).

### 6.6 CONCENTRATIONS OF LOCAL ANESTHETIC

In present study, all plasma concentrations of levobupivacaine were at safe levels during the first 48 postoperative hours with the highest value recorded being 1865 ng/ml whereas 2620 ng/ml is considered as a toxic levobupivacaine concentration (Bardsley et al. 1998). The blood concentrations of LA were further elevated during the second POP day and stayed high for many hours after continuous infusion was terminated. No studies concerning plasma concentrations following 24-48 h RSB could be found in literature. This phenomenon should be taken in account when conducting continuous block or repeated block for longer durations. This finding warrants a new study to determine these concentrations after 48 hours.
As has been found elsewhere (Webster 2010), levobupivacaine at 2.5 mg/ml concentration would have given a prolonged analgesia lasting up to 5-7 h, but we did not notice any shortage of duration with the concentration that we used (1.25 mg/ml). The workload of the nursing staff would have been less with a 2.5 mg/ml LA. Dutton et al. (2014) used levobupivacaine 2.5 mg/ml 4-hourly whilst in postoperative care unit and then top-ups every sixth hour in the ward department. In the present study, in the repeated dose-group, levobupivacaine at the dose of 1.25 mg/ml was given at 4-hourly intervals.

6.7 COMPARISON WITH RECENT STUDIES

The rectus sheath block seems to be both safe and effective when used instead of general anaesthesia in umbilical operations but the question remains whether it provides an opioid sparing effect after laparotomy? In previous studies, the RSB has been compared with placebo or no block at all. The RSB has been investigated using single dose infiltration of LA into the rectus sheath with or without US guidance (Yentis et al. 1999) and repeated doses or continuous infusion. The present study compared the three different modalities of RSB with a control-group without placebo infiltrations.

Bakshi et al. (2015) delivered intermittent doses every sixth hour, Bashandy & Elkholy (2014) used an US guided preoperative single dose RSB with periumbilical laparotomies in colon surgery. Beaussier et al. (2007) investigated continuous infusion in the preperitoneal space for 48 hours without RSB. They all detected reductions in pain score and opioid consumption. Charlton et al. (2010) could find only three randomised controlled trials of RSB (Smith et al. 1988, Isaac et al. 2006, Padmanabhan et al. 2007) and in only Smith et al. (1988) showed a reduction in postoperative analgesic requirements and more patients being pain-free for up to 10 h postoperatively. Some of the negative findings can be explained by the fact that the iliohypogastric nerve (ramus of L1), that innervates the fascia and skin above the pubis for approximately five centimetres, does not always penetrate the rectus sheath. Some cutaneous branches of the Th intercostal nerves may be formed before the rectus sheath and so they do not penetrate it but instead run anterior to the sheath in the subcutaneous fat tissue in up to 30% of population (Courreges et al. 1997).

Comparing LA with normal saline, Padmanabhan et al. (2007) found no difference in postoperative pain, consumption of opioid (iv.PCA) or postoperative pulmonary function with repeated doses every eight hours for 48 hours after the operation but found the same slight reduction in the need of opioids during the first 24 hours postoperatively as we found in this study with the continuous infiltration or repeated doses. One explanation for this result may be in the positioning of the catheters as the only information provided in the publication is a figure where the catheter did not reach to the outer half of the posterior sheath.

Opioid consumption seems to represent the differences in visceral pain. Most patients undergoing open radical cystectomy needed opioids but this was not the case in the open radical retropubic prostatectomy patients, in which there had been an extraperitoneal approach (Dutton et al. 2014). Dutton suggested that the visceral pain also seemed to be relatively short lived. The opioid consumption after open retropubic prostatectomy was 14 mg for the first 12 h, 7 mg for 12-24 h and 8 mg for 24-48 h.
In the present study, no difference is in PS when comparing upper or lower abdominal operations. A study with subcostal incisions showed that combining preoperative US guided TAP-block and RSB was significantly better than WI at the end of the operation when comparing pain scores, perioperative fentanyl consumption and postoperative need for opioids (Abdelsalam & Mohamdin 2016). Both the preoperative infiltration and TAP-block may have improved these results.

The results seem to be much better if RSB is administered before incision (Alsaeed et al. 2013, Dingeman et al. 2013). But even perioperative RSB delivered at least 10 min. before wound closure saves postoperative opioid consumption compared with WI at the end of operation (Flack et al. 2014). These cases were paediatric umbilical hernia operations. The efficiency of RSB for wound pain was demonstrated in a study which used RSB for diagnostic laparoscopy where there was no or only moderate visceral damage (Smith et al. 1988). Pain scores were significantly lower at each postoperative assessment at 1 h, 6 h and 10 h although control patients consumed more intramuscular analgesics. In the present study with patients undergoing procedures for cancer, most of the surgery involved extensive visceral trauma which demanded opioids. As one lady wrote in her patient satisfaction assessment after 48h: “It is easier to tolerate the visceral pain when the wound is painless”.

6.8 RECTUS SHEATH BLOCK IN CLINICAL PRACTISE

The different anaesthesia techniques used in ERAS protocols for colorectal surgery have been investigated from 15 different healthcare facilities located in North America and one in New Zealand. TEA was used most commonly, followed by TAP-block. RSB was mentioned only in one protocol (Helander et al. 2017). The best analgesia with RSB may be limited to surgery in the midline without large visceral damage, e.g. hernias, ovarian surgery and extraperitoneal urology. When longer postoperative analgesia is needed, RSB through catheters might be better than a single TAP-block.

6.9 LIMITATIONS OF THE STUDY

The blinding of the different dosing regimens was challenging. It was decided not to use an invasive placebo which meant that the control-group was without RSB catheterization. To conceal single dose or control-grouping, similar wound dressings were used in the same places in these two groups. The blinding between the control, single dose and repeated doses-group could have been done with normal saline infiltrations. However, there have been questions raised about invasive placebo with normal saline and its possible effects on inflammatory mediators and AE (McGuirk et al. 2011).

One aim of this study was to find if there were differences between all the three RSB methods with a control-group but unfortunately enough patients could not be collected in a reasonable time to conduct a sound statistical analysis with good confidence limits. A study protocol comparing only two methods would have been more satisfactory from a statistical point of view.
6.10 FUTURE ASPECTS

A study schema has been introduced to compare TEA vs RSB in major abdominal surgery within an ERAS Protocol (Wilkinson et al. 2014). The endpoints of that study will be pain relief, patience experience, functional recovery, safety and cost-effectiveness.

Another study protocol was published in 2015 to compare preoperative vs postoperative US-guided RSBs in patients undergoing gynaecological surgery (Jin et al. 2015). The primary outcomes were planned to be postoperative pain, sleep quality and changes in the cytokine concentrations. It would be interesting to study also if this timing of RSB would affect OCS which has a connection both with inflammation and carcinogenesis. Here, it was noted that the full analgesic effect of the block emerges only after one or two hours. Possible anti-inflammatory and anti-oxidative properties of RSB may be enhanced if the treatment is introduced before incisions.

In the present study, the plasma concentrations of levobupivacaine still ascended in the continuous infusion group during the second POP, highest values, being 1865 ng/ml while the toxic concentrations would be reached when they exceeded 2620 ng/ml. It appears that the rectus sheath reservoir may be filled and the plasma concentration therefore may subsequently rise in an unpredictable manner. The plasma concentrations after a second POP-day have not been published in any other studies as far. As RSB seems to benefit some patients still after two days, it would be important to study the plasma concentrations when RSB is performed longer than the 48-h applied in the present study.

In the study data, the effect of the different analgesic methods and PS of postoperative analgesia on possible chronic wound pain and visceral symptoms have not yet been analysed. In addition, the analysis of possible changes reported in the BPI questionnaires (before operation, one month and a year later) is a project for the future. The BPI questionnaires have been translated to Finnish. The validation of BPI in Finnish could be made by examining the consistency of its two-factor structure; severity of pain and impact of pain (Atkinson et al. 2011).

After open or laparoscopic cholecystectomy, the need for opioid analgesic in the early recovery period is not less after laparoscopic cholecystectomy compared to open surgery, contrary to common beliefs (Kokki et al. 2012). The reason may be that the visceral damage is similar with both techniques. Bisgaard et al. (1999) have studied the effect of intraperitoneal single installation or nebulization of LA with WI during laparoscopic cholecystectomy and found that ropivacaine reduced overall pain for 2 hours and incisional pain for 3 hours after surgery and that incisional pain dominated throughout the first postoperative week. Since RSB does not influence visceral pain, the combination of visceral infusion of LA and RSB with repeated dose should be studied and the plasma concentration of LAs should be measured to identify the safety limits. An intraperitoneal catheter could be used for 24 hours in the visceral damage area. The systemic inflammation response could be measured to evaluate the anti-inflammatory properties of LAs (Kahokehr et al. 2011, Kahokehr et al. 2011).

Some reports have warned about the harmful effect of NSAIDs, especially the COX-2 selective agents, on anastomotic healing (Klein 2012, Gorissen et al. 2012). LAs have been observed to suppress the inflammatory reaction in the bowel wall and to shorten the
duration of postoperative ileus (Rimbäck et al. 1986; 1988; 1990), and therefore its possible AE on anastomotic healing should be investigated.
7 Summary and conclusions

RSB is a useful component of the multimodal analgesia after midline laparotomy. It enhances PS when given repeatedly or as a continuous infusion. The postoperative opioid consumption does not diminish markedly but RSB helps to prevent extreme opioid consumption. RSB with levobupivacaine appears to be safe, at least for 48h. Continuous infusion and repeated doses schema seem to be reasonable alternatives to TEA after a midline laparotomy.

Conclusions:

1. Placement of RSB analgesia does not significantly alter the oxidative stress marker 8-OHdG concentrations in patients with benign disease or cancer. There is no significant correlation between the individual values of PS of postoperative analgesia and 8-OHdG postoperatively.

2. Placement of RSB analgesia does not significantly reduce the inflammatory biomarkers concentrations in patients with benign disease or cancer. There is a significant correlation between the individual values of PS of postoperative analgesia and postoperative IL-10 concentrations and between PS of postoperative analgesia with postoperative concentrations of IL-1β.

3. There is no statistical significant correlation in PS of postoperative analgesia between patients with benign disease and cancer patients, nor between PS and plasma concentrations of GPX1.

4. RSB with repeated-dose and continuous infusion administrations provides slightly decreased opioid consumption (not reaching the statistical significance) during the first 12 hours and enhanced PS with pain treatment after midline laparotomy.
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9 APPENDIX
Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?
   - Yes
   - No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.

   Front
   - Right
   - Left

   Back
   - Right
   - Left

3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.
   - 0
   - 1
   - 2
   - 3
   - 4
   - 5
   - 6
   - 7
   - 8
   - 9
   - 10
   Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.
   - 0
   - 1
   - 2
   - 3
   - 4
   - 5
   - 6
   - 7
   - 8
   - 9
   - 10
   Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.
   - 0
   - 1
   - 2
   - 3
   - 4
   - 5
   - 6
   - 7
   - 8
   - 9
   - 10
   Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.
   - 0
   - 1
   - 2
   - 3
   - 4
   - 5
   - 6
   - 7
   - 8
   - 9
   - 10
   Pain As Bad As You Can Imagine
7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

B. Mood

C. Walking ability

D. Normal Work (includes both work outside the home and housework)

E. Relations with other people

F. Sleep

G. Enjoyment of life

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ORIGINAL PUBLICATIONS (1-4)
Errata

Sivulla V: BSB p.o. RSB

Sivulla VII: keskilinja-avaus laparotomian... p.o. keskilinjalaparotomian


Sivulla: 41 (tables 2-4) p.o. (table 10).
Midline laparotomy is used in abdominal surgery. Peripheral neural blocks are part of the modern multimodal analgesia postoperatively and the rectus sheath block focus in the midline. This block can be administered once, in repeated doses or continuous infiltration. This study compares these three methods with a control group for 48 hours postoperatively. Long-lasting blocks via catheters enhance patient satisfaction and concentrations of anti-inflammatory cytokine IL-10.