Title: PREEMPTIVE LOCAL ANAESTHETIC IN GYNECOLOGICAL LAPAROSCOPY AND POSTOPERATIVE MOVEMENT EVOKED PAIN: A RANDOMISED TRIAL

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Disclosure of interest

The authors report no conflict of interest.

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Precis Letter Sample:

Preemptive local anesthetics in the trocar areas reduce postoperative movement-evoked pain in laparoscopic gynecological surgery within an enhanced recovery program.

ABSTRACT:

Study Objective: To evaluate whether preemptive local anesthetics injected into the trocar areas reduce post-operative movement-evoked pain within an Enhanced Recovery Program (ERP) in laparoscopic gynecological surgery.

Design: Randomized and double-blinded trial with parallel assignments. Canadian Task Force Classification I.

Setting: The study was conducted in the gynecological department at the University Hospital of Stavanger, Norway.

Patients: 24 women eligible for elective laparoscopic surgery for a benign indication within an ERP were included.

Interventions: The women were randomized to preemptive local injections of either 0.5% bupivacaine (Intervention Group) or 0.9% saline (Control Group) at each trocar site.

Measurements: The primary outcome measure of the study was movement-evoked pain 5 hours after surgery. The secondary outcome measures were pain at rest 2 and 5 hours after surgery and the use of rescue analgesics during the post-operative period. Pain was measured on a Numerical Rating scale of 0 to 10. Data was treated to a per-protocol analysis and a p-value of less than .05 was considered significant.

Results: 23 women completed the trial. The median score for movement- evoked pain 5 hours after surgery was significantly lower in the intervention group (1 vs 3; p-value .044). There was no difference in pain at rest after 2 and 5 hours, and no difference in the requirement for rescue analgesics.

Conclusion: Preemptive local anesthetics in the trocar areas are shown to be beneficial in laparoscopic gynecological surgery within an enhanced recovery program. Movement-evoked pain is far more intense than pain at rest.

Introduction

The increase in minimal access surgery has contributed to a considerable reduction in postoperative overnight stays. A substantial number of surgeries in the field of gynecology are now day case procedures. This has led to an increased need for optimal postoperative pain relief, in order to mobilize the patients and return them to normal, daily activities as soon as possible. The concept of Enhanced Recovery after Surgery (ERAS) was first described by Professor Henrik Kehlet in 1997 and later updated. [1,2] The Enhanced Recovery Program (ERP), with its emphasis on early discharge from hospital has been shown to improve patient outcomes and cost effectiveness.[3-5]

Local anesthesia in surgical incisions has been used within the ERP to reduce the need for opiates during and after surgery. The use of opiates in the postoperative period has side effects of nausea and vomiting in 25 to 35 % of patients, which in turn reduces mobilization and increases the length of their hospital stay.[6] Local anesthesia injected before incision (preemptive) may have an advantage over anesthesia given at wound closure. It has been shown that nociceptive stimuli can alter the electrophysiological processes in the neurons. [7] This alteration results in a lower pain threshold and an increased response to pain stimuli. By infiltrating a local anesthetic before the incision is made, these effects should in theory be avoided.

A review and meta-analysis [8] concluded that there is a statistically significant reduction in postoperative pain with the use of preemptive, incisional local anesthetic compared to placebo. The mean reduction in pain after 4 hours was only 0.95 cm (CI 1.55 – 0.35 cm) on a scale of 0 to 10. It is questionable if this difference is clinically significant. Two other reviews [9,10] conclude that there is no effect of local anesthetics. Most of the studies included in these reviews are on laparotomy.

The evidence of whether preemptive local anesthetics reduce post-operative pain in laparoscopic surgery is inconclusive. [11-18] Most studies do not distinguish between pain at rest or during movement. Movement-evoked pain is more clinically relevant in day case surgery, due to the need of patients to be fully ambulatory. Movement-evoked pain is also far more intense than pain at rest. [19] The aim of our study was to evaluate whether preemptive local injections into the trocar areas are able to reduce post-operative movement-evoked pain within an ERP.

Materials and Methods

Design

The study was double-blinded, placebo controlled with parallel assignments. The intervention group was given preemptive incisional injection of 5 ml bupivacaine (5 mg/ml) and the control group was given a 5 ml placebo injection (saline, NaCl 9 mg/ml). Bupivacaine is a long-lasting anesthetic with a half-life of 4 to 6 hours when injected into cutaneous and subcutaneous tissue. The anesthetic is effective within 1 to 3 minutes.

Participants and Recruitment

To indicate a clinically significant reduction of post-operative pain, a difference of 2 units on a 0 to 10 numerical rating scale was considered appropriate for the sample size calculation. The statistically significant difference of 0.95 in a review paper [8] was used to make the calculation. With a power of at least 80% and a p-value of less than .05, a sample size of 20 women (10 for each arm) was considered appropriate. The trial recruited 24 women to cover for any loss to follow-up.

Participants were recruited from a single-center Gynecological Department in the University Hospital of Stavanger, Norway. The hospital covers a heterogeneous population of

approximately 350,000 people. Consecutive women who were eligible for day case, laparoscopic surgery on the investigating surgeon's list were asked to participate at the pre-operative outpatient clinic. The inclusion criteria were healthy women (ASA 1-2) with a benign indication for surgery. Exclusion criteria were chronic pain, regular use of analgesic medication, pregnancy, allergy to bupivacaine, or those unable to give written informed consent. Written informed consent was obtained at the day of surgery.

Enhanced Recovery Program (ERP)

Laparoscopic surgery in the gynecological department for all women in the trial was day case surgery and followed this standardized ERAS protocol:

- Preoperative fasting: 6 hours for solids and 2 hours for liquids
- Consumption of 2 energy drinks in the evening and 1 in the morning before surgery
- Premedication:
  - Paracetamol 1g po
  - Cyclizin 50 mg po
  - Dexamethasone po
  - Oxycodone 10-20 mg po
  - Prophylactic antibiotics (when indicated)
- Anesthesia:
  - Total Intravenous Anesthesia (propofol/remifentanil/rokuronium)
  - Ketamine
  - Parekoksib
  - Bupivacaine 5mg/ml local injections, 5 ml in each port site
  - Oxycodone
  - Droperidol

- Postoperative:
  - Paracetamol 1g x 4 po
  - Diclofenac 50mg x 3 po
  - Oxycodone 2.5mg iv/5mg po, rescue analgesics
  - Thromboprophylaxis five hours postoperative

All procedures were performed by the same senior surgeon to ensure conformity. For participants in the intervention group, 5 ml of the study drug (bupivacaine 5 mg/ml) was injected into the trocar areas (preemptively) just before skin incision. Participants in the control group had 5 ml of saline preemptively injected into the trocar areas. The substance was deposited deep in the subcutaneous tissue, close to the fascia and the peritoneum. The injection was blind for the first trocar in the umbilical area, but for the other sites the injection was performed with laparoscope guidance. Two to four trocars were used depending on the type of surgery.

Measures

Postoperative pain was measured on a 0 to 10 numerical rating scale, where 0 is no pain and 10 is the worst imaginable pain. Movement-evoked pain 5 hours after surgery was chosen as the primary outcome measure. The objective of the ERP is to get the patients back to normal daily activity as soon as possible and movement-evoked pain was considered the most relevant outcome measure. Secondary outcome measures were pain at rest 2 and 5 hours after surgery and the need for oral rescue analgesics.

Pain scores were obtained with assistance from the nurses on the ward. Pain at rest was scored with the woman lying in bed. The first resting pain score was obtained 2 hours after surgery. 5 hours after surgery the women scored pain at rest again, and were then asked to

score movement-evoked pain when they walked around in the ward. Additional oral analgesics (oxycodone 5 mg) were administered on request and registered by the ward nurse.

Randomization

The 24 participants were computer randomized in blocks of 6 by an independent statistician, and the list was delivered to the hospital pharmacy in a sealed envelope. The randomization list contained numbers from 1 to 24 and the allotted local anesthesia or placebo, coded groups A and B. The pharmacist then decided which group bupivacaine and saline should represent and the code was concealed until the end of the study. The study drugs were prepared the morning before the scheduled surgery and arrived in consecutively-numbered 20 ml syringes according to the list. The syringes were labelled with the study number and the women's initials. If the surgery was not performed for any reason, the study number was used for the next potential candidate.

Blinding

The surgeon, the hospital staff and the participating women were all blinded to what the syringes contained. In order to make sure the groups were equal after randomization, we recorded the women's age, parity, BMI, procedure performed and operation time in minutes.

The surgery was divided into three categories according to complexity. Group 1 consisted of diagnostic laparoscopy or sterilization procedures, group 2 adnexal surgeries, and group 3 hysterectomies or myomectomies.

Statistical methods

The data was analyzed using IBM SPSS statistics, version 22.0.0.2. Data was subjected to a per protocol analysis. We had one conversion to laparotomy and data from the woman's primary and secondary outcomes were not included in the statistical analysis. A p-value of

less than .05 was considered significant. As all the data were not normally distributed they are reported with median values and interquartile range (IQR), nonparametric Mann Whitney U test was used for the statistical analysis

Ethical approval

The protocol was approved by the Regional Committee for Medical and Health Research Ethics of Western Norway (ref. 2012/292/REK vest) and the Norwegian Medicine Agency (ref. 12/07699-8) in December 2012.

The study was designed and performed in accordance with international guidelines (CPMP/ICH/GCP/135/95) and Norwegian laws and regulations (LOV 2008-06-20-44, FOR-2009-10-30-1321).

Results

In the period from March to September 2013 a total of 41 consecutive women were asked to participate (Figure 1). 5 women were unwilling and 12 were not included due to the following reasons: rescheduled surgery (n= 2), investigating surgeon not available (n=5), the study drug was not ready from the pharmacy (n=1) and the study was already finished (n=4). Of the 24 women included, one was lost from the intervention group due to conversion to laparotomy. Otherwise, no complications or adverse effects were registered for the study patients.

The 2 randomization groups were not statistically different according to age, parity and BMI (Table 1). There were no statistically significant differences between the groups in either the type of surgery or operation duration (Table 2).

For our primary outcome, movement-evoked pain at five hours postoperative, we found a statistically significant 2 unit reduction in median pain scores in the intervention group when compared to the control group (1.00 (IQR 3) versus 3.00 (IQR 2)), p-value .044 (Table 3).

Three women in the intervention group scored 0 (range 0 - 4) on movement-evoked pain 5 hours after surgery. Two of these had undergone adnexal surgery and 1 a hysterectomy. None of the women in the control group scored 0 at the same observation time (range 1 - 7).

There was no statistically significant difference between the participants in the intervention group when compared to the participants in the control group for pain at rest after 2 and 5 hours. There was also no difference in the amount of rescue medication given (Table 3).

Discussion

Principal findings

This RCT has shown that preemptive local injections of bupivacaine in the trocar areas reduce movement-evoked postoperative pain in gynecological laparoscopy. It is to our knowledge the first RCT on local anesthetics within a standardized ERP with movement-evoked pain as the primary outcome. The secondary outcomes of pain at rest and the need for rescue analgesics did not show any statistically significant differences.

The difference we found was larger than the findings in most other published studies. It has been suggested previously [8] that preemptive local anesthetics have a small but statistically significant effect with regards to laparoscopic surgery. However, the difference found, based on the reviewed papers (26 RCTs), was less than 1 unit on a 0 to 10 scale. In our opinion this difference is too small to be of clinical importance. That is why we chose a difference of 2 units for our power calculation. Other reviews have not found that local anesthetics have had any effect on postoperative pain. [9,10] None of the reviews considered local anesthetics in a

standardized ERP, and they did not distinguish between movement-evoked pain and pain at rest.

NRS is a validated tool to measure postoperative pain [20]. A study from Germany[21] found that the median cutoff point for pain-related interference of activity (walking, deep inspiration) and sleep was NRS score 3. Though this might be considered mild pain the study shows that it still is important to reduce the pain for the patient's comfort and to encourage activity.

The reason for the much greater effect found in this study may reflect the choice of movement-evoked pain as the primary outcome. Pain during movement is 100% more intense than pain at rest. [19] In our study the patients in the control group had a median pain-score of 1 at rest and 3 during movement, five hours post-surgery, which confirms the earlier study. Most of the published studies in the literature do not state whether movement-evoked or pain at rest was measured, or even distinguish between them, [19] and that makes it difficult to compare the results. Movement-evoked pain is also a more clinically relevant endpoint because it reflects the patient's ability to resume daily activities. [22]

Pain at rest did not show any significant difference between the groups, and this might explain why several other studies have concluded that local anesthetics have no effect. Generally low pain scores can partly explain why there are conflicting results in the literature. As in a lot of earlier studies we did not find any difference in pain score between the two groups 2 and 5 hours after surgery when the women were resting in bed.

Strengths and limitations

One strength of this study's design was that it was prospective, randomized, and double-blinded, with parallel assignments. All surgeries were done with the main surgeon as the investigator to ensure consistency in when and where the study drug was injected.

A second source of consistency was that the primary endpoint was obtained in a standardized way. Extremely varied exertions can be classified as “movement”: lifting an arm or a leg in bed, coughing, deep inspiration and so on. In our study, women were asked to walk in the ward room when they scored movement evoked pain, because this reflected the normal activity that the women need to be able to perform before they are discharged. It is important to define and report on the type of activity, as only in this way it is possible to compare the results from different trials.

Consecutive women were asked to participate in the study to avoid selection bias. However, the investigating surgeon was experienced and the distribution of surgery in the study perhaps did not reflect the general distribution of laparoscopic surgery in the department, and this might be a limitation in the selection.

Another limitation is **t**he wide variation in operation duration (15 – 218 minutes) was one parameter that as it showed an uneven distribution between the two randomization groups in the study. The distribution favored the intervention group who on average had a shorter operation time (median 67 minutes, compared to 115 minutes for the control group), though not statistically significant (p-value 0.13). It is however reasonable to believe that a longer operation time would result in greater postoperative pain. This may have affected the results to produce a higher pain score in the control group.

A further limitation to this study was that we included all types of laparoscopic surgery. A choice of just one category would probably have provided more readily comparable data, and may also have resulted in a more even spread of operation durations.

In the study protocol we decided to exclude women who had conversion to laparotomy from the statistical analysis of the primary and secondary outcomes of the study. The reason was

because patients have a lot more pain after laparotomy and take longer time to mobilization. In this small study it would have affected the results significantly to choose an intention to treat analysis. A per protocol analysis is also a limitation in this study with 1 woman excluded of the 24 participants.

This study has not investigated whether preemptive injections of local anesthetics are better than injection at the time of wound closure, in this case 0.5 % bupivacaine. In theory, pre-emptive infiltration has greater effect than infiltration at closure,[7] and the review that was used for our power analysis also found that pre-emptive local anesthetics had a small but statistically significant effect.[8]

If a reduction of 2 units on a 0-10 scale on postoperative pain is really of clinical importance we do not have an answer to. The study on cut-off point for post-operative pain [21] found that a NRS score of 3 interferes with activity and sleep, so it might be important to reduce pain from 3 to 1 as we found in this study. Another study of 2252 patients, in German hospitals, found that 55% of the surgical patient were dissatisfied with their pain management.[23] In hindsight we probably should have had a follow-up "quality of life" study, but this was not included in the original study protocol.

Conclusion

Our study has shown a statistically significant reduction in movement-evoked pain with preemptive local anesthetics injected into trocar areas during gynecological laparoscopic surgery. Local anesthetics are just one small element in the ERAS protocol, but our results indicate that they are an important factor into reducing postoperative pain caused by movement, and contribute to the ability of women to resume daily activities.

It is interesting to note that there was a statistically significant difference within the control group between movement-evoked pain and pain at rest after 5 hours (p-value .002). However, in the intervention group there was no difference in the median pain scores for movement-evoked pain and pain at rest after the same period (Table 3). The effect of local anesthetics seems to be primarily on pain caused by movement.

It is confirmed in this current study that movement-evoked pain is significantly more intense than pain at rest. Movement-evoked pain is also, in our opinion, more clinically relevant than pain at rest. The major aim with ERP is to encourage mobilization and further avoid thromboembolic and cardiopulmonary complications. For future studies on postoperative pain we will recommend movement-evoked pain as the primary outcome.

We will also recommend that all patients undergoing laparoscopic surgery should be given local anesthetics in the trocar areas, preferably preemptive.

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