Dissertation

Preemptive local analgesia at vaginal hysterectomy: a systematic review

Submitted by

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Statutory Declaration

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig angefertigt und abgefasst, und jene Personen und Institutionen, die am Zustandekommen der Forschungsdaten beteiligt waren, namentlich genannt habe. Andere als die angegebenen Quellen habe ich nicht verwendet und die benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen habe ich als solche kenntlich gemacht. Die Arbeit der Dissertation und daraus entstandener Publikationen wurden gemäß den Regeln der „Good Scientific Practice“ durchgeführt.

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organizations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the “Standards of Good Scientific Practice and Ombuds Committee at the Medical University of Graz.”

Graz, 23.7.2022
Dr. med. Univ. Nadja Taumberger, eh

Disclosures

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All co-authors consent to the use of published data in the dissertation and have given permission to reproduce figures and tables from their own publication. (1)

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Abbreviations

ACOG = American College of Obstetricians and Gynecologists
CCTR = Cochrane Central Register of Controlled Trials
CDC = Center for Disease Control and Prevention
CDSR = Cochrane Database of Systematic Reviews
CISH = Classic Intrafascial Supracervical Hysterectomy
COX = Cyclo-oxygenase
CSE = combined spinal-epidural block
ERAS = Enhanced Recovery after Surgery
FT = fast track
GA = general anesthesia
IPLA = intraperitoneal local anesthetic
LASH = Laparoscopic supracervical hysterectomy
LAVH = Laparoscopic assisted vaginal hysterectomy
MCID = minimal clinically important difference
MI = Minimal invasive
NSAIDs = nonsteroidal anti-inflammatory drugs
PCA = patient-controlled analgesia
PONV = Postoperative Nausea and Vomiting
POP = pelvic organ prolapse
QoL = Quality of Life
RA = regional anesthesia
RCT = Randomized controlled trial
SR = Systematic review
TAP = transversus abdominis plane
TEA = thoracic epidural analgesia
TIVA = Total intravenous anesthesia
TLH = Total laparoscopic hysterectomy
VAS = visual analogue scale

List of figures

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Zusammenfassung

Hintergrund: Die Hysterektomie als Therapie benigner Erkrankungen ist eine der am häufigsten durchgeführten Operationen bei Frauen. Einerseits wird, wenn möglich der vaginale Zugangsweg empfohlen und andererseits, um Leitlinien und ERAS-Protokoll Empfehlungen gerecht zu werden, eine multimodale Analgesie angewandt.

Zielsetzungen: Dies stellt eine systematische Übersichtsarbeit über die Wirksamkeit lokaler präemptiver Analgesie zur postoperativen Schmerzkontrolle bei Frauen dar, die sich einer vaginalen Hysterektomie unterziehen.

Suchstrategie: Wir durchsuchten systematisch MEDLINE, EMBASE, das Cochrane Central Register of Controlled Trials sowie die Cochrane Database of Systematic Reviews nach geeigneten Studien mit einem Publikationsdatum bis einschließlich 25. September 2019.

Auswahlkriterien: Randomisierte kontrollierte Studien und systematische Übersichtsarbeiten, die sich mit lokaler präemptiver Analgesie im Vergleich zu Placebo bei vaginaler Hysterektomie befassen.

Datenerhebung und -analyse: Zwei unabhängige Gutachter extrahierten getrennt voneinander die Daten. Die Ergebnisse wurden verglichen, und Unstimmigkeiten wurden durch Diskussion zwischen den Gutachtern ausgeräumt. Siebenundvierzig Studien erfüllten die Einschlusskriterien für die Volltextauswertung. Schlussendlich konnten vier RCTs, welche insgesamt 197 Patientinnen inkludierten, und 2 SRs eingeschlossen werden.

Ergebnisse: Es konnte eine signifikante Reduktion des postoperativen Schmerzes bis zu einem Zeitraum von 6 Stunden sowie eine Reduktion des postoperativen Opioid Bedarfs in den ersten 24 Stunden bei Patientinnen, die eine präemptive lokale Analgesie erhielten, nachgewiesen werden.

Schlussfolgerung: Eine präemptive Lokalanalgesie bei vaginaler Hysterektomie führt zu weniger Schmerzen und einem geringeren postoperativen Opioid Verbrauch.

Abstract

Background: Hysterectomy for benign indications is one of the most frequent operations performed in women. Vaginal hysterectomy is the recommended approach if feasible and guidelines and ERAS protocols recommend multimodal analgesia.

Objectives: A systematic review of the literature on the effectiveness of local preemptive analgesia in regard of postoperative pain control in women undergoing vaginal hysterectomy was performed.

Search Strategy: To identify appropriate studies which had been published until September 25th, 2019, MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews were searched systematically.

Selection criteria: Randomized controlled trials (RCTs) and systematic reviews (SRs) assessing the effect of local preemptive analgesia compared to placebo at the time of vaginal hysterectomy.

Data Collection and Analysis: Two independent reviewers extracted the data independently of each other. Those results were compared and disagreement was resolved by discussion between the reviewers. Considering the inclusion criteria for full-text review, forty-seven studies met those. Finally, four RCTs, with a total of 197 included patients as well as 2 SRs could be included in the review.

Results: A significant decreases in postoperative pain scores with an effect lasting up to 6 hours as well as reduced postoperative opioid requirement in the first 24 h after surgery in patients receiving preemptive local analgesia was found.

Conclusion: Preemptive local analgesia at vaginal hysterectomy leads to reduced postoperative pain as well as decreased postoperative opioid consumption.

1. Introduction

1.1. Background

Hysterectomy for benign indications is one of the most common performed operations in the field of gynecologic surgery and in women overall. The most common indications for benign hysterectomy are uterine fibroids, bleeding abnormalities, endometriosis and urogenital prolapse (3,4). Data show that 90% of all hysterectomies performed in the United States between 2000-2004 were for benign indications and only 10% were done because of cancer (4). In the U.S. about 590.000 hysterectomies are done per year and about 30% of all women by the age of 60 have had a hysterectomy performed for a benign indication (3).

Because of the high frequency of this procedure, multiple surgical approaches exist and the movement for faster recovery after surgery as well as improved perioperative care and cost reduction in the health care system are current topics of guidelines and ongoing studies.

The surgical approach has diversified over time from laparotomy (abdominal) to minimally invasive approaches such as vaginal, laparoscopic, and robotically-assisted hysterectomy (5).

In Austria, even though the number of hysterectomies is decreasing (5), the principles of the perioperative management are getting more and more important. ERAS protocols include recommendations for multimodal analgesia to reduce intra- and postoperative opioid needs which results in a faster recovery, fewer days of hospitalization and fewer complications (6). Other specialties have also implemented such protocols (7–9). The idea is to combine agents and modalities to reduce the use of opioids, which is associated with more side-effects for the patient and higher costs for the health care system (6).

Preemptive analgesia - which is defined as analgesia given to the patient before

the beginning of the operation, i.e., before any painful action to the body - is a part of this concept (10).

In the German-speaking countries Germany, Switzerland and Austria, vaginal hysterectomy is a major approach to this procedure with approximately fifty percent of all benign hysterectomies performed vaginally (5). This was the reason for choosing this specific topic and question of our systematic review and after some discussion, we decided to include just the local intervention used with vaginal hysterectomies because of three already published and well-known randomized controlled trials (RCTs) (11–13).

1.2. Aim and goal of the thesis

The aim of this particular systematic review is to summarize the existing literature focusing on local preemptive analgesia in vaginal hysterectomy and including all published RCTs and SRs. The objective was to systematically review all existing literature about women who undergo vaginal hysterectomy and receive any form of known local preemptive analgesia according with the goal of either postoperative pain reduction, reduced postoperative opioid requirement, readmission rate, perioperative management or quality of life. A paracervical block as a form of local preemptive analgesia has been implemented at our institution as a standard procedure when performing vaginal hysterectomy in 2015 because of 3 published RCTs, which showed postoperative pain reduction after implementation of the procedure. To evaluate the total amount of existing evidence-based data, we performed this SR.

1.3. Historical development of vaginal hysterectomy

Hysterectomies have been performed for centuries, with reports dating back into ancient times. Old reports indicate that VHs have been already performed 50 years before the birth of Jesus Christ by Themison of Athens (14). Until the sixteenth and seventeenth century, there are only a few reports of performed vaginal hysterectomy and then, the first authentic performed vaginal hysterectomy reported was performed in the year 1507 by the Italian anatomist Berengario da Carpi (15).

Almost 300 years later, the first “elective vaginal hysterectomy” was reported. Elective because up until that time, most of the procedures have been performed as emergency surgeries on puerperal uteri. Friedrich Osiander of Göttingen, Germany reported the first elective vaginal hysterectomy in 1801 (16) and Conrad Langenbeck was the first surgeon to treat endometrial cancer by performing an elective vaginal hysterectomy in 1813 (15).

1.4. Historical development of abdominal hysterectomy

Nearly 300 years after the first successful reported elective vaginal hysterectomy, the first successful abdominal hysterectomy has been performed in Manchester by Walter Burnham in 1853 (15). However, the mortality was somewhat between 70 and 90% at the time and almost all hysterectomies had been performed without any or only poor anesthesia. Hysterectomies then really became feasible with the advent of anesthesia in the 19th century.
In contrast to benign hysterectomy, which entails taking out the uterus with or without the tubes and ovaries, radical hysterectomy denotes removal of the uterus with the attendant tissue of the parametria and the upper vagina for the treatment of cervical cancer. Radical hysterectomy is associated with the names of Ernst Wertheim, who published a monumental series of 500 radical abdominal hysterectomies, and Friedrich Schauta, who published a similar

series of more than 300 extended vaginal hysterectomies (15).

1.5. Historical development of endoscopic hysterectomy

For decades vaginal and abdominal approaches were the only approaches for hysterectomy. In 1984 Kurt Semm completed the first endoscopic hysterectomy by using the CISH (Classic Intrafascial Supracervical Hysterectomy) technique in Kiel, although this was not classified as “completely laparoscopically” (15,17). In 1988 Dr. Harry Reich from the William Nesbit Memorial Hospital in Kensington, Pennsylvania, performed the first total laparoscopic hysterectomy (TLH) and published a report of exact methode in the 1989 (18). Dr. Reich introduced his procedure in the United States and in Europe, nevertheless, at this time the average operating time was about five hours. Concerning the postoperative outcome of the patient, postoperative pain was less when compared to the earlier used abdominal approach and also patient mobilization and discharge was possible earlier. Because of the long operating time, TLH was in some institutions supplanted by LAVH (laparoscopically assisted vaginal hysterectomy) because of shorter duration and easier implication of the already known skills of vaginal hysterectomy. Another development , mainly with the intention of reducing operating time, was the use of laparoscopic subtotal (supracervical) hysterectomy” (LASH) (15). Subtotal hysterectomy denotes removal of the uterine corpus (with or without the tubes and ovaries) whilst leaving the uterine cervix in situ.

Today, the approach to benign hysterectomy differs amongst countries and hospitals and depends among others on the training of the surgeon as well as cost-factors and shared decision making with the patient.

1.6. Most recent development of hysterectomy

In the early 21st century interest focused on replacing the “straight sticks” used in laparoscopic surgery with robotic arms and attached instruments which allow the surgeon full range of movement in the body cavity and slowed movement for fine dissection. Although some advantages have been published compared to conventional laparoscopic surgery for malignant or benign indications (19,20), the downside remains the high costs of robotic systems and equipment (15). Nevertheless, robotic techniques are gaining attention and traction and are likely to become more widely used in different fields of surgery.

1.7. Hysterectomy for benign indications

1.7.1. Indications and numbers

Hysterectomy means the surgical removal of the uterus and it can be done for either malignant or benign indications. Uterine fibroids, bleeding abnormalities, endometriosis/adenomyosis, dysmenorrhea or urogenital prolapse account for most of the benign indications and therefore, for most cases of hysteretcmy. Because of the frequency of those symptoms, hysterectomy was and is still is one of the most commonly performed gynecological surgeries worldwide (3,21–23), although rates have declined in recent years (24–27). This decline has been explained mostly by the ongoing development of different kinds of conservative treatment options for fibromas or abnormal uterine bleeding as well as alternative surgical options like hysteroscopic resection of the endometrium and/or fibromas. Although patients who opt for the conservative treatment avoid possible surgery related and/or anesthesia related complications, the remaining uterus and cervix remain at risk for developing uterine or cervical cancer in the future (28).

Interestingly, hysterectomy rates differ a lot amongst countries globally and the decline is not the same in all countries. For example, comparing the Scandinavian countries with the United States or Australia, their hysterectomy incidence rates are only half compared to the two other countries mentioned above (28).
Today, around 90% of the several million performed hysterectomies worldwide per years are done for benign conditions and thus to enhance quality of life rather than to lengthen life (3,4,29–31).

1.7.2. Surgical techniques

As mentioned above, there are four main approaches for hysterectomy. They can be divided into abdominal hysterectomy, done per midline or Pfannenstiel laparotomy, and the three minimally invasive approaches: vaginal, laparoscopic and robotically-assisted hysterectomies (3,32).

A meta-analysis found that patients who have undergone MIS hysterectomies had a shorter hospital stay, experienced less blood loss and could return quicker to their everyday lifes compared to abdominal hysterectomy. Nevertheless, MIS hysterectomies have a longer operating time and maybe also a increased rate of ureteric injuries than abdominal hysterectomy. However, no difference was found regarding morbidity between vaginal hysterectomy and laparoscopic hysterectomy (33).

Furthermore, there are data showing that the learning curve is steeper for laparoscopic hysterectomies and therefore, the risk for bowel or urethral injury may be higher than at abdominal hysterectomy (3,32,34–36).

Abdominal hysterectomy was long the standard approach for malignant conditions, a large uterus or in the presence of adhesions or endometriosis (3). However, with increasing experience and expertise there are now few barriers for laparoscopic hysterectomy. For example, on the basis of more than four large randomized trials, laparoscopic hysterectomy has replaced abdominal hysterectomy as the approach of choice for women with endometrial cancer

(37–40). These women benefit from the reduced trauma and fewer complications associated with the laparoscopic approach, with no detriment to recurrence or survival.

1.7.3. Choosing the approach for hysterectomy

Although much progress in minimally invasive approaches to hysterectomy has been made over the past decades, approximately 46% worldwide are still performed abdominally (41–43). Following the recommendation of the American College of Obstetricians and Gynecologists (ACOG) and other societies the vaginal approach should the chosen path whenever feasible (44). However, in cases where the vaginal approach is not feasible, surgeons need to choose another approach. Whereas laparoscopic hysterectomy has the advantage of a minimal invasive technique, it requires a lot of training and expertise (41). Abdominal hysterectomy is easier to teach, but has more morbidity for the patient and is not minimally invasive. For large uteri as well as obese patients, robotic surgery have shown a benefit (45–49). Also, it has been shown that the learning curve is shorter when compared to laparoscopic hysterectomy (50,51).

Preoperative evaluation should consist of detailed medical history, current complaints, physical examination as well as a pelvic examination to assess the mobility and size of the uterus and vaginal capacity. For the exact size of the uterus and also to exclude masses of the adnexa or pathology, a pelvic ultrasound should be done preoperatively to complete the evaluation. In the presence of abnormal uterine bleeding, an endometrial sample should be obtained beforehand to exclude malignancy (52).

1.8. Vaginal hysterectomy for benign indications

National and international guidelines as well as recent studies agree that the vaginal approach should be the favored one for benign indications if feasible (5,53–55). Therefore, the surgical steps of a standard vaginal hysterectomy will be explained in the following chapter.

1.8.1. Surgical steps of vaginal hysterectomy

When it comes to the surgical steps of vaginal hysterectomy, the main principal always stays the same whereas over the decades and in different countries, some small differences have developed. All figures were taken from the book „Die vaginalen Operationen: Chirurgische Anatomie und Operationslehre“, Reiffenstuhl, G; Platzer, W and Knapstein“, 1. Edition from the year 1974 with the approval of Elsevier publishing company (2).

- **Preparation** (52,56):
    - After positioning the patient in a dorsal lithotomy position, a Time out is completed with a standardized surgical safety checklist) is performed to ensure the identity of the patient, check allergies, ensure antibiotic prophylaxis, etc.
    - Under anesthesia, a pelvic examination is always performed to confirm the chosen approach for the hysterectomy and, if necessary, convert to another procedure if vaginal hysterectomy is not feasible.

- **Procedural steps** (52,56):
    - First, a preferably weighted speculum is placed into the posterior vagina and a Breisky speculum is placed in the anterior fornix of the cervix.

- Many departments at this point inject circumferentially vasoconstricting agents into the cervicovaginal junction for hemostasis and to reduce interoperative blood loss.
- This is the point where local preemptive analgesia, for example in form of a paracervical block injecting local anesthetic in all four quadrants of the cervix, can be performed.
- The cervix is grasped with single-toothed tenacula and a fishmouth-like circumcision of the portio is performed with a scalpel or diathermy (Figure 1 and Figure 2).
- The pouch of Douglas (posterior cul de sac) is entered and stay sutures applied to the peritoneum and the posterior vaginal wall (Figure 4, Figure 3).
- The left and right sacrouterine ligaments are clamped and cut (Figure 8). Now attention is directed anteriorly. The vesicocervical space is entered sharply and the bladder deflected anteriorly with a Breisky speculum. The ureters are lateralized by pushing them to the side with the finger. (Figure 5, Figure 6 and Figure 7).
- The uterosacral ligaments are palpated with the index finger and then clamped and cut. The claps are replaced by suturing and attaching the sacrouterine ligaments to the vaginal cuff. Attention is paid to the proximity of the ureters. (Figure 8).
- After that the parametrial tissue is detached from the uterus, either with clamps or bipolar vessel sealing. This includes the uterine arteries.
- Now the fundus of the uterus can be grasped with a tenaculum and the uterus delivered (Figure 9 and Figure 10).
- The uterus now remains attached only to the ligamenta ovaria propria, the fallopian tubes and the round ligaments. These structures are now clamped and the uterus detached.
- After a careful check to confirm hemostasis the peritoneum and the vagina are closed (Figure 11 and Figure 12).

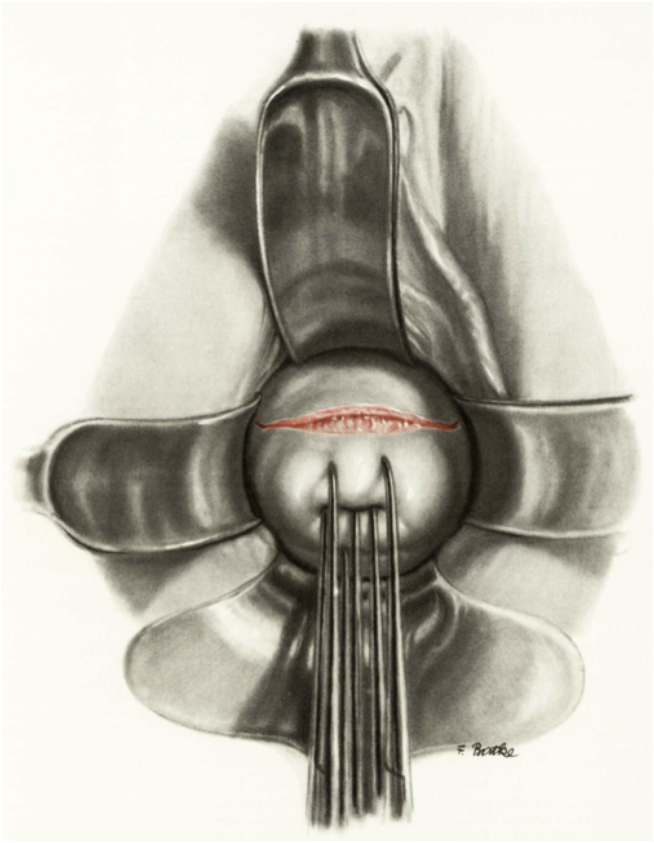

Figure 1 Fishmouth-like circumcision of the portio (2)

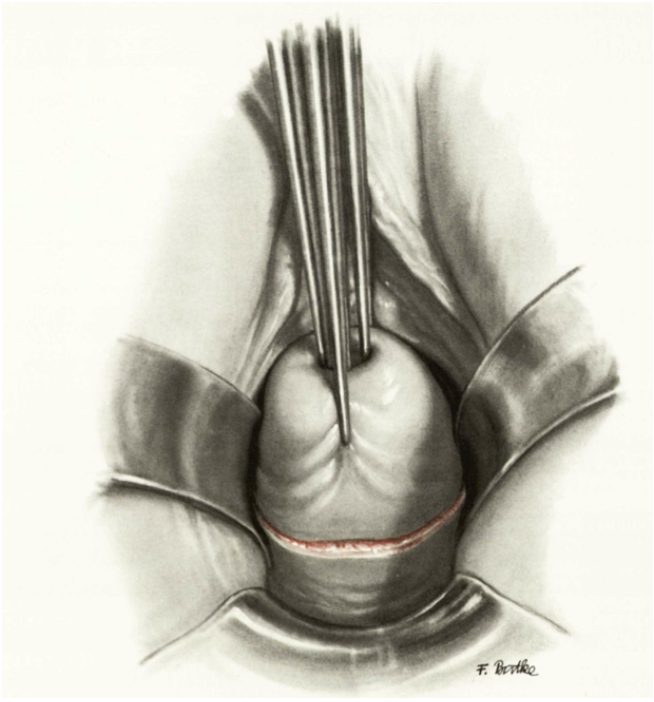

Figure 2 Fishmouth-like circumcision of the cervix.(2)

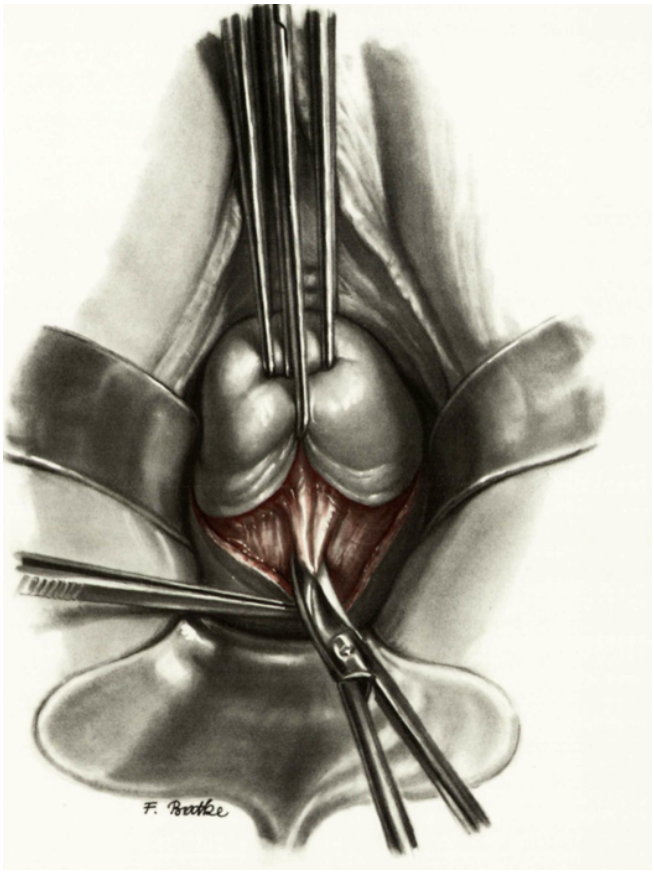

Figure 3 Opening the Douglas peritoneum (posterior cul de sac).(2)

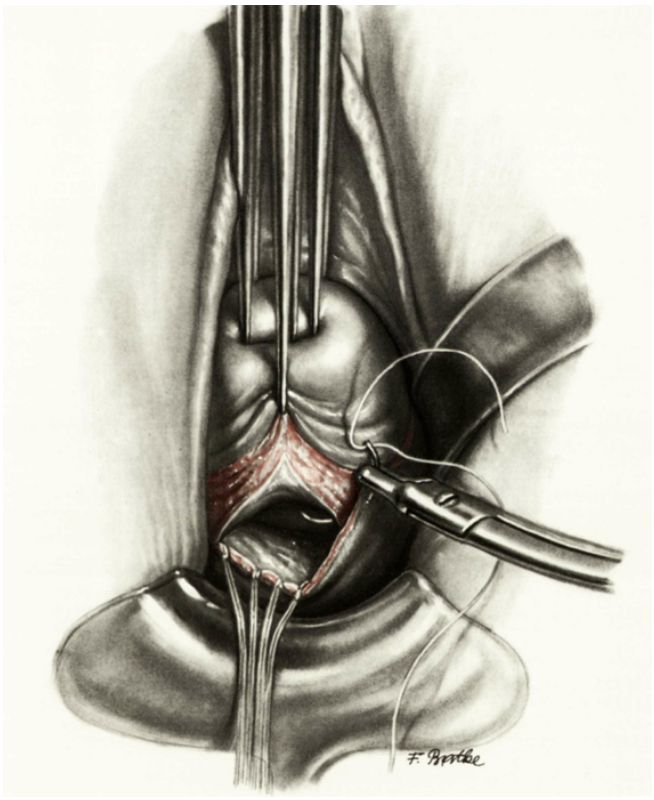

Figure 4. Attachment of the peritoneum to the posterior vaginal wall (2)

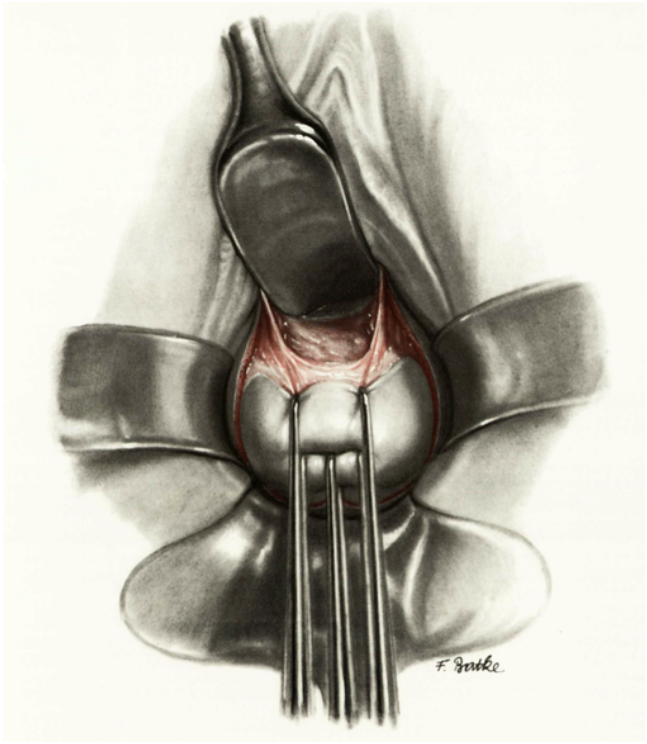

Figure 5 Exposure of the vesicocervical space (2)

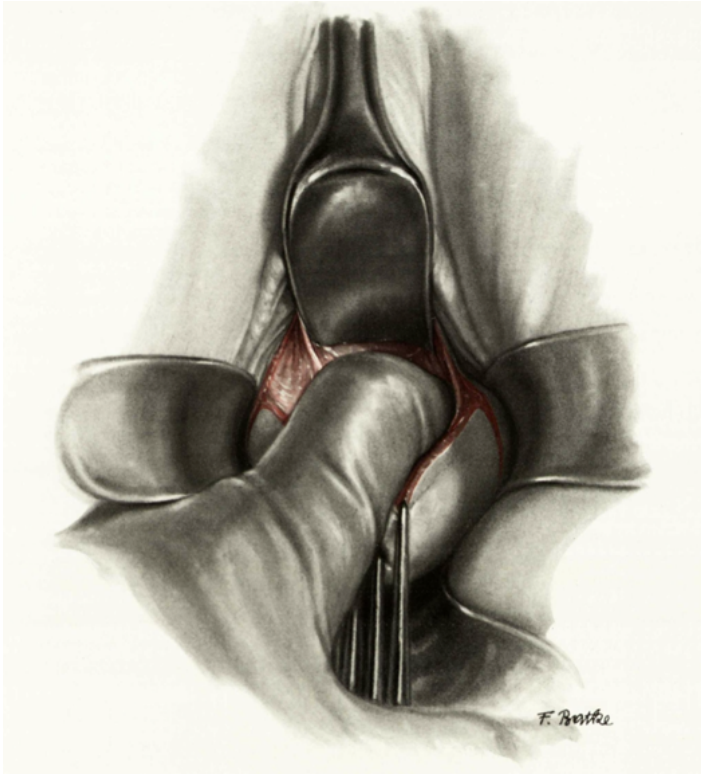

Figure 6 Opening of the vesicouterine space (2)

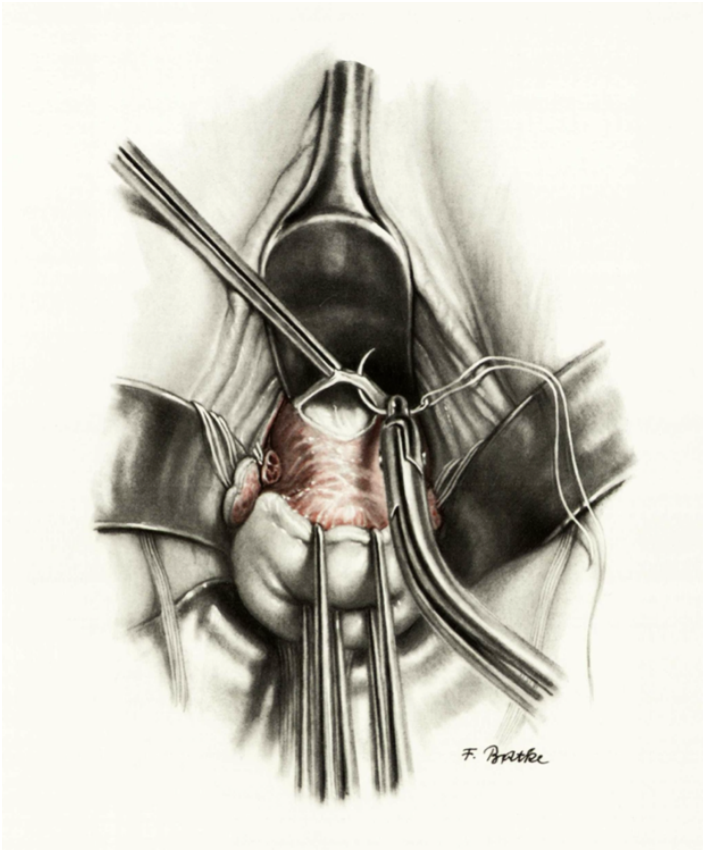

Figure 7 Suture for marking the vesicouterine peritoneum (2)

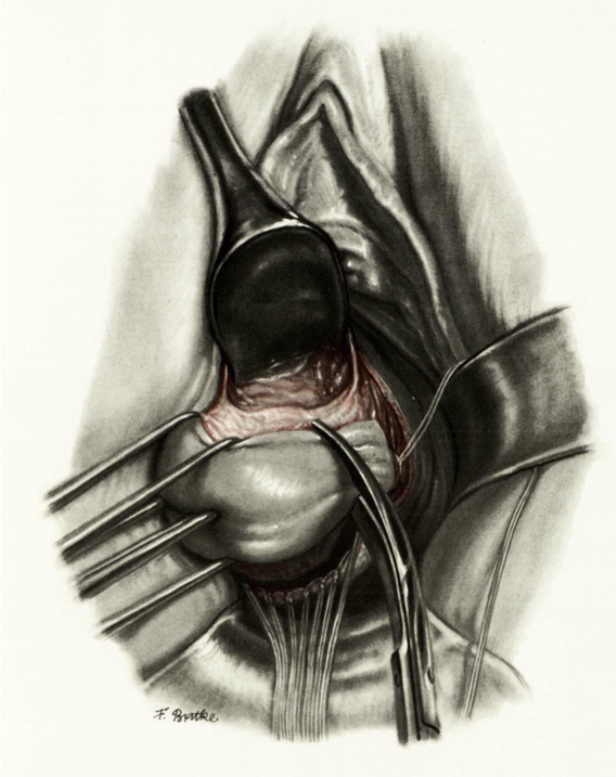

Figure 8. Dividing the left sacrouterine ligament and parametrial tissue (2)

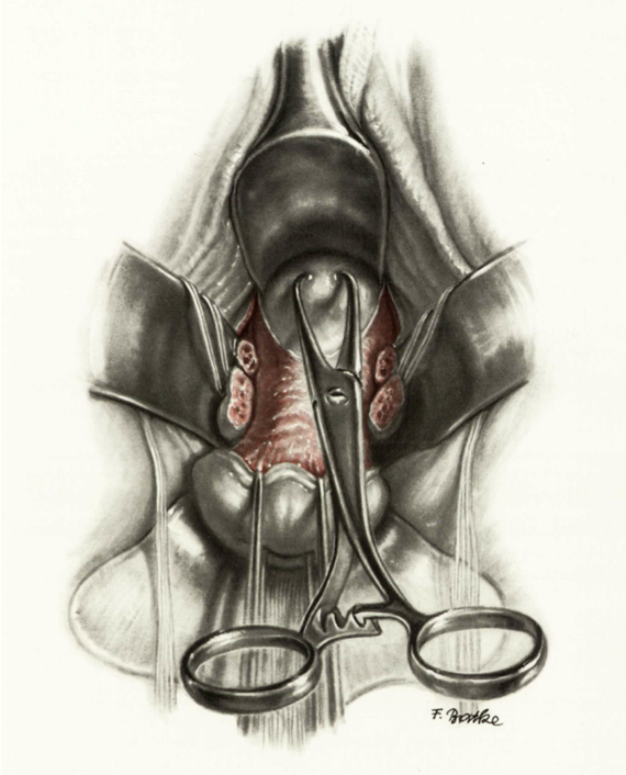

Figure 9 The uterus is grasped and delivered with a tenaculum (2)

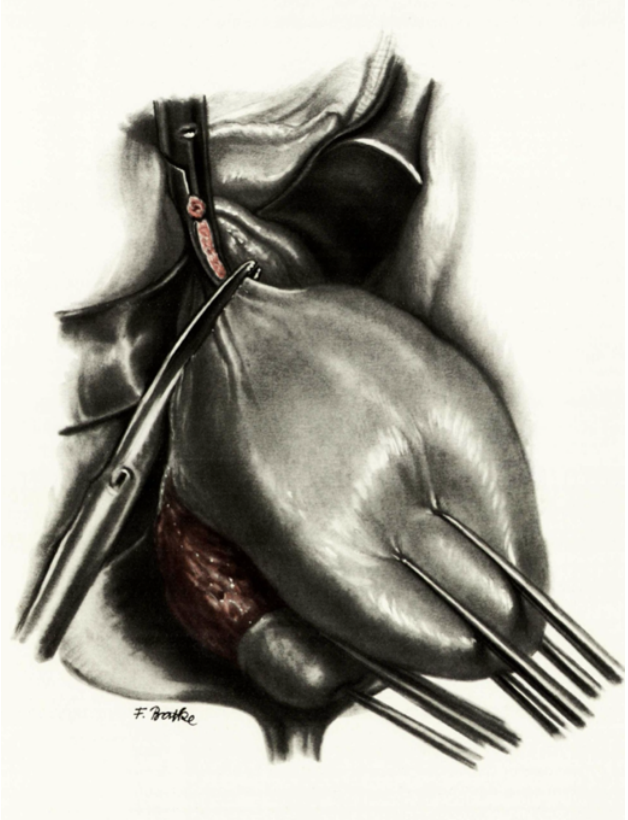

Figure 10 The uterus is detached from the right utero-ovarian ligament, round ligament and fallopian tube (2)

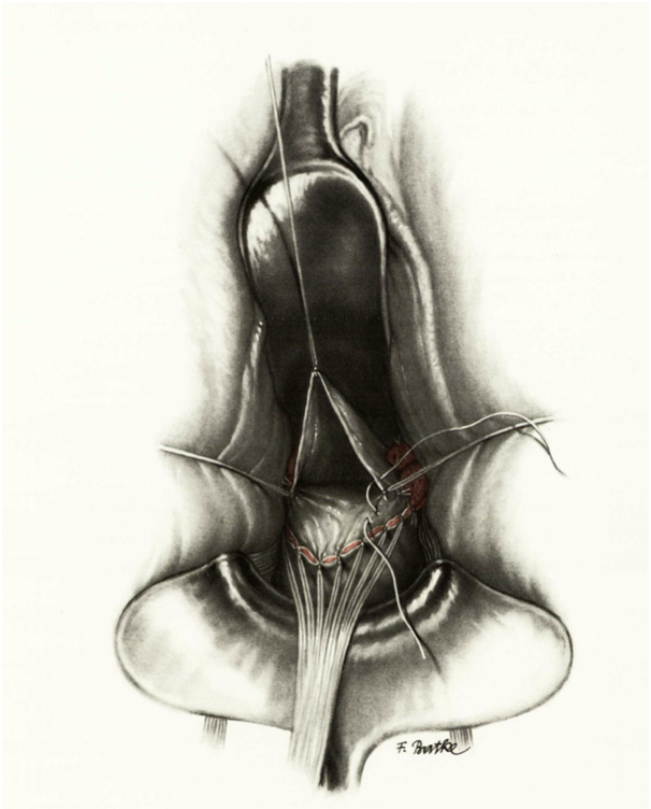

Figure 11 Closure of the peritoneum (2)

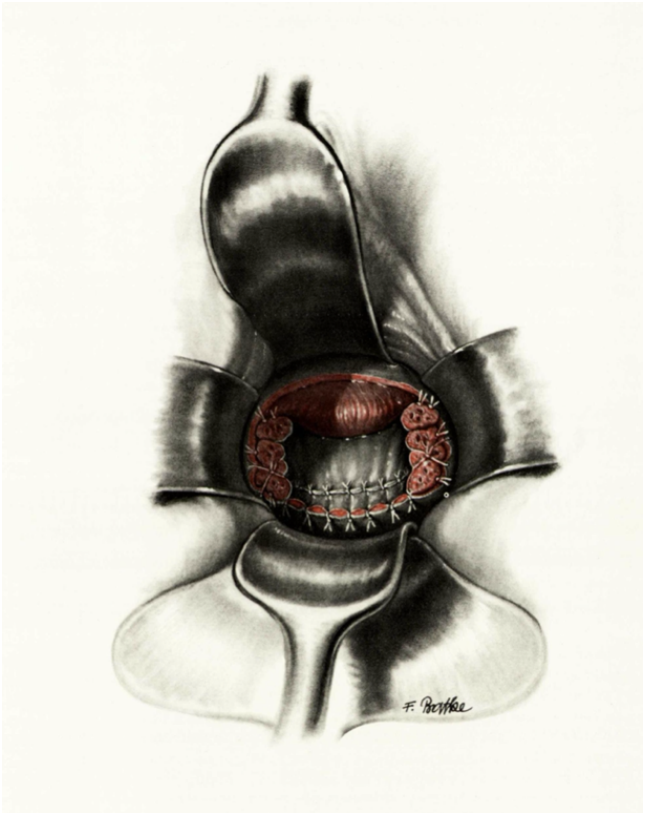

Figure 12 Closure of the vagina (2)

1.8.2. Anesthesia for vaginal hysterectomy

There are two approaches for anesthesia for vaginal hysterectomy: general anesthesia (GA) and regional, i.e., spinal or epidural, anesthesia (52,55,57). The goal is to provide sufficient pain control, decrease the response of the body to surgical stress and improve postoperative mobilization as well as oral food ingestion and hydration (6).

For general anesthesia short-acting agents such as sevoflurane, desflurane or permanent propofol are preferred to allow prompt awakening of the patient. Combining regional anesthesia to general anesthesia has been shown to reduce opioid need perioperatively and reduce PONV, which is important as gynecologic surgery itself is a risk factor for PONV (6). Up until today, there is an ongoing debate and numerous studies on the advantages and disadvantages of regional vs. general anesthesia – both modalities are effective and safe (58).

Specific groups of patients may be better served by general or regional anesthesia. In the elderly, general anesthesia may have more side effects like postoperative delirium and cognitive dysfunction for example (59). But also in young and healthy patients, general anesthesia can have a higher risk of pulmonary complications that regional anesthesia (60). Regional anesthesia has absolute and relative contraindications such as certain neurological conditions, elevated intracranial pressure, severe known thrombocytopenia or coagulopathy and all factors for severe hypotension (61,62). Many of those contraindications are more common in elderly patients however, regional anesthesia normally is the less traumatic approach and results in a shorter hospital stay and less pulmonary or cardiovascular complications (60,63). Local anesthesia, alone or on combination, has been shown to be a possible approach in POP repair or even vaginal hysterectomy, but should only be considered in multimorbid patients without other options for anesthesia (57,62,64).

1.9. Enhanced Recovery After Surgery (ERAS, formerly known as Fast Track)

1.9.1. Historical background

Dr. Emil Ries, a gynecologist from Chicago, already described and published his ideas about Fast Track Surgery in the year 1899. He wrote about his treatment of patients with vaginal celiotomy and that he experienced faster recovery by early mobilization, not artificially pushing the bowel as well as early feeding postoperatively (65).

In the modern era, the Danish surgeon Henrik Kehlet pioneered the focus on interdisciplinary, multimodal approaches to get better control over postoperative pathophysiology and improve reconvalescence (66). Kehlet understood the factor of the “surgical stress response” to be responsible for failure of surgical and anesthetic technique, as this often leads to increased demands on organ function. His goal was to better understand the role of pathophysiology according to the different postoperative parts of the surgical stress response and to evaluate if change of those can lead to a better patient outcome. His suggestion was the development and implementation of evidence-based multimodal regimens to improve postoperative recovery, reduce postoperative pain and morbidity and also overall costs (66).

Since the 1990s major efforts have been made to evaluate and implement many of the suggested multimodal changes in all surgical specialties (6,6,67–71,71–80). All guidelines are available on the website of the ERAS Society for free (81). Today, what Kehlet initially called Fast-track surgery is known as Enhanced Recovery after Surgery (ERAS), rapid recovery enhanced recovery (82,83).

Figure 13 Henrik Kehlet at the ERAS conference 2022, reproduced with permission of Prof. Karl Tamussino

But despite extensive evidence and publications implementation of ERAS principles has been rather slow (84). Although it is known that in healthcare, the implementation of new scientific evidence can take up to 15 years, it is an unexpected slow progress in the implementation of a simple and well described approach.

Obstacles to the implementation of ERAS include lack of knowledge of the evidence, lack of leadership, different approaches to practice according to culture, reimbursement issues, and the assumption that some of the approximately 30 ERAS steps may be complicated to implement (85).

1.9.2. The Enhanced Recovery After Surgery (ERAS) Society

The Enhanced Recovery After Surgery Society (ERAS, www.erassociety.org) was founded in 2010 (and out of the ERAS Study Group which was founded by Profs. Ken Fearon of the University of Edinburgh, Olle Ljungqvist from the Karolinska Institut in Sweden, Arthur Revhaug from the University of Tromsö and Martin von Meyenfeldt and Cornelius Dejong from the University of Maastricht in 2001 (86). The initial aim of the research group from northern Europe was to enhance current perioperative care of patients undergoing colonic resection (87). They decided to develop and advance the ideas of Henrik Kehlet about multimodal surgical care and soon discovered that there were different ways of traditional ways “things used to be done” in different units and that one of the biggest goals had to be to develop the best way to change habits to best-practice (87).

The first ERAS Symposium was held in 2003 and the first evidence-based protocol for patients undergoing colonic surgery was published in 2005 (88). In the following years many guidelines and consensus papers have been developed in collaboration with other societies and also an annual ERAS conference was implemented. Guidelines are available and can be downloaded from the ERAS website (www.erassociety.org).

1.9.3. Principles and aims of ERAS

It has been repeatedly demonstrated over the past two decades that ERAS protocols, when fully implemented, reduce hospital stay as well as peri- and postoperative morbidity and speed up the recovery process without increasing peri- or postoperative complications or readmission rates (82). ERAS pathways seek to improve the care of the patient given before, during, and after surgery and therefore minimize their surgical stress response. The pathways were developed as a multimodal regime and combine preoperative

education, minimally invasive surgery, regional anesthetic techniques, multimodal opioid-sparing pain management, early feeding, and ambulation.

The main principles can be summarized in a combination of best possible minimally invasive surgery, analgesia optimization in form of a multimodal approach, early oral refeeding and less preoperative fasting, and rapid postoperative mobilization of patients. The main aim of this approach is to minimize the reaction of the body due to the applied surgical stress by enhacing, among others, the perioperative nutritional status as well as encouraging opioid free analgesia and early postoperative feeding (89).

ERAS is a multimodal approach where a well-codified multidisciplinary collaboration among surgeons, anesthetists, and the nursing team is necessary and required. The patient is at the center of this concept and plays a major role in the success of the program, making appropriate patient information, education and high patient motivation an indispensably part (90).

- **Preoperative Pathways**

- Patient counseling and education is a crucial to successfully implement ERAS. Active participation of the patient is required. Counseling should include explanation of the ERAS concept from the beginning and inform about the principles such as early postoperative mobilization and feeding as well as the used pain management. Patients should already know before admission how to get ready for surgery, what to expect when arriving at the hospital and how their postoperative recovery will be supported. Proper information and patient education is associated with improved postoperative pain control, less postoperative complications and shorter all over recovery time (83,91). Also, early discharge is associated with early information about anticipated length of hospital stay as well as used discharge criteria (92).
- Preoperative fasting, which was considered important to avoid aspiration of gastric content during anesthesia, has been nearly outdated and is associated with negative effects such as dehydration and different

metabolic changes at a time when the body needs to be in good shape for the postoperative healing process. Changes associated with at least 12 hours fasting have been shown to negatively affect perioperative outcomes (93). Therefore, current American guidelines recommend fasting not more than 6 hours for a light meal and not more than 2 hours for clear liquids before planned procedures that generally require either general or regional anesthesia or sedation (94). Also, preoperative carbo-loading with the use of special drinks can be used according to ERAs guidelines (95).

- Avoiding mechanical bowel preparation is another central principle of ERAS. Earlier, bowel preparation, either mechanical and antibiotic, in abdominal and also gynecologic surgery had been done with the aim of decreasing the risk of anastomotic leaks and preventing perioperative infections (96). However, a meta-analysis focused on gynecologic procedures stated that there is no evidence that patients benefit from mechanical bowel preparation or enemas and furthermore, there is also no benefit regarding intraoperative visualization or bowel handing (96–98).
- Preemptive analgesia is analgesia before any painful stimulus to the body and is an important principle of ERAS pain management. The theory behind this is that analgesics block the activation of pain receptors before they are even triggered by any stimulus. This results in better pain control and in a decrease in analgesic requirements such as opioids. The most used and recommended multimodal systemic approach includes the preoperative use of gabapentin, oral or intravenous cyclo-oxygenase (COX) -2 inhibitors, metamizole and oral or intravenous paracetamol because they have been shown to decreased the use of opioids postoperatively (99–104).

- **Perioperative Pathways**

- Anesthetic principles aim to reduce surgical stress and pain as well as the known and possible side effects of anesthesia. In summary, short-

acting volatile anesthetics or propofol via continuous perfusor as well as the use of short-acting opioid analgesics intraoperatively are recommended whereas total intravenous anesthesia (TIVA) with propofol is conjoined with less postoperative side effects and less postoperative nausea and vomiting (PONV) (95,105–107). Besides, it has been shown that regional anesthesia with or without concomitant general anesthesia has positive effects such as less perioperative opioid needs and less PONV (63,108,109).

- Intraoperative normothermia is another cornerstone of ERAS as an intraoperative body temperature less than 36°C is related to increased risk of intraoperative bleeding, different metabolic factors as well as wound infections (110–112). Therefore, it is recommended to use active warming techniques pre-, intra- and also postoperatively such as warm air blankets, or prewarmed IV fluid and to monitor core body temperature to prevent hypo- and hyperthermia (113,114).
- Intraoperative fluid overload should be avoided. Euvolemia is associated with fewer postoperative complications and less hospital stays as well as less morbidity (115,116).
- Prevention of PONV is especially relevant in the female patient because female gender, gynecologic surgery, and also MIS are known risk factors for this (107,117). PONV can prolong hospital stay and slow postoperative mobilization. ERAS pathways attempt to minimize PONV by using at least two different antiemetic drugs during surgery, minimize the use and need for opioids and favor TIVA (107,117,118).
- Nasogastric tubes should be avoided according to ERAS protocols as data show the restrictive use or even no nasogastric tube is associated less pulmonary complications, no change in anastomotic leak rates and higher rates of postoperative pneumonia for example (6,119).
- Prophylactic peritoneal drains were initially implemented to avoid postoperative fluid collections and detect postoperative hemorrhage or anastomotic leak (120,121). Most of the existing data come from the general and colorectal surgery and therefore the data is only of limited use for gynecologic surgery, but the few existing studies in gynecological

patients do not support the routine use of prophylactic drainage, even after operations including bowel resection (121–123).

- **Postoperative Pathways**

- Early postoperative feeding, meaning the start of oral fluid and solid food within the first 24 hours postoperatively, is an important part of postoperative recovery and several trials have shown advantages for this regime in gynecologic surgery (124–126). Also, patients satisfaction is higher when early feeding protocols is allowed (127).
- Early postoperative mobilization prevents muscle loss as well as immobility and reduces the incidence of thromboembolic complications (128).

Urinary catheters, if placed at all, should be removed within the first 24 hours after surgery. Early catheter removal leads to shorter hospitalization stay and less frequent urinary tract infections(129,130). Perioperative pain management is one of the most central pathways in the ERAS concept. The aim is to increase pain control and decrease opioid use. Opioids increase PONV, impair bowel function, delay postoperative mobilization and entail a risk of postoperative addiction. Therefore, a multimodal analgetic regimen is recommended by the combination of at least two or more synergistically acting agents (131).Generally, NSAIDs/COX-2 inhibitors can help control postoperative pain and reduce opioid requirements and PONV at the same time (99,132,133). Also, an additional dose of paracetamol leads to better pain control when combined with any other drug mentioned above (134). Regional analgesic techniques such as thoracic epidural analgesia (TEA), transversus abdominis plane (TAP) blocks, wound infiltration with local anesthetic, and intraperitoneal local anesthetic (IPLA) can and in an appropriate case should also be implemented into protocol. Whereas TEA mostly implemented nowadays in colorectal, thoracic, vascular, hepatobiliary and urologic surgery (135), the role in gynecologic surgery is still to be investigated.

A multimodal pharmacologic postoperative applied, preferably oral, regime with

paracetamol, NSAIDs and opioids on request in combination with surgical site infiltration with local anesthetic before the closure of the skin has shown less postoperative pain and more than 75% reduction of postoperative opioid need as well as a reduced hospital stay (127). Wound infiltration with a local anesthetic is an effective and easy implemented as well as safe method to reduce postoperative pain, preferably with a long-acting local anesthetic, called liposomal bupivacaine (136,137). Furthermore, the ERAS considerations on vaginal hysterectomy are that in addition to the multimodal analgesic regime, local anesthetic infiltration as a paracervical block or intrathecal morphine may be applied (6).

Postoperative fluid management should be handled like preoperative and intraoperative fluids with the goal of euvolemia. Patients can and should drink immediately after surgery, and IV fluids should be restricted to a minimum. Prevention of postoperative ileus is recommended and should performed with the early use of laxatives such as magnesium or suppositories or even osmotic laxatives as this results in less postoperative hospital stay and earlier time to first bowel movement with no increased side-effects (138,139). Also, chewing gum has proven to be effective for prevention of postoperative ileus (140).

1.9.3.1. ERAS in Gynecology

ERAS concepts have been shown to enhance patients' outcomes as well as costs in many surgical disciplines (71,141). The first ERAS guidelines dealing specifically with gynecology and gynecologic oncology were published in 2016 (142,143) and updated in 2019 (6). In 2020 a ERAS guideline for vulvar and vaginal surgery was published, summarizing all existing data and literature on this topic (58). Furthermore, cesarean section guidelines were issued in 2018 (78).

The main points of focus in gynecologic surgery are: Patient information before admission as well as patient education and counseling, preoperative bowel

preparation, venous thromboembolism prophylaxis, standard anesthetic protocol and fluid management, urinary drainage, postoperative analgesic protocols, preoperative and postoperative nutrition management, postoperative dressing care and postoperative drains and adjuvant procedures (6,58,68,69,144,145).

Data has shown that extending ERAS principles to the field of gynecologic surgery provides a number of advantages similar to the other specialties. Lambat Emery et al. published the results of their RCT which showed that the implementation of a ERAS protocol for TLH for benign indication resulted in significantly reduced hospital stay without more postoperative complication or less patient satisfaction (90,146).

Scheib et al. performed a literature review showing that the need to decrease the length of hospital stay in gynecologic patients as well as the cost-cutting are only two reasons named why surgeons and healthcare workers are under a lot of strain to implement cost-saving measures. ERAS protocols have been shown to reduce length of hospital stay in all fields of gynecologic surgery: laparoscopic, vaginal and abdominal. Crucial are factors such as early and proper patient education, removal of the urinary catheter at the earliest possibility, multimodal analgesia and early feeding. By reducing the length of hospital stay, the costs are simultaneously lowered. Most of the ERAS principles are of low or even no cost, can easily be implemented and improve patient comfort and recovery (147).

The ERAS society recommends specific protocols developed for gynecologic surgery which include procedures ranging from simple hysterectomies for benign indications to cytoreductive cancer surgeries. Data show these protocols to improve physical and psychological patient condition such as reduced postoperative pain and postoperative opioid requirement, length of hospital stay and enhance postoperative outcomes (141,148–150).

Furthermore, spinal anesthesia seems to reduce postoperative opioid needs and, if morphine is given intrathecally, to speed postoperative recovery after abdominal hysterectomy (148,151).

Nevertheless, due to the lack of specific RCTs more studies are necessary to define and underline ERAS recommendations regarding the adoption of those protocols in all gynecologic surgeries for benign and oncologic indications (148).

Bahadur et al. focused on length of hospital stay and quality of life when comparing ERAS protocols in gynecology to standard protocols. They found quicker recovery results, decreased hospital stay as well as improved quality of life and patient satisfaction in the group that followed ERAS protocols (152). Another study focusing on patient satisfaction reported similar results with regard to patient satisfaction and also confirming overall support of ERAS measures by all healthcare professionals (153).

1.10. Preemptive analgesia at hysterectomy

ERAS protocols recommend multimodal perioperative pain management protocols with the goal of different agents targeting different analgetic mechanisms. For gynecologic surgery in particular, the recommendations for systematic use suggest a combination of acetaminophen, in Austria commonly referred to as paracetamol, NSAIDs and gabapentin – preferably given orally (6,144,154).

- **Paracetamol:** The addition of preemptive paracetamol, which has a very good safety profile, has been shown to reduce opioid consumption and therefore should be implemented in all patients without contraindications (68). The oral use has no disadvantages compared to the intravenous application so whenever feasible administration should be oral (144,155).
- **NSAIDs** are nonsteroidal drugs that reduce postoperative opioid requirements, minimize PONV and have a synergistic positive effect given together with paracetamol (99,134,156,157).
- **Pregabalin and gabapentin,** which are normally used in the treatment of epilepsy, have shown benefit in the preemptive setting to optimize

perioperative pain control, reduce perioperative opioid requirements and nausea (100,158–160).

Regional anesthetic techniques, such as thoracic epidural analgesia or the transversus abdominis plane block, have not become standards in gynecologic surgery, but have been used widely in colorectal surgery (68). However, spinal anesthesia with intrathecal morphine has been implemented in gynecologic surgery and is beneficial in terms of ERAS protocols. It leads to quicker postoperative recovery, shorter sick leave and therefore improved quality of life when compared with general anesthesia (151,161).

Preemptive local wound infiltration has been studied for many different surgical specialties and procedures, including gynecological procedures and cesarean section (162). At cesarean section, good postoperative pain control is especially important as patients want to be mobile as soon as possible. Therefore, early mobilization, patient satisfaction and independence to ensure providing for the newborn is crucial and, besides peri- and postoperative outcome and as little as possible complications, the most important goal. The positive effect of local wound infiltration prior to incision and fascial plane block has been shown. However, due to the easy implementation of preemptive wound infiltration with a local anesthetic, this is probably the easier procedure to establish (163). The effect of an decrease in postoperative opioid consumption and postoperative pain scores up to 24 h postoperative have also been demonstrated (164). Those positive effects have also been shown at abdominal hysterectomy (6,165,166).

In summary, in both procedures the use of presurgical local wound infiltration has demonstrated reduced pain scores postoperatively and therefore, seems to be an easy and low-cost procedure to implement to significantly reduce postoperative pain and speed recovery (78).

Surgical approach also influences postoperative pain even when local infiltration is used. Minimally invasive approaches are generally associated

with lower opioid requirements and less pain than open procedures (162). Local anesthetic agents including levobupivacaine, bupivacaine and liposomal bupivacaine as well as ropivacaine and lidocaine have been used in published studies and all showed significantly lower postoperative analgesic requirements, lower pain scores and faster recovery times (167–170).

Liposomal bupivacaine, which is only recently available in Europe however can, due to its longer half-life period, reduce postoperative pain also on the second and third day after surgery in women undergoing laparoscopic or robotic hysterectomy (169).

1.10.1. Preemptive analgesia at vaginal hysterectomy

In 2020, the ERAS Society published guidelines for vulvar and vaginal surgery including urogynecology (58).

The routine use of preoperative oral paracetamol and a NSAID is recommended to accomplish a decrease in opioid requirements and therefore should be a routinely implemented in all ERAS pathways (134,157). However, anticonvulsants and opioids have been shown to entail a larger risk for postoperative delirium and cognitive dysfunction and should therefore be avoided, particularly in elderly patients (59,171,172).

In contrast, the routine application of local anesthetic medication especially in vaginal surgery is supported for a paracervical or vaginal cuff blocks (157,173). The routine use of liposomal bupivacaine, which was not available in Europe until 2021, may be considered but still needs further evaluation in randomized controlled trials (157,174).

1.10.2. The opioid crisis

The use, abuse and misuse of opioids has been a major medical, political and public health issue in the last 10 years, particularly in the United States. In the United States the ongoing “Opioid crisis” is claiming about 100,000 lives per year (175). While pain control is critical and patients should not be undermedicated, opioids should not be overprescribed (176–179). Furthermore, unused, unlocked or undisposed postoperative opioids stand for another aspect of this pressing health issue as recent studies showed that a large portion of the prescribed medication is not used (179,180) properly and therefore leaves room for misuse. Accordingly, reducing the need for opioids has become a central issue in perioperative management and pain control (173,181–186).

The U.S. Centers for Disease Control and Prevention (CDC) have estimated that 42 persons per day die due to opioid prescription overdose in the United States (178). Because of campaigns and efforts, the prescription rate per year in-between 2006 and 2017 has decreased from 72.4 to 58.5 per 100 persons for all opioids in the United States. Opioid prescribing keep on decreasing through the year 2017 (187) suggesting that at least some prescribing practices continued to enhace but still more efforts are necessary to help develop and keep safe prescribing behaviors.

Despite all efforts, in the year 2016 still a total of approximatively 17,000 people in the United States died from drug overdoses involving prescription opioids with 14,432 persons dying from unintentional drug overdoses involving prescription opioids (175,187).

1.11. Hypothesis

As mentioned, preemptive analgesia is defined as any form of analgesia given before a painful stimulus to the body. The goal is to decrease perioperative and postoperative pain and therefore, opioid and analgesic needs. For the ERAS

concept, and also to the ongoing need to improve surgical care, decreasing postoperative pain and opioid requirements is an essential mission.

Decreasing postoperative pain scores increases postoperative mobility, speeds up postoperative recovery and enhances reconvalescence. Enhanced recovery with shorter hospital stays benefits patients and healthcare systems in terms of cost- effectiveness and capacity.

Many developments and concepts over the years have led to huge improvements in peri- and postoperative management. However, postoperative opioid requirements and postoperative pain remain a challenge. To reduce those two factors, new concepts should focus on patient safety, easy implementation and also cost-effectiveness to reach the most benefit.

In our institution as in many gynecology units in German - speaking countries, vaginal hysterectomy Is a common procedure and therefore, an improved of postoperative pain control and reduction of postoperative opioid requirements are an issue. Three RCTs on this topic led to the implementation of the standard use of local preemptive analgesia at vaginal hysterectomy at our institution about 10 years ago. However, we could not find a systematic review that addresses this research question and summarizes the existing data.

We assume that this systematic review will support our hypothesis and implemented clinical practice that additional application of local preemptive analgesia in patients undergoing vaginal hysterectomy leads to less postoperative pain in a certain number of hours postoperatively and to a reduction of postoperative opioid requirements compared to placebo. Also, we assume that this additional intraoperative intervention is simple to apply, does not prolong operative times or increase intra- or postoperative complications. All these features would support the general use and recommendation for preemptive local analgesia at vaginal hysterectomy.

The results of this systematic review, which will only include RCTs and SRs, should provide guidelines, medical societies and clinicians with the highest possible, current evidence to form evidence-based recommendations. Such recommendations could improve a common gynecologic procedure in terms of postoperative pain reduction, reduced postoperative opioid requirements, increased QoL, faster postoperative recovery, and optimization of cost-effectiveness.

2. Materials and Methods

This SR was limited to the application of preemptive local analgesia in vaginal hysterectomy; other techniques of hysterectomy such as laparoscopic, abdominal, robotic and other forms of preemptive analgesic interventions such as systemic or intrathecal procedures were excluded. This was done to perform the most homogenous literature search possible because hysterectomy is a common procedure and its various approaches and different known preemptive routes.

The protocol was developed before the start of the literature search in September 2019 at the Department of Obstetrics & Gynecology and the Institute of General Practice and Evidence-based Health Services Research of the Medical University of Graz. After resolving all open questions and defining the exact inclusion, exclusion, primary and secondary outcome parameter as well as the planned analysis and the time frame, the final protocol, was registered at PROSPERO can be retrieved under: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020144709.

Only RCTs and SRs with a patient cohort of adult women undergoing vaginal hysterectomy for benign and selected malignant indications with no major concomitant surgeries were included. Bilateral salpingo-oophorectomy and minor concomitant surgeries such as colporrhaphy anterior or posterior were permitted. The intervention needed to be local preemptive analgesia with local anesthetics in vaginal hysterectomy compared either to placebo or to no intervention at all. Major concomitant surgeries were excluded. Current PRISMA guidelines were followed (188).

2.1. Data sources and search strategy

MEDLINE (1946 to present), EMBASE (1974 to present), the Cochrane Central Register of Controlled Trials (CCTR) and the Cochrane Database of Systematic Reviews (CDSR) were systematically searched to identify relevant RCTs and SRs until 25th of September 2019. Subject headings as well as keywords for vaginal hysterectomy were combined with the ones for local preemptive analgesia, local anesthetics and filters for RCTs or SRs. No restrictions for date of publication were made before 25th of September 2019. Included texts had to be published full text articles which had been published either in English or German. Due to feasibility and also few expected articles and therefore relevance, all other languages were excluded.

Furthermore, after the initial literature search, all reference lists of qualified RCTS and SRs have also been screened and searched for articles which had been missed.

After receiving the full list of abstracts resulting from the search of the databases, two reviewers screened them independently using prespecified extraction templates. In the first step, all duplicate entries were removed individually and then the remaining list was compared among the two reviewers.
After this, all abstracts were screened individually and divided into two lists: relevant articles for inclusion and full-text screening and non-relevant abstracts for exclusion. After finishing the screening of all abstracts, those two lists were compared among each other and occurring conflict was resolved by consent. Finally, screening of the full texts started with the retrievement of all full texts of potentially relevant abstracts and screening was performed using the same strategy as before. Occurring conflict was resolved by consent and comparing the extracted data and, if this left open questions, by consulting a third party with more expertise.

Extracted data included information on the study type and methodology, country/place of the study, inclusion and exclusion criteria, participant demographics, number of participants, measured primary and secondary

outcomes and effects. The screening and selection process as well as the results were documented in spreadsheets and Excel documents (Appendix 1).

2.2. Study selection

This systematic review included only RCTs and SRs which strictly focused on the use of local preemptive analgesia applied before vaginal hysterectomy for any benign indication with the goal of postoperative pain reduction or decreased peri- and postoperative opioid requirement. The literature search was conducted until 25th of September 2019, just before the beginning of the systematic literature search and after finishing the protocol and PROSPERO registration.

It was specified that local preemptive analgesia in the RCT had to be compared to no local treatment or placebo. Laparoscopically assisted vaginal hysterectomies (LAVH) and laparoscopic hysterectomies as well as robotic and abdominal ones were excluded. For more homogenous data about the anesthetic and the effect on peri- or postoperative pain as well as peri- and postoperative opioid use, preemptive systemic interventions and spinal interventions for pain reduction were excluded. Included were studies with vaginal hysterectomy done for prolapse as well as those with concomitant adnexectomy or small prolapse repairs like anterior or posterior colporrhaphies, all other major concomitant surgeries were excluded. Sample size, country or date of publication have not been a limitation.

First, all abstracts were screened and each reviewer separately classified in an Excel sheet if the abstract should be included in the full-text screening because of matching the inclusion criteria, should be included because it cannot be ruled out for sure at this point or scan be excluded definitely without reading the full-text article.

Those results were compared and if disagreement appeared, a third party was consulted for clarification. After clarification, no open questions remained.

In the next step, the full-text screening included classifying the full-texts into either inclusion into the SR or exclusion due to one or more of the following reasons:

- Population: no women aged 18 years or older with vaginal hysterectomy included, nor any such subgroup
- Intervention: no local preemptive analgesia, not even as a subgroup
- Comparison intervention: no placebo administration (blinded) or no local analgesic treatment
- Outcome: no predefined endpoint reported
- Study design: no RCT
- Study design: no SR
- Study design: No human study
- Full-text: No full text publication available – for example conference abstracts
- Double publication: double publication without relevant additional information
- Publication language: full text was ultimately not available in an English- or German-language

After the articles were classified independently, results were compared and if disagreement appeared, a third party was consulted for clarification.
All data was summarized in a final Excel sheet and afterwards, primary and secondary end points of the remaining four RCTs were compared according homogeneity and comparability.

2.3. Data extraction and quality assessment

RCTs were assessed individually by the reviewers with the up-to-date version of the Cochrane Risk of Bias Tool (189) , which evaluates different fields of the structure of the RCT like: randomization, shift from intended interventions, outcome data and probably missing data, measurement of the outcome and

presentation of the reported result. It was not necessary to categorize the different interventions according to their location of application because only local procedures were included. Nevertheless, classification of the interventions according to their comparison to placebo or no local treatment as well as patient characteristics and intervention details such as infiltration site, used local anesthetic and volume as well as the anesthesia protocol, was made if available.
Two members of the gynecology department performed the systematic review of the literature in collaboration with specialized methodologists from the department of General Medicine and Evidence Based Medicine and Research.

2.4. Planned analysis

The summarization and processing of the results of the included RCTs was planned in form of a meta-analyses, where for continuous data standardized mean differences and relative risks (RR) for dichotomous data would have been calculated.
In corporation with the Institute of General Practice and Evidence-based Health Services Research of the Medical University of Graz a primary comparison of the end points was conducted.

At this point it became obvious that the planned meta-analysis was not possible due to diverse timepoints and conditions while measurement of the outcomes and the small remaining number of studies included after exclusion of all unsuitable studies. After this was confirmed, discussed and coordinated with the statisticians of the Medical University of Graz, the results of the studies could only be analyzed descriptively.

Therefore, a descriptive analysis in regard of primary and secondary outcomes, study design, timepoints for measurement of the pain scores as well as pain scales used, anesthetic protocol and results was conducted.
Pain scores were compared among all studies as well as used local anesthetic

in regard of pharmacological effects and possible differences. Results were compared with the two included SRs and then summarized in tables using Microsoft Word (Version 16.58 for Mac).

Simultaneously, a publication was submitted in 2020 with acceptance and publication in December 2021 in the *International Urogynecology Journal* and is available under: https://link.springer.com/article/10.1007/s00192-021-04999-1.

3. Results

The database search retrieved seven hundred and thirty-three abstracts for abstract screening and after removal of the duplicates, five hundred and thirty-nine abstracts remained. After screening, only forty-four studies were selected for full-text screening and further assessment.

Due to the strict focus on preemptive local analgesia in vaginal hysterectomy in the end only four RCTs which included a total of 197 patients and two SRs remained for final inclusion (Figure 1). Each one of the chosen RCTs compared local preemptive analgesia with placebo by applying a different local anesthetic before vaginal hysterectomy.

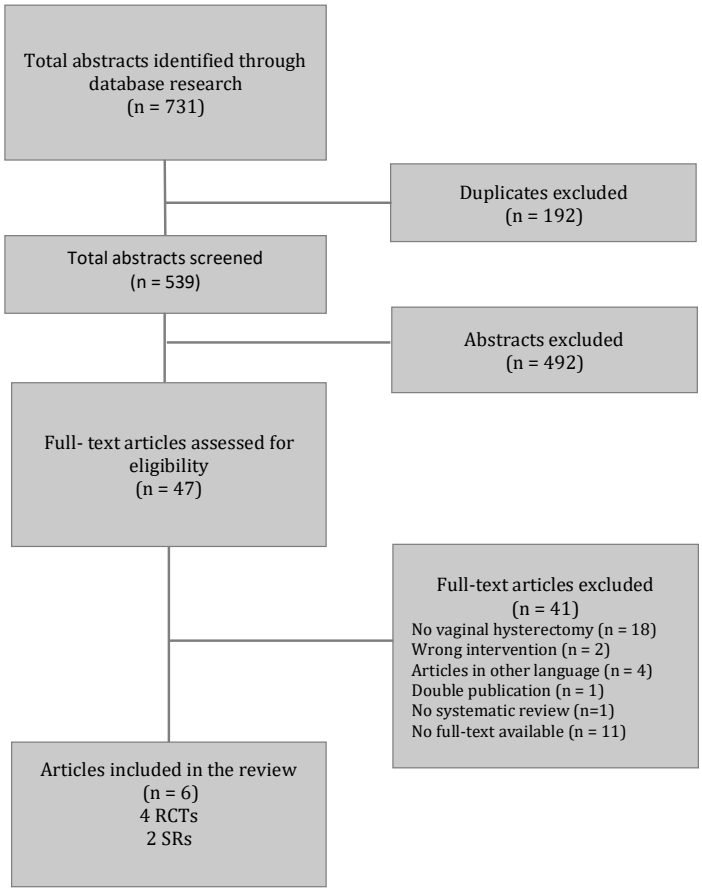

Figure 14 Literature selection process (1)

3.1. Main outcome

Table 1 and 2 sum up all key features of the included studies. All outcomes as well as significant ones and the different study characteristics are displayed accordingly.

Primary outcomes have been defined as postoperative pain measured with different scales in all four studies.
For the structured measurement of the postoperative pain scores, either the visual analogue scale (VAS) or the verbal analogue pain score from 0 to 10 was applied. Those time points of pain score measurement were predefined and stretched from 30 minutes (min) until 32 hours (h) postoperatively. Two out of four studies assessed postoperative pain only at rest for a primary end-point, one defined primary end-point as pian while resting and coughing, and one specified primary outcome as postoperative pain intensity while coughing.
The two included RCTs which assessed pain during rest were able to demonstrate significant reduction in postoperative pain scores reaching from thirty min up to six hours postoperatively.
Accordingly, evaluated pain scores during coughing were also significantly lower at one and four hours after surgery in the groups receiving local preemptive analgesia (Table 2).

Table 1.
Study characteristics and significant results

Authors	Study type	N	Surgery	Medication	Injection Technique	Comparison	Baseline medication	VAS or NRS pain score	Postoperative opioid consumption (24h)	Conclusion
O'Neal et al. (11)	Randomized, double-blind, placebo-controlled trial	20	VH	20 ml 0.5% bupivacaine with 1:200.000 epinephrine	Five milliliters were injected at the 3, 5, 7, and 9 o'clock positions of the cervicovaginal junction	20 ml 0.5% saline with 1:200.000 epinephrine	No information regarding preoperative pain medication or anesthesia protocol. Morphine patient-controlled analgesia (PCA) at the post-anesthesia care unit (PACU). Ketorolac for breakthrough pain.	1.7 vs. 3.3 (4h) 1.8 vs. 3.6 (6h) *p = 0.003*	22 mg vs. 37 mg *p = 0.01*	Significant decrease in pain scores and reduction in morphine requirements in the first 24 hours after surgery.
Long et al. (10)	randomized, double-blind, placebo-controlled trial	90	VH	20 ml 0.5% bupivacaine with 1:200.000 epinephrine	10 ml (5 ml into each uterosacral ligament) in a paracervical block fashion using a 22-gauge needle 4 min prior to initial incision. Additional 10 ml (5 ml into each uterosacral ligament) was injected into the more proximal uterosacral ligaments just prior to placement of McCall culdoplasty sutures.	20 ml 0.5% saline with 1:200.000 epinephrine	Routine preoperative administration of famotidine and dexamethasone. General anesthesia: fentanyl 2 µg/kg and propofol 2 mg/kg, nitrous oxide 70%, sevoflurane and additional fentanyl as needed. At conclusion, either ketorolac and/or ondansetron were administered. Postoperatively, patients were given narcotics, ketorolac and antiemetics as needed.	2.5 (3.1) vs. 4.4 (3.0) (30 Min) *p = 0.003* 2.4 (2.4) vs. 3.6 (2.0) (3h) *p = 0.02*	16 mg vs. 23 mg *p = 0.009*	Significant decrease in pain scores after 30 minutes and 3h after surgery. Significant reduction of opioid use over 24h.
Hristovska et al. (12)	randomized, double-blind, placebo-controlled trial	37	VH	30 ml ropivacaine 0.5%	30 mL was injected in a systematic fashion as a modified paracervical block. First, 5 mL was injected through the vaginal fornices at 02.00, 04.00, 06.00, 08.00, 10.00 and 12.00 hours at 2 cm depth while the needle was retracted.	30 ml saline	Routine preoperative administration of celecoxib 400 mg and slow-release paracetamol 2 g. General anesthesia: propofol 2–3 mg/kg and remifentanil 0.5 lg/kg/min, continuous infusion of propofol 10 mg/mL, 4–6 mg/kg/h and remifentanil 2 mg, 0.25–0.5 lg/kg/min. PACU: Sufentanil 5 lg until the VAS was ≤3. Ward: celecoxib 200 mg/12 h and slow-release paracetamol 2 g/12 h, as well as oral oxynorm 5 mg on request if the VAS was ≥5.	Resting: 10 (0-35) vs. 60 (30-90) (1h) 15 (0-52) vs. 45 (17-80) (4h) 19 (4-45) vs. 40 (8-53) (8h) *p ≤ 0.001–0.01* Coughing: 10 (0-45) vs. 70 (30-96) (1h) *p = 0.001* 18 (0-77) vs. 50 (18-82) (4h) *p = 0.003*	10 mg vs. 25 mg *p ≤ 0.007*	Significant decrease in pain scores after 1h,4h and 8h at rest and 1h and 4h at coughing. Significant reduction in opioid consumption over 24h.
Athanasiou et al. (184)	randomized, double-blind, placebo-controlled trial	59	VH	30 ml ropivacaine 0.5%	infiltration of 30 ml ropivacaine 0.5% [5 ml in round ligament and 5 ml in uterosacral ligament bilaterally, and 10 ml in perineal body, while the placebo group received an infiltration of 30 ml placebo solution in the same fashion.	30 ml saline	CSE block was performed with 2.5 ml ropivacaine 0.75% plus 15 mg fentanyl. Preoperative administration of antibiotics, metoclopramide 10 mg, ranitidine 100 mg, diclofenac 75 mg and paracetamol 1 g. Postoperative PCA containing 40 mg morphine (0.5 mg/ml) plus 8 mg ondansetron (0.1 mg/ml) was used. All participants received metoclopramide 10 mg/12 h i. v., ranitidine 100 mg/12 h i.v., paracetamol 1 g/8 h i.v. and diclofenac suppository 75 mg/12 h. Additionally, ondasetron 4mg i.v. for nausea and vomiting.	Resting: 0.5 (0.1–7.2) vs. 1.1 (0.2–9.3) (2h) *p = 0.007* 1.3 (0.1–5.1) vs. 3.1 (0.1–9.8) (4h) *p = 0.02* Coughing: 0.9 (0.1–8.9) vs. 1.9 (0.1–10) (2h) *p = 0.03* 1.6 (0.1–4.7) vs. 3.2 (0.3–9.6) (4h) *p = 0.009*	4 mg vs. 7 mg *p = 0.02*	Significant decrease in pain scores 2h and 4h at rest and 2h and 4h at coughing. Significant reduction of opioid consumption over 24h after surgery.

Table 1 Important study characteristics (1)

Table 2.

All pain scores with significant results in bold

	Athanasiou et al.	**Hristovska et al.**	**Long et al.**	**O'Neal et al.**
	25 (IG) vs 25 (CG*)*	*20 (IG) vs 17 (CG)*	*45 (IG) vs 45 (CG)*	*9 (IG) vs 11 (CG)*
post OP time (h)	*Pain at rest (median VAS)*	*Pain at rest (median VAS)*	*Pain (mean VAS)*	*Verbal analog pain score*
0,5	-	-	**2.5 vs 4.4**	
1	-	**10 vs 60**	-	*5.3 vs 4.8*
2	**0.5 vs 1.1**	*20 vs 35*	-	*3.4 vs 4.9*
3	-	-	**2.4 vs 3.6**	*3.1 vs 4.6*
4	**1.3 vs 3.1**	**15 vs 45**	-	**1.7 vs 3.3**
6	-	-	-	**1.8 vs 3.6**
8	*1.3 vs 2.6*	**19 vs 40**	-	-
12	-	*24 vs 29*	*3.0 vs 2.7*	-
24	*0.5 vs 0.6*	*2 vs 2*	*2.2 vs 2.0*	*1.4 vs 1.7*
32	-	*no data*	-	-
	Pain during cough (median VAS)	*Pain during cough (median VAS)*	-	-
1	-	**10 vs 70**	-	-
2	**0.9 vs 1.9**	*22 vs 35*	-	-
4	**1.6 vs 3.2**	**18 vs 50**	-	-
8	*1.7 vs 4*	*20 vs 46*	-	-
12	-	*29 vs 38*	-	-
24	*0.5 vs 1*	*19 vs 20*	-	-
32		*no data*	-	-
	VAS ≥ 4 (n/N)	**-**	**VAS = 0 (n/N)**	**-**
0,5	-	-	*25/45 vs 11/45*	-
2	*1/25 vs 8/25*	-	-	-
3	-	-	*14/45 vs 6/45*	-
4	*4/25 vs 11/25*	-	-	-
8	*3/25 vs 10/25*	-	-	-
12	-	-	*12/44 vs 13/45*	-
24	*2/25 vs 1/25*	-	*16/44 vs 14/45*	-

*IG: Intervention group
*CG: Control group

Table 2 Pain scores, significant ones in bold (1)

3.2. Indications for hysterectomy

Vaginal hysterectomy done for vaginal prolapse was excluded as indication in one RCT (11), another RCT included vaginal hysterectomies done for vaginal prolapse (13), one RCT included only vaginal hysterectomies done for prolapse (190) and one RCT is unclear on the exact indications, just stating that they were benign (12).

3.3. Local anesthetic agent applied

Two out of the four included RCTs compared 30 milliliters of 0.5% ropivacaine to placebo (13,190) whereas the other two RCTs compared 20ml of 0.5% bupivacaine in combination with 1:200,000 epinephrine to placebo infiltration (11,12).

3.4. Mode of Anesthesia

In three of the RCTs, vaginal hysterectomies were performed with general anesthesia GA (11–13). The perioperative anesthetic protocol was not described in detail in these three studies, but postoperative analgesia included opioids and, in two studies, ketorolac.

One RCT, being also the most recent published one, used a CSE block. Postoperative analgesia included patient-controlled analgesia (PCA) with morphine and antiemetics (190).

From clinical routine it is known that a standardized anesthetic protocol sometimes is difficult to implement because of patient's individual characteristic as well as anesthetist preferences. Nevertheless, at least three RCTs used the same route of anesthesia all four applied postoperative morphine.

3.5. Time points of postoperative pain score measurement

All four RCTs evaluated multiple postoperative pain scores at different predefined postoperative time points. Those time points ranged from 30min until 24h postoperative in both groups. Although not one time-point could be found where pain scores were evaluated, all four studies found a homogenous reduction in postoperative pain scores from 30 min up to 8 hours postoperatively. The duration is probably explainable due to the known half-life of the applied local analgesics in the studies and explains why this effect receded after 8 hours.

3.6. Other outcomes

Intraoperative blood loss, length of hospital stay, different kinds of adverse events, overall duration of surgery, PONV as well as time to first mobilization were all predefined secondary outcomes which have been assessed in the included studies. None of the predefined, above mentioned secondary outcomes showed a significant difference in-between the two study groups. Factors like Quality of Life (QoL), rate of readmission as well as differences in perioperative care protocols or outcomes have not been evaluated by any of the included studies. Therefore, no statement can be made on behalf of those.

Those RCTs which assessed pain at rest or during movement as secondary outcomes could show a significant reduction in pain scores up to 8 hours postoperatively.

3.6.1. Postoperative opioid requirements

All four studies assessed postoperative opioid requirement and overall opioid use. All fours RCTs found a significant decrease in morphine-controlled patient analgesia and/or overall opioid requirements in the group receiving local preemptive analgesia up tot 24 hours postoperatively.

3.6.2. Risk of Bias

The Cochrane Risk of Bias Tool (189) was used to evaluate all four included studies. Three of them (11,13,190) achieved to reach a low risk of bias with clear methods, study design and outcomes.

Only one out of the four studies included (12) was defined as high risk of bias because of unspecific descriptive statistical analysis and lacking information on different statistical features such as confidence intervals and whether means or medians were reported in the figures. The authors displayed all evaluated pain scores in only one figure which showed that the greatest gab in pain scores appeared after four and six hours. There was no more information on the used statistical methods. We analyzed the data and the figure together then concluded, that the columns of the figure are most likely the means of the evaluated pain scores.

3.7. Conclusions of the two included SRs

The conclusion of the two included SR, which addressed non-opioid pain management in benign minimal invasive hysterectomy and preemptive analgesia in all minimal invasive gynecologic surgery, are in line with our results. However, this topic was only addressed as small part of their research question (157,173).

4. Discussion

This SR assessed local preemptive analgesia at the time of vaginal hysterectomy. We were able to include four RCTs which enrolled nearly two hundred randomized patients and two SRs at the end of literature selection (11–13,157,173,190). According to our information at the time, this is the first systematic revied addressing this specific research question.

The challenge of improving perioperative patient care is, among reduction of complications, PONV and other predefined goals, to minimize postoperative pain. This is a goal of ERAS concepts and guidelines (143,165), and general perioperative care in gynecologic surgery and recommended by various guidelines and societies (10,55,117,152,185,191,192).
Optimizing postoperative and general pain control has always been an important issue, but since the 1990s when organizations, such as the American Pain Society, started to realize that optimal pain management as an important factor of good patient care, it gained even more attention (186). As postoperative pain plays a significant role in patients' recovery, it is critical for healthcare professionals to also understand patients´ concerns regarding postoperative pain. Despite many changes in the inpatient and outpatient setting over the last decades, adequate postoperative pain control is still an issue.

Even though postoperative pain is predictable, well treatable if recognized and can be anticipated properly, if its treatment is inappropriately, it can lead to decreased QoL as well as to increased morbidity and health care costs (193). Poor postoperative pain control is associated with increased readmissions, visits to the outpatient clinic and emergency department as well as prolonged hospital stay (194,195). Moreover, complications such as thromboembolic events, pneumonia, failure of tissue repair as well as psychological issues are more likely to manifest in these patients (173,193). Earlier studies showed that high pain scores after surgery can lead to decreased QoL in patients, delay their rehabilitation and mobilization and chronification of pain (196).

Pain management in women can differ from pain management in men. Women tend to have higher acute pain scores (197), may need different medication than men (198) and are more likely to develop chronic postoperative pain (199,200). This is especially important as gynecologic and obstetric procedures still belong to the operations with the highest acute pain scores (196).Therefore, specific strategies and regimes need to be developed and implemented to either manage or preferably prevent postoperative pain.

ERAS has been one of the developed strategies which aim to, among other goals, reduce postoperative pain by introducing a multimodal perioperative, opioid sparing, pain management (201). This concept has been incorporated in many different surgical specialties nowadays, including gynecology, gynecologic oncology and also obstetrics (81,135,143,149,191).

One part of multimodal perioperative, opioid sparing, pain management is the implementation of preemptive local analgesia. According to earlier studies, preemptive peripheric blocks have shown a positive effect in terms of perioperative pain control. Furthermore, there seems to be also a positive and preventive long-lasting effect when it comes to chronic postoperative pain. By establishing an adequate afferent blockade before any painful stimulus to the body, for example before the surgical incision, the nociceptive barrage is reduced which leads to central sensitization and subsequent development of chronic pain (202).
The most common agents used for preemptive local anesthesia are lidocaine, bupivacaine, and ropivacaine (162,203). The goal is to block the sodium channels of the nerves however, one limitation of the effectiveness of the analgetic effect of all local analgetic agents is the duration of the analgesic effect. This is different for every agent and can be modified by either combining two agents or adding an additive such as epinephrine (162).

One of the most important features of a local anesthetic is to alterably stop the nerve impulses and produce a sensory or motor blockade with the goal of efficient anesthesia

during and after surgery. This should result in lower doses of peri- and postoperative analgesic, and resulting opioid, need of the patient (186,204).
Local agents used in the included studies were either 0,5% ropivacaine without an additive (13,190) and 0.5% bupivacaine combined with 1:200,000 epinephrine (11,12) without one being superior to the other because the ideal combination as well as the ideal additive still need further investigation (203).

In light of the ongoing opioid crisis in the United States,, opioid sparing perioperative pain management is essential and should be favored whenever possible (185,205). Because of the efforts to properly treat pain in patients, beginning in the 1990s, systemic application of pain medication has led to an enormous increase of opioid prescriptions in the U.S. (186).
One reason for this were recommendations for better pain management, which led to dramatic increases in opioid prescriptions, resulting in 259 million prescriptions by American physicians for opioids in the year 2012 (186,206). This, among other factors, lead to the fact that in 2017, 91 Americans each day died from an opioid overdose, and the majority of these overdoses where associated prescribed opioids (207).
In laparoscopic and abdominal hysterectomy, local infiltration of the incision site has proven helpful in decreasing postoperative pain scores which lead to clinical implementation of the practice (166–169). As vaginal hysterectomy is the most common approach in hysterectomies for benign indications in Austria, standardized local preemptive analgesia as part of a multimodal pain concept seems plausible and desirable, given its easy implementation.

A statistically significant decrease in the reported postoperative pain scores of the treatment group has been used has been demonstrated in each one of the four included studies. The reduction of postoperative pain after application of local preemptive analgesia in form of a paracervical block was statistically significant at different times of measurement, reaching from thirty minutes up to eight hours postoperatively. Furthermore, there was a statistically significant reduction in postoperative opioid requirement up to 24 hours postoperatively.

The known half-life of the used local anesthetic agents however manages to explain why the positive effect of better postoperative pain control is only seen in the first 8 hours after surgery. As a result, this effect is only quantifiable on the day where surgery is performed and not afterwards. Being consistent with the used local anesthetic agents and their known half-life, it explains the absence of difference regarding hospitalization in-between both groups (208,209). This has also been investigated as a secondary outcome by two out of four studies (11,13).
Pain at rest was evaluated in all four RCTs whereas pain during coughing and walking, a surrogate for pain during any movement, was assessed by only two of the four RCTs (13,190). Although those scores may not be comparable to those during rest, the significant reduction in those scores is especially important as this equals less postoperative opioid consumption and faster mobilization , preventing thromboembolic complications and speeding up recovery (13).

Regarding the findings of other secondary outcomes, no statistically significant difference concerning either PONV nor opioid related adverse events like nausea, vomiting or sedation has been demonstrated (13,190). Although those results were consistent in all four studies, the statement is not sufficiently informative due to the quite small number of cases of the study population. To further evaluate these secondary outcomes, larger RCTs with a larger number of included patients would be necessary.

When assessing the outcomes of postoperative pain and postoperative opioid requirement, their statistically significant reduction was clinically measurable, but nevertheless was the overall number of randomized study participants in the RCTs, as mentioned earlier, rather small.
Still, all reported postoperative pain score values had a mean and/or median below 45 millimeters on the VAS scale with the exception of the reported pain scores of Hristovska et al. (13). When it comes to postoperative pain scores, it is not only important if they can be reduced, but that a reduction is clinically relevant.
The different cut-offs for either mild, moderate or severe pain on the VAS scale range from 30, 70 and 100 mm (210) to 44, 74 and 100 mm (211). Nowadays, there is a

consensus based on multiple studies, different statements and guidelines that a VAS of ≤ 33mm postoperatively should be achieved when patient-controlled analgesia is used. Those scores are considered to be tolerable in case of postoperative pain right after surgery (210). According to this definition, a large proportion of the included patients already have sufficient and very good postoperative pain control, even without preemptive analgesia. The reasons for this observation could either be a good perioperative pain regimen, minimal invasive techniques or a combination of both.
However, a reduction of 1 cm of postoperative pain on the ten centimeter VAS scale has been stated to be clinically significant and this has been achieved in almost all significant pain reduction scores (210).

The RCT done by Athanasiou et al. (190) included only patients who underwent surgery due to vaginal prolapse and general anesthesia was replaced by a combined with spinal-epidural block (CSE) which makes the results harder to compare. This was also pointed out as a limitation in their study as they stated that the PCA allowed the patient administration of morphine ad libidum, which could have masked the effect of the administered ropivacaine.
Regarding their results, first the overall opioid requirement in the treatment group was significant lower up to 24h postoperatively. Second, they achieved to show a statistically significant reduction of patients who reported higher pain scores up to 8 hours after surgery in the treatment group. And third, the reported reduction of postoperative pain scores was seen seen up to 8 hours after surgery in the treatment group, whereas it was only clinically meaningful up to 4 hours postoperatively.
Concerning the effect of postoperative pain reduction up to 8 hours after surgery, this can be explained by the length of the sensory block of the used anesthetic agent which is stated as lasting approximately 6-10 hours (13,212). Although there was a tendency towards a lower number of reported opioid related side-effects in the study group, the numbers were not statistically significant and the effect is probably explainable the general application of antiemetics and intravenous NSAIDs (190).
Furthermore, they evaluated a second primary endpoint. Besides the assessment of postoperative pain scores, also the percentage of patients reporting moderate or severe postoperative pain, defined as a VAS score ≥ 4 on a 10cm VAS scale, was

assessed. The number of patients who have reported moderate or severe pain scores was significantly lower in the treatment group with a reduced likelihood of up to 90% (190).

Hristovska et al. (13) applied bupivacaine as anesthetic agent for the paracervical block and their results also showed significant lower postoperative pain scores in the treatment group up to 8 hours postoperatively. This is in agreement with the known effective period of bupivacaine (212).
Although they also found a decrease in postoperative opioid requirement, the opioid-related side-effects in the treatment group did not differ from those in the non-treatment group. In contrast, the reported postoperative pain scores reached a median VAS of 60mm at rest and 70mm while coughing, which - by definition - is referred to as moderate postoperative pain (13). These were considerably higher scores compared to the other three included studies. No obvious reason could be found in the published study protocols or data however, it can be assumed that there was some difference between this study and the other three. All other three studies together included a total of 160 patients and reported similar postoperative pain scores. Therefore, we assumed that there was either a difference in the surgical method or that the applied perioperative pain as well as anesthetic management must have been different.

The RCT with the largest number of 90 randomized and included patients (11) applied 20 ml of 0.5% bupivacaine combined with 1:200.000 epinephrine.
One the one hand, postoperative pain scores decreased significantly in the treatment group up to 3 hours postoperatively and a statistically significant reduction in opioid consumption has been reported in the first 24 hours after surgery. Opioid-related adverse events have not been evaluated therefore a statement about a possible trend is not possible.

The discussion about the clinically relevant change of postoperative pain scores measured on the VAS scale has been going on for years now. A prospective observational study enrolling 224 patients suggested the minimal clinically important difference (MCID) to be 10 mm in the postoperative setting measured by the VAS scale

(210). However, up until today no validated and evidence-based recommendations exists on the MCID in the postoperative setting due to the heterogenous nature of surgical procedures, preexisting disorders and individuality of patients (213).
According to the reported postoperative pain scores in these RCTS, it seems that most patients nowadays undergoing vaginal hysterectomy for benign indications already have sufficient and satisfying postoperative pain control, with or without local preemptive analgesia. The reported medians and means of the included studies were 3.1, 4.5, 3.6 and 3.3 points between 3 and 4 hours postoperatively, meaning that almost all included patients reported postoperative pain scores that can be considered as acceptable by definition (210).
However, when only assessing the reported medians and means of 1.3, 1.5, 2.4 and 1.7 of the treatment group in each RCT, those values are significantly lower than in the control-group. Furthermore, the proposed MCID of at least one point on the VAS scale could be reached in all four RCTs highlighting the benefit added by preemptive local analgesia.

All four studies in this systematic review reported and stated less postoperative opioid requirement during the first 24 hours postoperatively (11–13,190). Surprisingly, the adverse events due to morphine consumption did not differ between the groups. This could be explained by the rather small number of patients and therefore, insufficient power to show a difference in that matter. The second possible explanation for this missing effect could be the standard and sometimes prophylactic systemic administration of antiemetic agents and NSAIDs, which nowadays is often considered a standard and was also described in the included studies (11,190).

Not only in behalf of the current opioid crisis but also due to the aim of better postoperative pain control on gynecologic patients, multiple studies and alterations in recommendations on postoperative pain management have been performed. Those concepts and results led to the implementation of different shared decision-making models (181) as well as quality-improvement intervention protocols (214) and furthermore, to shifts in discharge regimes in minimal invasive surgeries in gynecologic patients and also in other surgical specialties (185), just to name a few of them.

The general recommendations and systemic approaches to a multimodal analgesic regime nowadays consists of different systemic application of analgetic agents such as acetaminophen, anti-inflammatory drugs like NSAIDs and/or gabapentin (101,144,171,172,205,215,216).

Our results concerning the beneficial use of local preemptive analgesia on form of a paracervical block at the time of vaginal hysterectomy for benign indications are in accordance with the conclusions with the findings of Blanton et al. and Long et al. (157,173).

4.1. Strengths

We performed a systematic review that is the first one to evaluate the benefit of this simple and low-cost intervention in one of the most often performed operations in gynecology with a clear result. The focus lays on a single analgetic intervention, preoperative and therefore preemptive infiltration of a local anesthetic in the regime of multimodal perioperative analgesia which improves patient outcomes in terms of postoperative pain as well as postoperative opioid us. Regarding bias and quality assessment of the included studies, a validated tool of the Cochrane Collaboration was used to secure quality.
Given the frequency of vaginal hysterectomy, optimization and improvement of postoperative pain control as well as reduction in opioid requirement are relevant topics.

4.2. Limitations

The results of our systematic review are limited by the studies we were able to include. Our review included only four RCTS with a total of less than 200 patients and therefore the primary intended meta-analysis was not possible due to heterogeneity of the

evaluated end-points of the included studies. We observed the absence of standardized measurement of postoperative pain scores and scales as well as different time-point where pain scores were evaluated and different analgetic regimens and applied anesthetic agents. Therefore, it was not possible to conduct a meta-analysis.

4.3. Conclusion

The results and conclusions from the four included studies, whereas three out of four being of good quality, show and verify the benefit of local preemptive analgesia as a paracervical block at the time of vaginal hysterectomy. It is a straightforward, easy to apply and low-cost procedure that achieves lower postoperative pain scores and a decrease in postoperative opioid requirement. However, the rather low number of included patients suggests the need for further randomized controlled trials which is also in accordance with the conclusions of the two other SRs included which have already pointed out the urgent need for further evidence on local preemptive analgesia in minimally invasive hysterectomies, including vaginal hysterectomies (217).

Nevertheless, national and international guidelines nowadays are already clear and in line with the recommendation of the vaginal approach for hysterectomy in benign cases whenever feasible (3,5,53,192). When performing a vaginal hysterectomy, consensus exists that multimodal analgesia protocols should be followed to preferably reduce postoperative opioid requirement on the one hand and enhance postoperative pain control on the other hand to speed up patient recovery according to published fast-track pathways (218) and ERAS protocols (6,58,69,144).

Given the easy application and procedure as well as the good cost-benefit relation, local preemptive analgesia in vaginal hysterectomy should be applied as is it is an easy and yet very effective way to gain better postoperative pain control in gynecologic patients undergoing vaginal hysterectomy for benign indications and to reduce postoperative opioid requirement at the same time.

However, none of the included RCTs performed the paracervical block with a long-acting, liposomal-bound anesthetic agent. Therefore, the lack of difference in hospital stay may be explainable by this fact and make the use of a long-acting, liposomal-bound anesthetic agent in local preemptive analgesia in form of a paracervical block an interesting topic for possible future research.
Up until today, one RCT published in the year 2018 by Jones et al. has compared long-acting liposomal bupivacaine vs. placebo for patients undergoing posterior vaginal wall surgery. The study found no statistically significant reduction neither in postoperative pain control nor in postoperative opioid requirement in the treatment group (174).

Therefore, no studies in vaginal hysterectomy using a long-acting, liposomal-bound agent which became available in 2011 in the United States and later in 2021 in Europe, have been conducted. Because of the longer half-life of those agents, it would be, among others, interesting to assess if the missing effect on postoperative hospitalization with the short-acting agents can be shown when a long-acting agent is used. This could, besides possible reduction of postoperative pain, also reduce costs.

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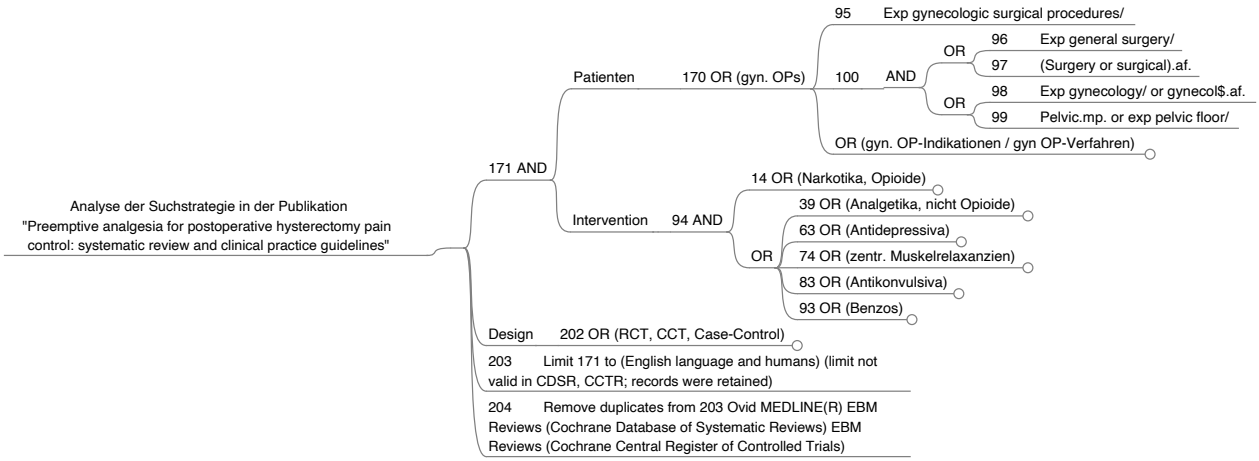
6. Anhang


Analyse der Suchstrategie in der Publikation "Preemptive analgesia for postoperative hysterectomy pain control: systematic review and clinical practice guidelines"
171 AND
Patienten
170 OR (gyn. OPs)
95 Exp gynecologic surgical procedures/
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96 Exp general surgery/
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99 Pelvic.mp. or exp pelvic floor/
OR (gyn. OP-Indikationen / gyn OP-Verfahren)
Intervention
94 AND
14 OR (Narkotika, Opioide)
OR
39 OR (Analgetika, nicht Opioide)
63 OR (Antidepressiva)
74 OR (zentr. Muskelrelaxanzien)
83 OR (Antikonvulsiva)
93 OR (Benzos)
Design
202 OR (RCT, CCT, Case-Control)
203 Limit 171 to (English language and humans) (limit not valid in CDSR, CCTR; records were retained)
204 Remove duplicates from 203 Ovid MEDLINE(R) EBM Reviews (Cochrane Database of Systematic Reviews) EBM Reviews (Cochrane Central Register of Controlled Trials)

Literature selection after abstract screening

Reference ID	Reviewer A	Reviewer B	Reviewer A	Reviewer B	Notes	Reference ID	Author	Year	Title	Journal	Vol (Issue) Page	
6	10	10	10	10	no results posted	6	Nct	2019	*Liposomal Bupivacaine in Vaginal Hysterectomy*	Https://clinicaltrials.gov/show/nct03907033		http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=cctr&AN=CN-01912113
13	0	0	0	0	downloaded	13	Athanasiou, S	2019	*Intraoperative local infiltration with ropivacaine 0.5% in women undergoing vaginal hysterectomy and pelvic floor repair: Randomized double-blind placebo-controlled trial*	European Journal of Obstetrics, Gynecology, & Reproductive Biology	236 (154-159)	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=prem&AN=30927707
15	8	8	8	8	downloaded	15	Suh, C	2018	*Enhanced recovery after surgery (eras) for benign minimally invasive gynecology*	Obstetrics and Gynecology	Conference: 66th Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists. United States. 131 (Supplement 1) 41S-42S	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emexa&AN=622555816
21	1	1	1	1	downloaded	21	Moon, A	2018	*Enhanced Recovery after Surgery (ERAS) in Gynecologic Surgery-A Review*	Current Obstetrics and Gynecology Reports	7 (3) 122-132	http://www.springer.com/medicine/gynecology/journal/13669 http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emexa&AN=623141275
24	10	10	10	10	kein Volltext/Publikation	24	Eutr, GR	2018	*Study of efficacy of ibuprofen vaginal solution*	http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2018		http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=cctr&AN=CN-01904920
29	1	1	1	1	downloaded	29	Sandberg, EM	2017	*Total Laparoscopic Hysterectomy Versus Vaginal Hysterectomy: A Systematic Review and Meta-Analysis. [Review]*	Journal of Minimally Invasive Gynecology	24 (2) 206-217.e22	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med13&AN=27867051
33	10	10	10	10	recruiting completed, finde noch kein paper	33	Nct	2017	*Local Analgesia to Prevent Pain in Patient Undergoing Removal of the Uterus Through Vaginal Route*	Https://clinicaltrials.gov/show/nct03099720		http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=cctr&AN=CN-01563086
34	10	10	10	10	recruiting	34	Nct	2017	*The Effect of Local Anesthesia on Postoperative Pain in Vaginal Hysterectomy*	Https://clinicaltrials.gov/show/nct03268525		http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=cctr&AN=CN-01496242
42	10	10	10	10	results overdue lt hp	42	Isrctn	2017	*Role of analgesia given in the peritoneum and through the site of wound before the end of operation in patients undergoing removal of undescended uterus through the vaginal route*	http://www.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN59760944.		http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=cctr&AN=CN-01850417
51	0	0	0	0	downloaded	51	Blanton, E	2017	*Non-opioid pain management in benign minimally invasive hysterectomy: A systematic review. [Review]*	American Journal of Obstetrics & Gynecology	216 (6) 557-567	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med13&AN=28043841
89	0	0	0	0	downloaded	89	Hristovska, AM	2014	*Effect of systematic local infiltration analgesia on postoperative pain in vaginal hysterectomy: a randomized, placebo-controlled trial*	Acta Obstetricia et Gynecologica Scandinavica	93 (3) 233-8	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med10&AN=24576202
102	10	10	10	10	kein Volltext/Publikation	102	Eutr, GB	2013	*Trial to assess if pain after surgery to remove their womb via the vagina is reduced using local anaesthetic in addition to the usual general anaesthetic*	http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2013		http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=cctr&AN=CN-01864108
142	0	0	0	0	downloaded	142	Long, JB	2009	*Randomized trial of preemptive local analgesia in vaginal surgery*	International Urogynecology Journal	20 (1) 5-10	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med6&AN=18830553
150	10	10	10	10	recruiting completed, finde noch kein paper	150	Nct	2008	*Local Infiltration Analgesia With Ropivacaine Versus Placebo in Vaginal Hysterectomy: a Randomized, Double-Blind Study*	Https://clinicaltrials.gov/show/nct00768456		http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=cctr&AN=CN-01484902
151	11	11	11	11	downloaded	151	Long, JB	2008	Preemptive local analgesia in vaginal surgery	Journal of Pelvic Medicine and Surgery	Conference: 29th Annual Scientific Meeting of the American Urogynecologic Society. Chicago, IL United States. Conference Publication: (var.pagings). 14 (4) 239	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed10&AN=70011971

161					kein Volltext/Publikation	161	Nct	2006	*Preemptive Local Anesthesia in Vaginal Surgery*	Https://clinicaltrials.gov/show/nct00318292		http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=cctr&AN=CN-01481738
	10	10	10	10								
174	0	0	0	0	downloaded	174	O'Neal, MG	2003	*Utility of preemptive local analgesia in vaginal hysterectomy*	American Journal of Obstetrics & Gynecology	189 (6) 1539-41; discussion 1541-2	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med4&AN=14710057
177					ausgeschlossen da französisch	177	Clave, H	2003	*[Painless hysterectomy: an innovative technique]. [French]*	Journal de Gynecologie, Obstetrique et Biologie de la Reproduction	32 (4) 375-80	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med4&AN=12843887
			0	2								
199			0	2	ausgeschlossen da japanisch	199	Sato h, O	1994	*[Ar]. [Japanese]*	Masui - Japanese Journal of Anesthesiology	43 (8) 1212-5	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med3&AN=7933504
205	0	0	0	0	downloaded	205	Striebel, HW	1992	*[A comparison of a tramadol/metamizole infusion with the combination tramadol infusion plus ibuprofen suppositories for postoperative pain management following hysterectomy]. [German]*	Anaesthesist	41 (6) 354-60	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med3&AN=1636921
363	1		1		downloaded	363	Moulder, JK	2019	*Opioid Use in the Postoperative Arena: Global Reduction in Opioids After Surgery Through Enhanced Recovery and Gynecologic Surgery. [Review]*	Clinical Obstetrics & Gynecology	62 (1) 67-86	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=30407228
364	0	0	0	0	downloaded	364	Long, JB	2019	*Preemptive Analgesia in Minimally Invasive Gynecologic Surgery*	Journal of Minimally Invasive Gynecology	26 (2) 198-218	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=30064006
369	2	2	2	2	downloaded	369	Johnson, CM	2019	*A Systematic Review of Perioperative Opioid Management for Minimally Invasive Hysterectomy*	Journal of Minimally Invasive Gynecology	26 (2) 233-243	http://www.elsevier.com/wps/find/journaldescription.cws_home/704371/description#description http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emexb&AN=2001172694
370	1	1	1	1	downloaded	370	Grant, MC	2019	*Evidence review conducted for the AHRQ Safety Program for Improving Surgical Care and Recovery: focus on anesthesiology for gynecologic surgery*	Regional Anesthesia & Pain Medicine	07 07	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medp&AN=30737316
378	10	10	10	10	Abstract, kein Volltext (Kongress)	378	Raw al, N	2018	*Pro*	Regional Anesthesia and Pain Medicine	Conference: 37th Annual European Society of Regional Anaesthesia and Pain Therapy Congress, ESRA 2018. Ireland. 43 (7 Supplement 1) e10-e11	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emexa&AN=624139929
380	1	1	1	1	downloaded	380	Munro, A	2018	*Anesthesia and analgesia for gynecological surgery. [Review]*	Current Opinion in Anaesthesiology	31 (3) 274-279	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med13&AN=29474216
383	1	1	1	1	downloaded	383	Kenner, JL	2018	*ERAS in Minimally Invasive Gynecology: A Meta-Analysis of the Literature*	Journal of Minimally Invasive Gynecology	Conference: 47th American Association of Gynecologic Laparoscopists (AAGL) Global Congress on Minimally Invasive Gynecologic Surgery (MIGS). MGM Grand Conference Center, United States. 25 (7 Supplement) S51	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emexa&AN=2001201586
387	11	11	11	11	Duplikat	387	Doleman, B	2018	*Pre-emptive and preventive opioids for postoperative pain in adults undergoing all types of surgery*	Cochrane Database of Systematic Reviews	12 (CD012624)	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medc2&AN=30521692
396	1	1	1	1	downloaded	396	Steinberg, AC	2017	*Preemptive analgesia for postoperative hysterectomy pain control: systematic review and clinical practice guidelines. [Review]*	American Journal of Obstetrics & Gynecology	217 (3) 303-313.e6	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med13&AN=28351670
406	0	0	0	0	downloaded	406	Blanton, E	2017	*Non-opioid pain management in benign minimally invasive hysterectomy: A systematic review. [Review]*	American Journal of Obstetrics & Gynecology	216 (6) 557-567	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med13&AN=28043841
412	1	1	1	1	downloaded	412	Raw al, N	2016	*Regional anaesthesia and outcome: Infiltrative techniques*	Regional Anesthesia and Pain Medicine	Conference: 35th Annual European Society of Regional Anaesthesia and Pain Therapy Congress, ESRA 2016. Netherlands. 41 (5 Supplement 1) e9-e10	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed17&AN=612172890
415	1	1	1	1	downloaded	415	Miralpeix, E	2016	*A call for new standard of care in perioperative gynecologic oncology practice: Impact of enhanced recovery after surgery (ERAS) programs. [Review]*	Gynecologic Oncology	141 (2) 371-378	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med12&AN=26906066
417	0	0	0	0	downloaded	417	Kalogera, E	2016	*Enhanced Recovery Pathway in Gynecologic Surgery: Improving Outcomes Through Evidence-Based Medicine. [Review]*	Obstetrics & Gynecology Clinics of North America	43 (3) 551-73	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med12&AN=27521884

432						432	Raw al, N	2015	*Refresher course: Infiltrative techniques-the way forward inpostoperative pain management?*	Regional Anesthesia and Pain Medicine	Conference: 34th Annual European Society of Regional Anaesthesia and Pain Therapy Congress, ESRA 2015. Ljubljana Slovenia. Conference Publication: (var.pagings). 40 (5 SUPPL. 1) e18-e20	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed16&AN=72027043
	10	1	10	1	downloaded								
447						447	Bauchat, JR	2015	*Evidence-based anesthesia for major gynecologic surgery. [Review]*	Anesthesiology Clinics	33 (1) 173-207	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med11&AN=25701935
	1	1	1	1	downloaded								
465						465	Collins, SA	2014	*Pain management strategies for urogynecologic surgery: a review. [Review]*	Female Pelvic Medicine & Reconstructive Surgery	20 (6) 310-5	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med10&AN=25185632
	8	8	8	8	downloaded								
518						518	White, PF	2010	*Improving postoperative pain management: What are the unresolved issues?*	Anesthesiology	112 (1) 220-225	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed11&AN=358125566
	1	1	1	1	downloaded								
519						519	Werner, MU	2010	*Prediction of postoperative pain: A systematic review of predictive experimental pain studies*	Anesthesiology	112 (6) 1494-1502	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed11&AN=50909779
	1	1	1	1	downloaded								
521						521	Power, I	2010	*Regional anaesthesia and pain management. [Review] [79 refs]*	Anaesthesia	65 Suppl 1 (38-47)	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med7&AN=20377545
	1	1	1	1	downloaded								
534						534	Chelly, JE	2010	*Continuous peripheral nerve blocks in acute pain management. [Review]*	British Journal of Anaesthesia	105 Suppl 1 (i86-96)	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med7&AN=21148658
	1	1	1	1	downloaded								
551						551	D'Arcy, Y	2008	*First strike: does preemptive analgesia work?. [Review] [22 refs]*	Nursing	38 (4) 52-5	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med6&AN=18360248
	1	1	1	1	downloaded								
572						572	Bromley, L	2006	*Pre-emptive analgesia and protective premedication. What is the difference?*	Biomedicine and Pharmacotherapy	60 (7) 336-340	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed9&AN=44308577
	1	1	1	1	downloaded								
579					fällt raus da französisch	579	Bolandard, F	2005	*[Paracervical block]. [Review] [11 refs] [French]*	Annales Francaises d Anesthesie et de Reanimation	24 (3) 312-4	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med5&AN=15792574
611					russisch	611	Mizikov, VM	2000	*[New long-acting local anesthetic: ropivacaine hydrochloride (naropin)]. [Review] [86 refs] [Russian]*	Anesteziologiia i Reanimatologiia	(4) 72-7	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med4&AN=11014004
634						634	Levy, BS	1995	*Perioperative pain management. [Review] [24 refs]*	Journal of the American Association of Gynecologic Laparoscopists	2 (4) 381-7	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med3&AN=9050589
	1	1	1	1	downloaded								
670						670	Weinstein, EJ	2018	*Local anaesthetics and regional anaesthesia versus conventional analgesia for preventing persistent postoperative pain in adults and children*	Cochrane Database of Systematic Reviews	-6	http://dx.doi.org/10.1002/14651858.CD007105.pub4
	1	1	1	1	downloaded								
673						673	Doleman, B	2018	*Pre-emptive and preventive opioids for postoperative pain in adults undergoing all types of surgery*	Cochrane Database of Systematic Reviews	-12	http://dx.doi.org/10.1002/14651858.CD012624.pub2
	1	1	1	1	downloaded								

Final literature selection of included RCTs and SRs

13	0	0		0	0	downloaded	**13**	Athanasiou, S	2019	*Intraoperative local infiltration with ropivacaine 0.5% in women undergoing vaginal hysterectomy and pelvic floor repair: Randomized double-blind placebo-controlled trial*	European Journal of Obstetrics, Gynecology, & Reproductive Biology	236 (154-159)	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=prem&AN=30927707
51	0	0		0	0	downloaded	**51**	Blanton, E	2017	*Non-opioid pain management in benign minimally invasive hysterectomy: A systematic review. [Review]*	American Journal of Obstetrics & Gynecology	216 (6) 557-567	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med13&AN=28043841
89	0	0		0	0	downloaded	**89**	Hristovska, AM	2014	*Effect of systematic local infiltration analgesia on postoperative pain in vaginal hysterectomy: a randomized, placebo-controlled trial*	Acta Obstetricia et Gynecologica Scandinavica	93 (3) 233-8	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med10&AN=24576202
142	0	0		0	0	downloaded	**142**	Long, JB	2009	*Randomized trial of preemptive local analgesia in vaginal surgery*	International Urogynecology Journal	20 (1) 5-10	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med6&AN=18830553
174	0	0		0	0	downloaded	**174**	O'Neal, MG	2003	*Utility of preemptive local analgesia in vaginal hysterectomy*	American Journal of Obstetrics & Gynecology	189 (6) 1539-41; discussion 1541-2	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med4&AN=14710057
364	0	0		0	0	downloaded	**364**	Long, JB	2019	*Preemptive Analgesia in Minimally Invasive Gynecologic Surgery*	Journal of Minimally Invasive Gynecology	26 (2) 198-218	http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=30064006

Citation

Nadja Taumberger, Anna-Maria Schuetz, Karl Tamussino, Andrea Siebenhofer-Kroitzsch, Klaus Jeitler. Local preemptive analgesia at vaginal hysterectomy: a systematic review . PROSPERO 2020 CRD42020144709 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020144709

Review question

The primary objective of this study is to evaluate whether local preemptive analgesia at vaginal hysterectomy has an impact on postoperative pain, postoperative opioid requirements, readmission rates, perioperative management and quality of life.

Searches

We will systematically search MEDLINE (1946 to present), EMBASE (1974 to present), the Cochrane Central Register of Controlled Trials (CCTR) and the Cochrane Database of Systematic Reviews (CDSR) to identify relevant randomised controlled trials and systematic reviews. Subject headings and keywords for vaginal hysterectomy are suitably combined with those for local preemptive analgesia or local anesthetics as well as filters for randomised controlled trials or systematic reviews. No restrictions for date of publication will be used, included languages will be English and German. If the article has no published full text, we will exclude it. Furthermore, reference lists of eligible studies and review articles will also searched.

Types of study to be included

We will include randomised controlled trials and systematic reviews.

Condition or domain being studied

The efficacy and impact of local preemptive analgesia in women undergoing vaginal hysterectomy for benign and selected malignant indications with no major concomitant surgeries (salphingo-oophorectomy permitted). We will summarize the effect on postoperative pain, postoperative opioid requirements, readmission rates, perioperative management and quality of life as well as any other impact described.

Participants/population

Inclusion: Adult women undergoing vaginal hysterectomy
Exclusion: Vaginal hysterectomy including major concomitant surgeries

Intervention(s), exposure(s)

Local preemptive analgesia by local anesthetics

Comparator(s)/control

Placebo or no local treatment at all

Context

Main outcome(s)

The aim of the study is to summarize the existing data and results on local preemptive analgesia used with vaginal hysterectomy according to postoperative pain, postoperative opioid need.

Measures of effect

Postoperative pain and opiod need measured by standardized scales up to one week after surgery.

Additional outcome(s)

Perioperative management, readmission rate, Quality-of-life measured by validated questionnaires and side-effects

Measures of effect

Above mentioned additional outcomes measured by validated questionnaires in an appropriate time window according to surgery.

Data extraction (selection and coding)

Two reviewers will independently screen all abstracts resulting from the search in the databases and remaining after the removal of duplicate entries for their compliance with the inclusion criteria. Subsequently, all full texts of potentially relevant abstracts will be retrieved and screened in the same way. Any discrepancies will be resolved by consensus or by involving a third reviewer. The screening process and its results are documented in a spreadsheet.
Data extraction will independently be performed by two reviewers using prespecified extraction templates. Extracted data will include information on the study type and methodology, country/place of the study, inclusion and exclusion criteria, participant demographics, number of participants, measured outcomes and effects. Disagreements will be resolved by comparing the extracted data and if relevant information is missing, it will be requested from the original authors of the study.

Risk of bias (quality) assessment

To assess the quality of the randomised controlled trials we will use the current version of the Cochrane Risk of Bias Tool, which comprises the following domains possibly biasing the results: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result.
Two reviewers will assess the studies independently and any disagreement will be resolved by consensus or by involving a third person.

Strategy for data synthesis

If possible, we will combine the results of the included RCTs in meta-analyses. For continuous data standardised mean differences (SMD) will be calculated and relative risks (RR) for dichotomous data. Statistical heterogeneity between the included studies will be assessed using the I^2 statistic. A random effects model will be used to synthesize data in case of substantial heterogeneity ($I^2 > 50\%$). Otherwise, a fixed effects model will be applied.

Analysis of subgroups or subsets

Not planned.

Contact details for further information

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Organisational affiliation of the review

Medical University of Graz

www.medunigraz.at

Additional outcome(s)
Perioperative management, readmission rate, Quality-of-life measured by validated questionnaires and side-effects

Measures of effect
Above mentioned additional outcomes measured by validated questionnaires in an appropriate time window according to surgery.

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Analysis of subgroups or subsets
Not planned.

Contact details for further information
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Dr Anna-Maria Schuetz. Department of Gynecology, University clinic of Graz, Graz, Austria
Professor Karl Tamussino. Department of Gynecology, University clinic of Graz, Graz, Austria

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.
The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

28 April 2020

Athanasiou 2019	25 (T) + 25(P) Pat.	
pain at rest	VAS (median, min-max)	

	0.5 (0.1–7.2) vs. 1.1 (0.2–9.3)	2h post-OP

	1.3 (0.1–5.1) vs. 3.1 (0.1–9.8)	4h post-OP

	1.3 (0.2–8.4) vs. 2.6 (0.1–9.1)	8h post-OP

	0.5 (0–7) vs. 0.6 (0–5.5)	24h post-OP

	Pat. mit VAS >= 4 (n/N)	
	1/25 vs. 8/25	2h post-OP
	4/25 vs. 11/25	4h post-OP
	3/25 vs. 10/25	8h post-OP
	2/25 vs. 1/25	24h post-OP
pain during cough	VAS (median, min-max)	

	0.9 (0.1–8.9) vs. 1.9 (0.1–10)	2h post-OP
	1.6 (0.1–4.7) vs. 3.2 (0.3–9.6)	4h post-OP
	1.7 (0.2–8.5) vs. 4 (0.1–9.5)	8h post-OP

	0.5 (0.1–5.8) vs. 1 (0–6.4)	24h post-OP

	Pat. mit VAS >= 4 (n/N)	
	2/25 vs. 10/25	2h post-OP
	4/25 vs. 13/25	4h post-OP
	5/25 vs. 13/25	8h post-OP
	3/25 vs. 1/25	24h post-OP
morphine administration	mg (median, min-max)	
	1 (0–7) vs. 2 (0–6)	2h post-OP
		------
	3 (0–16) vs. 6 (0–18)	4h post-OP
	4 (0–16) vs. 7 (0–19)	8h post-OP
		------
	4 (0–17) vs. 7 (0–24)	24h post-OP

	Pat. using morphine (n/N)	
	20/25 vs. 19/25	2h post-OP
	15/25 vs. 20/25	4h post-OP
	14/25 vs. 19/25	8h post-OP
	12/25 vs. 14/25	24h post-OP
nausea	Pat. reporting (n/N)	
	3/25 vs. 5/25	2h post-OP
	3/25 vs. 4/25	4h post-OP
	3/25 vs. 7/25	8h post-OP

	3/25 vs. 1/25	24h post-OP
		------
vomiting	Pat. reporting (n/N)	
	0/25 vs. 1/25	2h post-OP
	2/25 vs. 4/25	4h post-OP
	1/25 vs. 4/25	8h post-OP

	2/25 vs. 2/25	24h post-OP
		------
intensity of sedation	VAS (median, min-max)	
	2 (0-10) vs. 0 (0–9)	2h post-OP
	5 (0-10) vs. 2 (0–9)	4h post-OP
	5 (0-10) vs. 2 (0–10)	8h post-OP
	0 (0-8) vs. 0 (0–7)	24h post-OP

Hristovska 2013	20 (T) + 17(P) Pat.	
pain at rest	VAS grafisch (median, IQR, 5th-95th perc.)	
	0 [0-0] (0-22) vs. 5 [0-19] (0-55); (-5)	pre-OP
	------	------
	10 [0-25] (0-35) vs. 60 [42-73] (30-90); (-50)	1h post-OP
	20 [4-31] (0-62) vs. 35 [16-50] (0-62); (-15)	2h post-OP
	------	------
	15 [1-29] (0-52) vs. 45 [30-59] (17-80); (-30)	4h post-OP
	------	------
	19 [10-34] (4-45) vs. 40 [26-48] (8-53); (-21)	8h post-OP
	24 [5-42] (1-64) vs. 29 [16-46] (3-54); (-5)	12h post-OP
	2 [0-3] (0-11) vs. 2 [1-4] (0-16); (0)	24h post-OP
	k.A.	32h post-OP
pain during coughing	VAS grafisch (median, IQR, 5th-95th perc.)	
	0 [0-8] (0-38) vs. 5 [0-19] (0-76); (-5)	pre-OP
	10 [0-34] (0-45) vs. 70 [49-80] (30-96); (-60)	1h post-OP
	22 [5-41] (0-68) vs. 35 [16-55] (0-76); (-13)	2h post-OP
	18 [1-35] (0-77) vs. 50 [30-73] (18-82); (-32)	4h post-OP
	20 [16-45] (11-69) vs. 46 [34-54] (4-63); (-26)	8h post-OP
	29 [6-50] (3-68) vs. 38 [26-56] (4-68); (-9)	12h post-OP
	19 [10-29] (0-36) vs. 20 [7-40] (0-49); (-1)	24h post-OP
	k.A.	32h post-OP
pain during walking	VAS grafisch (median, IQR, 5th-95th perc.)	
	0 [0-21] (0-59) vs. 10 [0-38] (0-71); (-10)	pre-OP
	k.A.	1h post-OP
	20 [10-40] (1-66) vs. 20 [0-60] (0-60); (0)	2h post-OP
	17 [6-30] (0-50) vs. 40 [29-60] (0-90); (-23)	4h post-OP
	27 [11-43] (5-54) vs. 40 [31-50] (8-65); (-13)	8h post-OP
	26 [10-40] (2-62) vs. 26 [13-60] (2-61); (0)	12h post-OP
	13 [9-31] (0-39) vs. 20 [6-29] (0-35); (-7)	24h post-OP
	k.A.	32h post-OP
sufentanil in PACU	µg (median, IQR)	
	10 µg (0–20) vs. 70 µg (40 –90)	
morphine administration	mg, kumulativ (median, IQR)	
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	10 mg (0–12.5) vs. 25 mg (10 – 31.25)	24h post-OP
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nausea	Pat. reporting (n/N)	
		(2h post-OP)
		(4h post-OP)
		(8h post-OP)
		(12h post-OP)
		(24h post-OP)
		(32h post-OP)
vomiting	Pat. reporting (n/N)	
		(2h post-OP)
		(4h post-OP)
		(8h post-OP)
		(12h post-OP)
		(24h post-OP)
		(32h post-OP)
time to first mobilization	time median (IQR)	
	2.0 h (2–3.6) vs. 4.0 h (3 –6)	
time spent in PACU	time median (IQR)	
	60 min (43–90) vs. 130 min (110 –180)	
length of stay	time median (IQR)	
	29 h (26–30) vs. 30 h (29 –50)	

Long 2009	45 (T) + 45 (P) Pat.	
pain	VAS (mean, SD)	
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	2.5 (3.1) vs. 4.4 (3.0)	0,5h post-OP
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	2.4 (2.4) vs. 3.6 (2.0)	3h post-OP
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	3.0 (2.6) vs. 2.7 (2.5)	12h post-OP
	2.2 (2.3) vs. 2.0 (2.0)	24h post-OP
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	Pat. mit VAS = 0 (n/N)	
	25/45 vs. 11/45	0,5h post-OP
	14/45 vs. 6/45	3h post-OP
	12/44 vs. 13/45	12h post-OP
	16/44 vs. 14/45	24h post-OP
total narcotic dose	mg, kumulativ (mean, SD)	
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	6.7 (6.6) vs. 13.2 (7.3)	3h post-OP
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	10.6 (9.3) vs. 18.6 (9.2)	12h post-OP
	16 (14) vs. 23 (12)	24h post-OP
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keterolac	Pat. getting keterolac (n/N)	
	36/45 vs. 37/45	
length of stay	days (mean, SD)	
	1.4 (1.5) vs. 1.4 (1.2)	

O'Neal 2003	9 (T) + 11 (P) Pat.	
pain score	"verbal analog pain score" grafisch (mean??; k.A.)	

	5,3 vs. 4,8 (+0,5) [CI??; Sig??]	1h post-OP
	3,4 vs. 4,9 (-1,5) [CI??; Sig??]	2h post-OP
	3,1 vs. 4,6 (-1,5) [CI??; Sig??]	3h post-OP
	1,7 vs. 3,3 (-1,6) [CI??; Sig??]	4h post-OP
	1,8 vs. 3,6 (-1,8) [CI??; Sig??]	6h post-OP

	1,4 vs. 1,7 (-0,3) [CI??; Sig??]	24h post-OP
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morphine in PACU	mg (??mean +/- ??SD)	
	4.7 ± 3.9 vs. 7.7 ± 5.0	time in PACU
morphine after discharge from PACU	mg (??mean +/- ??SD)	
	17.8 ± 8.7 vs. 29.8 ± 15.8	time after PACU
patient-controlled analgesia attempts	Pat. (mean, +/- ??SD)	
	18.5 ± 7.3 vs. 42.8 ± 36.0	
morphine use	mg (??mean +/- ??SD)	

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	22 ± 10.0 mg vs. 37 ± 16 mg	total
keterolac	Pat. getting keterolac (n/N)	
	2/9 vs. 2/11	