REGION KRONOBERG

Comparative Analysis of Spinal and Epidural Analgesia in Total Abdominal Hysterectomy

A Prospective Randomized Trial Assessing the Impact on Acute and Chronic Pain Outcomes

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Introduction

Hysterectomy is the second most common gynecological surgical procedure performed in several Western countries and is the most common for women aged over 40 years old.[1,2] Indications include uterine fibroids, gynecological cancers, abnormal uterine bleeding, endometriosis, and pelvic organ prolapse.[3] Vaginal or laparoscopic approaches are typically preferred due to lower complication risks, including postoperative pain. However, abdominal hysterectomy through laparotomy may be necessary in cases of technical challenges, typically large uterine volumes.[3]

Persistent Post-Surgical Pain (PPP) was defined by Werner and Kongsgaard in 2014 as *"pain that develops after a surgical procedure or increases in intensity after a surgical procedure. It should be of at least 3-6 months duration and significantly affect the health-related quality of life. The pain is either a continuation of acute post-surgery pain or develops after an asymptomatic period. It is localized to the surgical field, projected by a nerve from the surgical field or referred to a dermatome. Other causes of pain should be excluded"*.[4] PPP is a common complication of any operation and can lead to impairment of physical function, psychological well-being, and reduced quality of life. In a Danish study among women undergoing hysterectomy for benign indications, the general prevalence of PPP one year after surgery was 32%. The prevalence was 14.9% in women with no previous history of chronic pain.[5] One important risk factor for PPP after hysterectomy is high acute postoperative pain intensity.[2,6] Hence, it is crucial to effectively manage acute peri- and postoperative pain in hysterectomy patients to prevent PPP as a complication.

Common practice for anesthesia and analgesia during abdominal hysterectomy typically involves general anesthesia, sometimes with adjunct pain management. Such adjuncts include epidural infusion, preoperative spinal injection of opioids and/or local anesthetics, or regional nerve blocks. Neuraxial blocks and regional nerve blocks are proven to effectively mitigate acute and chronic postoperative pain development following surgery.[7,8] Additionally, neuraxial blocks have demonstrated significant acute and chronic pain improvement after hysterectomy specifically.[5,9-11] However, the optimal use of these adjuncts for hysterectomy, considering their impact on pain management, operating room (OR) time consumption, and hospital stay length, remains debated.

Catarci et al. and Bang et al. found that an adjunct spinal opioid injection, with or without local anesthetics, improved postoperative pain in the first 48 hours for hysterectomy patients.[12,13] The Catarci study also suggested reduced post-anesthesia care unit (PACU) admittance time and time until hospital discharge, though this failed to reach statistical significance.[12] Several studies have also concluded that epidural infusion is superior to intravenous analgesics in mitigating postoperative pain after hysterectomy.[14-16]
The transverse abdominal plane (TAP) block, a regional nerve block of the lower abdominal wall, has also been evaluated as a potential adjunct to general anesthesia for pain management. However, it failed to prove more effective than epidural infusion in reducing acute postoperative pain, hypothetically because it does not reach the visceral pain components after hysterectomy.[17]

In our hospital, the most common practice for anesthesia during abdominal hysterectomy includes general anesthesia supplemented with a neuraxial adjunct for analgesia. These adjuncts typically comprises either an epidural infusion or a preoperative spinal block containing local anesthetics and opioids. However, there is no consensus on the comparative effectiveness of these modalities regarding pain management quality, OR and PACU time consumption, and hospital stay duration. While it's widely accepted that placing an epidural catheter extends OR preparation time compared to a spinal injection, its necessity for pain management is debated. Concerns have also been raised about its potential to prolong time until hospital discharge.
To our knowledge, two studies have compared intrathecal injection with epidural infusion in the context of gynecological abdominal surgery. Kjølhede et al. found spinal administration of bupivacaine, morphine and clonidine comparable to epidural infusion regarding pain management and quality of recovery post-surgery for gynecological malignancies. Additionally, the spinal group showed shorter hospital stay durations.[18] Similarly, Hassan et al demonstrated improved postoperative pain reduction with spinal administration of bupivacaine and morphine compared with epidural infusion after abdominal hysterectomy.[19] Neither of these studies, however, assessed the development of PPP.

This prospective, randomized, single-blinded study aims to evaluate the effectiveness of spinal anesthesia versus epidural anesthesia as adjuncts to general anesthesia in patients undergoing elective total abdominal hysterectomy. The study focuses on assessing acute pain management, duration of hospital stay, and the development of PPP as a complication.

Materials and Methods

Study Population

The study will be conducted at the operating theatre and the gynecological ward of Centrallasarettet Växjö (Växjö Hospital), Växjö, Region Kronoberg, Sweden. All patients assessed as American Society of Anesthesiologists Physical Status Class (ASA) 1-3 scheduled for elective total abdominal hysterectomy will be included in the study. Exclusion criteria are age <18 years, ASA >3, contraindications to neuraxial anesthesia, spinal stenosis, laparoscopic procedure, extensive surgery involving more than the uterus, adnexa, appendix and omental resection, diagnosed chronic pain disorders unrelated to the current illness, chronic use of opioid analgesics, unwillingness to participate in the study and inability to comprehend information about the study and make an informed decision, including psychiatric and cognitive disorders. Figure 1 illustrates the participant identification, inclusion and exclusion process.

Methods

Patients eligible for inclusion in the study will undergo a preoperative assessment by an anesthesiologist in an outpatient setting days before the surgery. During this visit, patients will receive information and give written consent of participation. Following consent, each patient will fill out a 1-month Graded Chronic Pain Scale (GCPS 1-month)-score (Fig. 2). The GCPS-Score is a validated questionnaire to grade the severity of chronic pain intensity and pain interference in daily life over a 6-month period[20], but has also been validated for 1 month study durations.[21] All participants will be given a study ID-number to facilitate blinding and follow-up.

On the day of the surgery, patients will be randomized to receive either adjunct spinal or epidural anesthesia alongside standardized general anesthesia. Randomization and blinding will occur through an allocation concealment method with sealed envelopes containing the assigned method, and will be paired with the study ID. The randomized method of anesthesia will be performed by an anesthesiologist without connection to the study to avoid performance biases. All patients will receive oral premedication with Acetaminophen (Alvedon 500mg) 2000mg, Etoricoxib (Arcoxia 120mg) 120mg and Oxycodone (Oxikodon 10mg) 10mg unless contraindicated.

In the spinal anesthesia group, before general anesthesia and under sterile conditions, a mixture of Bupivacaine (Marcain Spinal 5mg/ml) 10mg, Fentanyl (Fentanyl 50µg/ml) 10µg and Morphine (Morfin Special 0.4mg/ml) 100µg will be injected at level L2-L3, L3-L4 or L4-L5. Following confirmation of block success, the anesthesiologist will proceed with administering general anesthesia.

In the epidural group, before general anesthesia and under sterile conditions, an epidural catheter will be placed at level Th10-Th11 (or adjacent interspinal spaces if anatomical conditions require). A test dose of 2ml of Mepivacaine 20mg/ml with adrenalin 5mg/ml (Carbocain adrenalin 20mg/ml + 5mg/ml) will be administered preoperatively to confirm catheter placement. Following general anesthesia, a bolus dose mixture of Ropivacaine (Ropivacain 7.5mg/ml) 60mg and Fentanyl (Fentanyl 50µg/ml) 50µg will be given through the epidural as a single-shot bolus.

Both groups will receive induction anesthesia with Propofol (Propolipid 10mg/ml) 2-3mg/kg, Fentanyl (Fentanyl 50µg/ml) 2µg/kg and Rocuronium (Esmeron 50mg/ml) 0.6mg/kg intravenously (iv). Anesthesia will be maintained with Sevoflurane targeting a minimum alveolar concentration (MAC) of 0.9-1.2. Additional boluses of Fentanyl 50µg iv will be administered and recorded if the patients exhibit signs of perioperative pain or discomfort. Patients will also receive perioperative iv anti-emetics Ondansetron (Ondansetron 2mg/ml) 4mg and Betamethasone (Betapred 4mg/ml) 4mg. Approximately one hour before the end of surgery, an iv diluted morphine bolus of 5mg (Morfin 10mg/ml 1ml + NaCl 9mg/ml 9ml = 1mg/ml) will be administered to preempt postoperative pain in case of neuraxial block dysfunction.

Patient and procedure characteristics will be documented and presented, including age, BMI, ASA-classification, indication for surgery, and type of skin incision (Pfannenstiel, mini-laparotomy or laparotomy). Surgical extension, such as adnexa removal, omental resection, and appendectomy, will also be noted. Additionally, total operating time, total amount of administered Fentanyl, and Sevoflurane MAC-levels will be recorded and compared between groups.

Postoperative pain will be evaluated upon admission to the PACU and at 6h, 12h, 24h and 48h using a numerical rating scale (NRS) at rest and during movement. PACU staff will administer additional opioid injections of diluted Morphine 2.5-5mg iv if the resting-NRS exceeds 4. Total opioid consumption in the PACU and throughout the hospital stay will be recorded for intergroup comparison. Failure to control pain through neuraxial blocks and iv opioids will also be

documented. In the epidural group, this is defined as the requirement to administer continuous epidural infusion, and in the spinal group, as necessitating postoperative epidural catheter placement for pain management. Additionally, OR preparation time, PACU discharge time, and hospital discharge time will be recorded.

To evaluate the incidence of PPP development, evolution of pain characteristics, and pain interference, patients will receive a modified GCPS-1-questionnaire similar to the preoperative assessment (Fig. 2) four months after the operation. The questionnaire will be anonymously linked to the preoperative GCPS-1-questionnaire using the patient's study ID.

Statistics and Analytics

We will initiate this investigation with an internal pilot study aimed at conducting a power calculation to ensure adequate enrollment in the trial. The pilot study will enroll the first 12 patients, constituting approximately 20% of the anticipated study population based on similar study structures. The power calculation will be conducted with a power of 0.8 and a significance level of 0.05.

Continuous patient characteristics (Age, BMI) will be presented as mean ± standard deviation, while categorical data (ASA-classification, indication for surgery, skin incision type) will be presented numerically and as percentages for each group.
For singular continuous data measurements, including time measurements, total perioperatively administered fentanyl and sevoflurane, opioid consumption and pain management failure, statistical analysis will be conducted using independent Student's t-test for parametrical data and Mann-Whitney U-test for non-parametrical data. Results will be presented as a mean ± standard deviation. Assessment for normal distribution within these data sets will be performed using the Shapiro-Wilks test.
Repeated measures, such as NRS-grading and GCPS-questionnaire items, will be analyzed using repeated measures analysis of variance (ANOVA) for parametric data, or by Linear Mixed Model for non-parametric data. Results will be presented as median and interquartile range.

All statistical analyses will be performed using SPSS Statistics 28 (IBM). Statistical significance will be defined as a calculated P-value <0.05 and be reported alongside 95% confidence intervals where applicable.

Ethics

All experiments to be conducted in this study will undergo ethical review and approval by the local ethical committee in Region Kronoberg in accordance with the Declaration of Helsinki. Prior to inclusion in the study, all patients will receive comprehensive verbal and written information regarding study objectives, procedures, risks and benefits. Patients will also be assured that their personal information will remain confidential and will not be disclosed in any published material resulting from the trial. Written consent will be obtained from each patient before their participation, and they will be explicitly informed of their right to withdraw from the study at any time without consequences or questioning.

Addressing informed consent in a clinical setting always poses significant ethical considerations. The clinical setting and the inherent power dynamics within the doctor-patient relationship places the patient in an inferior and dependent position which may influence their decision making. Patients may feel obligated to consent driven by concerns of impairing the relationship with the physician, of receiving inferior treatment, or due to a sense of obligation to compensate the physician for the given treatment. We try to mitigate these factors by inviting patients to a preoperative outpatient meeting days before the surgery to make their decision in a less stressful environment. Patients will also be thoroughly informed of their rights to revoke their consent for any reason and at any time. To ensure informed decision-making, patients deemed unable to provide informed consent for any reason will be excluded from the study.

Another ethical concern is the risk of caregivers inadvertently under- or overtreating patients' postoperative pain due to their knowledge of the study and potential biases. In this regard, it is very important that before treating study patients, healthcare providers receive comprehensive guidance on pain management protocols to avoid any unacceptable treatment of study patients.

Other ethical issues regard the study structure. To mitigate potential researcher biases, the study will be blinded from the researchers using an allocation concealment method with envelopes. Additionally, all neuraxial blocks will be performed by an experienced anesthesiologist not involved with the study. To ensure a qualitative study structure, a statistical power calculation will be conducted before the main study to determine an appropriate sample size. This ensures the study's reliability and interpretability while minimizing the number of participants needed.

Study Timeline

Month 1-(6-10)

- Apply for Ethical review and approval.
- Construct protocols for patient information, blinding, treatment and follow-up.
- Enroll patients for the internal pilot study and commence data collection.
- After Month 4: Commence distributing and collecting GCPS-questionnaires for analysis.
- After receiving enough data, perform a power calculation to determine sample size requirements for the main study.
- Begin drafting the Introduction and Ethical Standpoints sections of the manuscript.

Year 1

- Launch the main study and continue patient enrollment and data collection.
- Review the study plan and assess if any revisions to the study plan are necessary based on power calculation results.
- Finalize the study plan and protocols and ensure adequate time and resource availability, and adherence to ethical guidelines.
- Begin drafting the Materials and Methods section of the manuscript and, when possible, the Results section.

Year 2

- Complete data collection for the main study and commence data analysis.
- Conduct statistical analysis of collected data and interpret results.
- Draft the Results and Discussion sections of the manuscript.
- Construct Tables and Figures based on data analysis for the manuscript.
- Finalize the entire manuscript in collaboration with co-authors.

Financing

All potential requests for research funding will be submitted to the Department of Research and Development, Region Kronoberg, Växjö, Sweden.

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Tables and Figures

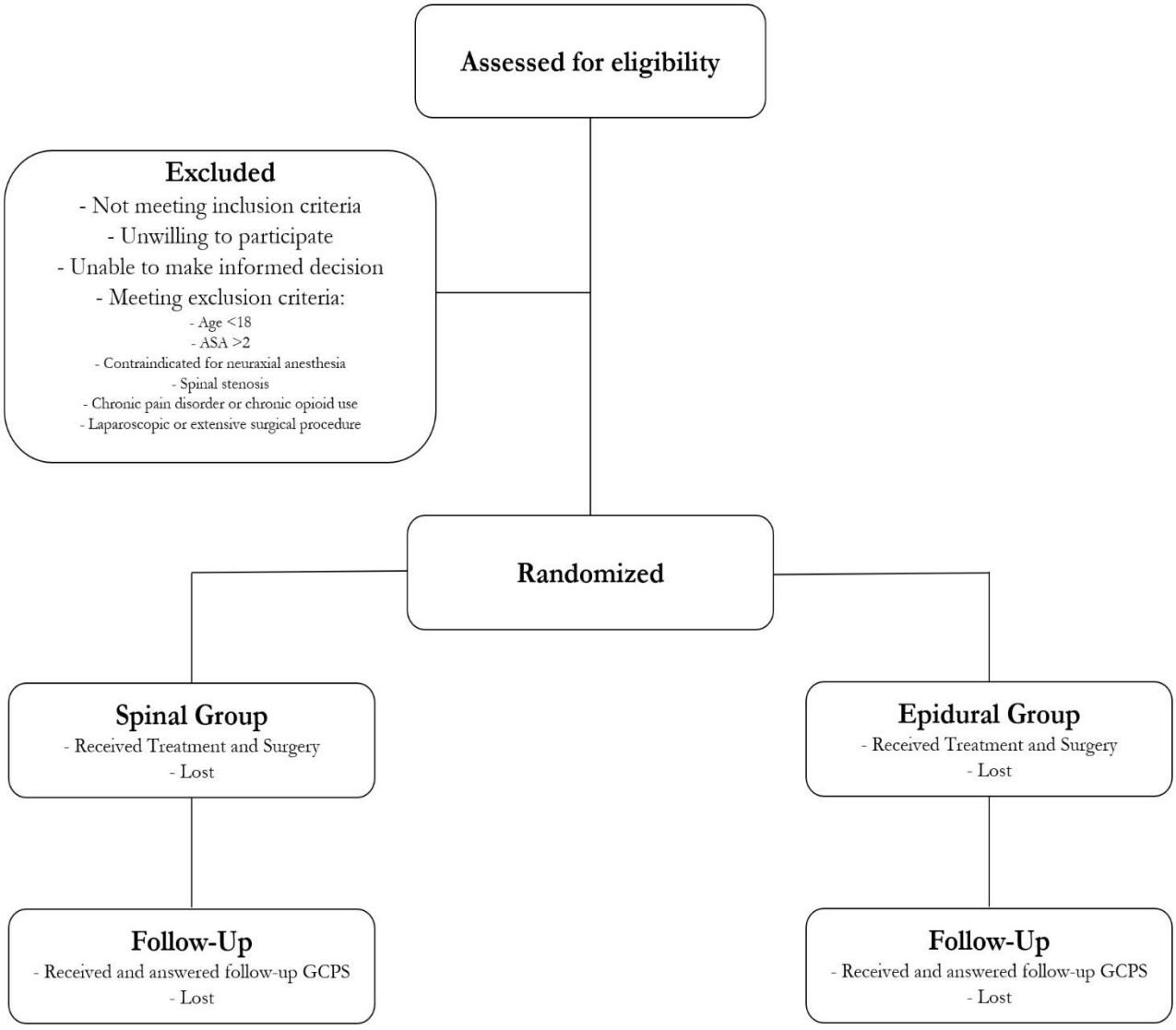
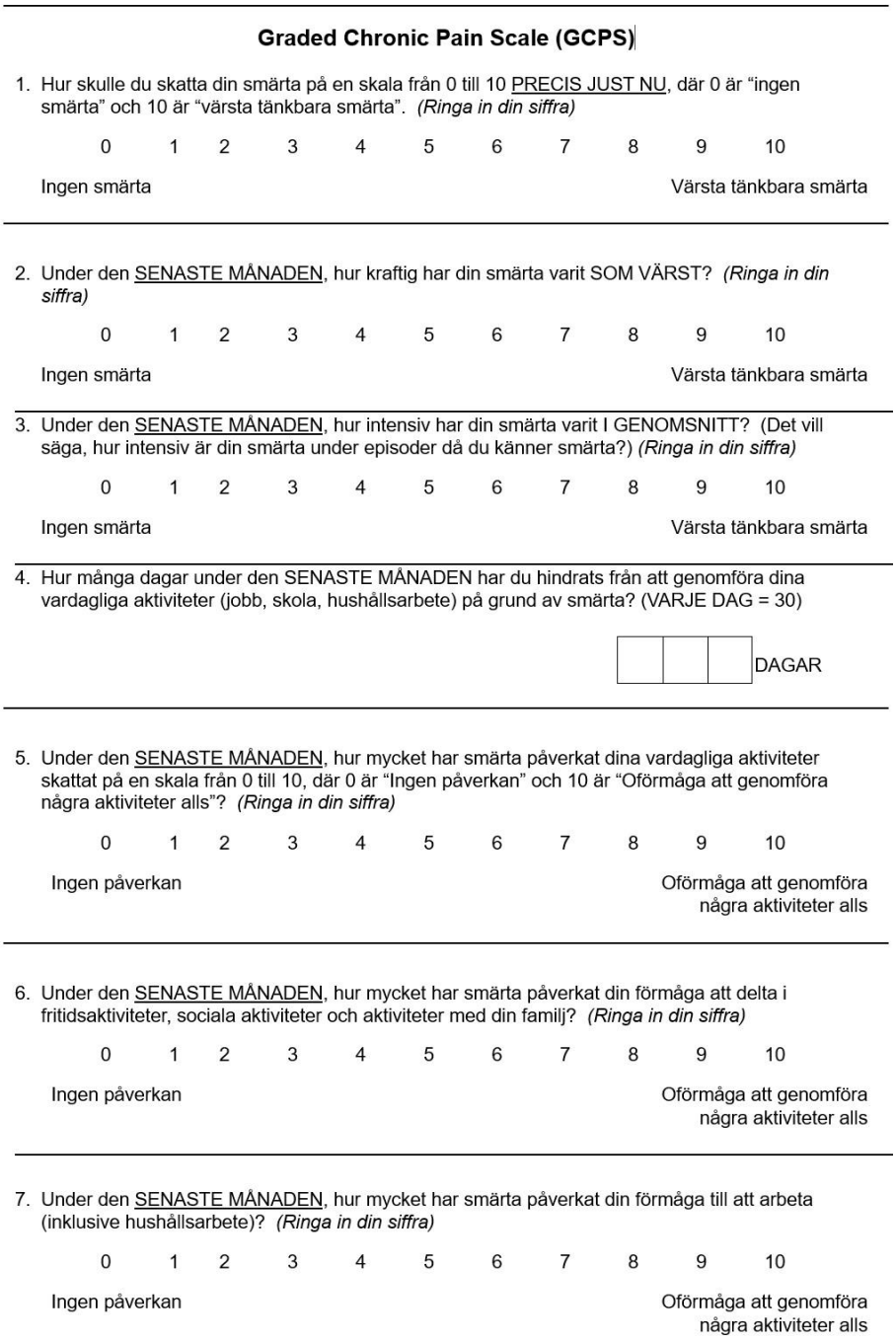


Figure 1: Flowchart of identification, inclusion, exclusion, randomization and dropout of study participants. All patients scheduled for elective total abdominal hysterectomy will undergo eligibility assessment. Subsequently, patients will be excluded based on the predefined exclusion criteria, unwillingness to participate or inability to provide informed consent. Included patients will then be randomized into either adjuvant spinal or epidural pain management groups. Potential dropouts may occur due to various factors, including changes in surgical procedures or difficulties in administering neuraxial blocks. Four months after surgery, participants will be sent a follow-up GCPS questionnaire. Failure to reach patients or retrieve answers could lead to additional dropouts.



Graded Chronic Pain Scale (GCPS)

1. Hur skulle du skatta din smärta på en skala från 0 till 10 PRECIS JUST NU, där 0 är "ingen smärta" och 10 är "värsta tänkbara smärta". *(Ringa in din siffra)*

   0 1 2 3 4 5 6 7 8 9 10

   Ingen smärta — Värsta tänkbara smärta

2. Under den SENASTE MÅNADEN, hur kraftig har din smärta varit SOM VÄRST? *(Ringa in din siffra)*

   0 1 2 3 4 5 6 7 8 9 10

   Ingen smärta — Värsta tänkbara smärta

3. Under den SENASTE MÅNADEN, hur intensiv har din smärta varit I GENOMSNITT? (Det vill säga, hur intensiv är din smärta under episoder då du känner smärta?) *(Ringa in din siffra)*

   0 1 2 3 4 5 6 7 8 9 10

   Ingen smärta — Värsta tänkbara smärta

4. Hur många dagar under den SENASTE MÅNADEN har du hindrats från att genomföra dina vardagliga aktiviteter (jobb, skola, hushållsarbete) på grund av smärta? (VARJE DAG = 30)

   [ ][ ][ ] DAGAR

5. Under den SENASTE MÅNADEN, hur mycket har smärta påverkat dina vardagliga aktiviteter skattat på en skala från 0 till 10, där 0 är "Ingen påverkan" och 10 är "Oförmåga att genomföra några aktiviteter alls"? *(Ringa in din siffra)*

   0 1 2 3 4 5 6 7 8 9 10

   Ingen påverkan — Oförmåga att genomföra några aktiviteter alls

6. Under den SENASTE MÅNADEN, hur mycket har smärta påverkat din förmåga att delta i fritidsaktiviteter, sociala aktiviteter och aktiviteter med din familj? *(Ringa in din siffra)*

   0 1 2 3 4 5 6 7 8 9 10

   Ingen påverkan — Oförmåga att genomföra några aktiviteter alls

7. Under den SENASTE MÅNADEN, hur mycket har smärta påverkat din förmåga till att arbeta (inklusive hushållsarbete)? *(Ringa in din siffra)*

   0 1 2 3 4 5 6 7 8 9 10

   Ingen påverkan — Oförmåga att genomföra några aktiviteter alls

Figure 2: Graded Chronic Pain Scale (GCPS) for assessment of chronic pain during the last month, translated into Swedish. The GCPS questionnaire is a validated tool used to grade chronic pain and its interference in daily life activities. Participants will be instructed to complete this questionnaire before surgery and four months after surgery, focusing on pain related to the indication for surgery and/or postoperative pain. Forms will then be paired using the participant ID and evaluated to determine the occurrence of PPP following hysterectomy.