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Research Article

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Preoperative quantitative sensory testing and robot-assisted laparoscopic hysterectomy for endometrial cancer: can chronic postoperative pain be predicted?

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Abstract

Objectives: Chronic postoperative pain is prevalent after robot-assisted laparoscopic hysterectomy for endometrial cancer. Preoperative Quantitative Sensory Testing (QST) has been utilized to identify patients at risk of developing chronic postoperative pain after a range of surgical procedures. The aim of this prospective, observational study was to (1) determine the prevalence of chronic postoperative pain, (2) assess selected preoperative risk factors for chronic postoperative pain, and (3) evaluate if preoperative QST profiling could predict the development of chronic postoperative pain following robot-assisted laparoscopic hysterectomy for endometrial cancer.

Methods: One-hundred and sixty consecutive patients were included and handheld pressure algometry, cuff pressure algometry, temporal summation of pain, conditioned pain modulation, and heat pain thresholds were assessed prior to surgery. Patients were asked to fill out a questionnaire concerning pain in the pre- and postoperative time period six months after surgery. Chronic postoperative pain was defined as persistent, moderate to severe pain (mean visual analogue scale (VAS)≥3) on a daily basis six months after surgery.

Results: The prevalence of chronic postoperative pain after robot-assisted laparoscopic hysterectomy for endometrial cancer was of 13.6% (95% CI 8.4–20.4%). Patients that would develop chronic postoperative pain had a lower BMI (p=0.032), a higher prevalence of preoperative pelvic pain (p<0.001), preoperative heat pain hyperalgesia (p=0.043) and a higher level of acute postoperative pain (p<0.001) when compared to patients that would not develop chronic postoperative pain. A logistic regression model demonstrated that the presence of preoperative pelvic pain was a significant, independent predictive risk factor for development of chronic postoperative pain (OR=6.62, 95% CI 2.26–19.44), whereas none of the QST parameters could predict postoperative pain.

Conclusions: Preoperative QST assessment could not predict the development of chronic postoperative pain despite preoperative heat pain hyperalgesia in patients that would develop chronic postoperative pain.

Keywords: chronic postoperative pain; endometrial cancer; robot-assisted laparoscopic hysterectomy.

Introduction

Chronic postoperative pain is believed to be initiated by a combination of nociceptive-, inflammatory-, and neuropathic pain following a surgical procedure [1, 2]. In the case of hysterectomy, surgical nerve injury can arise as afferent sensory nerves of the skin and connective tissue trespass the surgical field and as the visceral nerve fibers from the uterus and adnexa to the dorsal horn of the spinal segments T-12–L-3 and S-2–S-4 are transected [3]. This acute tissue injury elicits a surgical stress response, which can initiate a peripheral and central sensitization with lowered excitatory thresholds [1, 4]. The transition from acute to chronic postoperative pain is poorly understood and is driven by complex interactions between biologic, psychologic, and socioenvironmental factors [5]. Studies have shown that most cases of chronic postoperative pain resemble neuropathic pain, including chronic postoperative pain after

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hysterectomy [6–8]. A previous hysterectomy study demonstrated pain hyperalgesia located to the same spinal segments receiving the afferent visceral nerves from the uterus and adnexa [9], thereby supporting the convergence-projection theory of referred pain [10, 11]. Chronic postoperative pain has a substantial negative effect on the quality of life for the affected individual and poses a significant socioeconomic burden for the society [12–14].

Several studies have examined the prevalence of chronic postoperative pain after hysterectomy by various surgical techniques (abdominal-, vaginal- or laparoscopic approach) and on various benign indications (e.g., uterine fibroids, excessive bleeding, endometriosis or pelvic pain) [14–20]. Yet, only one published study has examined the prevalence of chronic postoperative pain after robot-assisted laparoscopic hysterectomy for endometrial cancer [9]. This questionnaire-based, retrospective study found a prevalence of chronic postoperative pain of 14.9% [9]. Numerous aspects have been shown to constitute potential, predisposing factors for development of chronic pain, spanning from pre- and post-operative pain intensities, surgical techniques, and psychological phenotypes with high levels of preoperative pain catastrophizing to demographic factors such as young age and lower socioeconomic status [9, 21–24]. In addition, recent studies have found that preoperative sensitization of peripheral or central pain pathways might be associated to chronic postoperative pain in a variety of surgical procedures [25–28].

Mechanistic pain profiling using quantitative sensory testing (QST) has been suggested useful for predicting outcome after e.g., surgery [29, 30]. An array of various QST modalities have been developed and refined over the years, each exploring different aspects of the endogenous adaptive and maladaptive response to tissue injury: Pain thresholds can be utilized to assess primary hyperalgesia when assessed at a local painful site, whereas pain thresholds assessed at a remote anatomical position from the initial painful site generally reflect widespread hyperalgesia, which is believed to be a component of central pain amplification [31]. Thermal stimulation with heat pain thresholds (HPT) has been shown to predict development of chronic postoperative pain after arthroscopic knee surgery [32], thoracotomy [33], and caesarean section [34]. Also, reduced tolerance to both heat and cold evoked pain stimuli was associated with increased postoperative analgesic requirements [35]. Temporal summation of pain (TSP) is believed to be a proxy for the excitability of dorsal horn neurons and thereby reflects the level of central sensitization [31]. Facilitated preoperative TSP has been associated with chronic postoperative pain following total joint arthroplasty [36–38]. Conditioned pain modulation (CPM) assesses the descending pain inhibitory pathways and is defined as the difference in the response to a noxious stimulus applied before and during a secondary noxious stimulus [30, 39]. An impaired CPM has been associated with chronic postoperative pain following thoracic surgery [30] and abdominal surgery [40].

The aim of this study was to determine the prevalence of chronic postoperative pain following robot-assisted laparoscopic hysterectomy for endometrial cancer and assess selected preoperative risk factors. Furthermore, we hypothesized that preoperative QST profiling by handheld algometry, cuff pressure algometry, TSP, CPM, and thermal stimulation could predict the development of chronic postoperative pain.

Methods

Study design and participants

The study was designed as a prospective, observational cohort study. Inclusion criteria were Danish speaking women between 18 and 85 years-of-age diagnosed with endometrial cancer and scheduled for robot-assisted laparoscopic hysterectomy and bilateral salpingo-oophorectomy at the Department of Obstetrics and Gynecology, Aalborg University Hospital, Denmark from July 1st, 2015 till December 31st, 2018. Exclusion criteria were conversion to laparotomy during surgery or subsequent laparotomy, use of cannabis or opioids, neurologic, mental or severe musculoskeletal illnesses.

All study participants were given verbal and written information regarding the study and signed informed consent forms. The study was approved by The North Denmark Region Committee on Health Research Ethics (N-20150028) and The Danish Data Protection Agency (2008-58-0028). The study was furthermore conducted in agreement with the Declaration of Helsinki and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Quantitative sensory testing

The study participants were included consecutively throughout the study period and subjected to a test platform of selected QST modalities 2–3 days prior to the surgical procedure. All participant information and testing were carried out by one of the authors (SL). Due to the exploratory nature of the study, the specific QST modalities were chosen since preoperative thermal pain thresholds [41, 42], pressure pain thresholds [37, 43–46], temporal summation of pain [18, 36, 37, 42, 47] and conditioned pain modulation [30, 40, 48] have been associated with chronic postoperative pain in previous studies.

Handheld algometry

A handheld algometer (Somedic AB, Hörby, Sweden) with a 1 cm^2 probe was placed perpendicular on the skin. Pressure was applied and increased gradually at a rate of 30 kPa/s until the Pressure Pain Threshold (PPT) was reached. The PPT was defined as ‘‘the point at

which the pressure sensation becomes painful". The PPT was assessed at eight different landmark locations on the body, four on each side. The locations were: 1) m. erector spinae; 3 cm lateral of the processus spinosus of the L2 vertebra. 2) m. erector spinae; 3 cm lateral of the processus spinosus of the S2 vertebra. 3) m. tibialis anterior; 5 cm distal to the tibial tuberosity. 4) m. extensor carpi radialis longus; 5 cm distal to the lateral epicondyle of the humerus. An interval of minimum 20 s was kept between each PPT assessment. The mean PPT of the landmark locations on the lower back [1, 2], leg [3] and arm [4] were used in the further analysis.

Cuff pressure algometry

Deep-tissue pain sensitivity was assessed by cuff pressure algometry in which a double-chamber 13 cm wide tourniquet cuff (VBM Medizintechnik GmbH, Sulz, Germany) was placed on the right lower leg at the level of the head of the m. gastrocnemius. The cuff was connected to a computer-controlled compressor and an electronic Visual Analogue Scale (VAS) from 0 to 10 (Cortex Technology and Aalborg University, Aalborg, Denmark). The cuff was inflated at 1 kPa/s. The pain intensity during inflation of the cuff was recorded via the electronic VAS and sampled at 10 Hz. The VAS 0 and 10 extremes on the VAS were defined as "no pain" and as "maximum pain", respectively. The patient was instructed to rate the pain intensity continuously on the VAS from the first sensation of pain until the pain intensity was so high, that she wanted to terminate the test (Pain Tolerance Threshold (PTT)). The Pain Detection Threshold (PDT) was defined as the pressure at which VAS had exceeded a score of 2. This method has been shown to have a high degree of reliability (interclass coefficients above 0.75) [49].

Temporal summation of pain

The cuff pressure algometry device was further utilized to assess the Temporal Summation of Pain (TSP). The average of the previously obtained PDT and PTT levels was automatically calculated, and the cuff was now inflated to this pressure in a series of 10 stimuli at 0.5 Hz. During the series of stimuli, the patient was instructed to rate the pain intensity on the electronic VAS. The mean VAS during stimuli number 1–3 (VAS-I) and stimuli number 8–10 (VAS-III) was calculated and TSP was defined as the difference between the first and the last mean values (VAS-III minus VAS-I), as used in previous studies [46, 50].

Conditioned pain modulation

A second, double-chamber 13 cm wide tourniquet cuff (VBM Medizintechnik GmbH, Sulz, Germany) connected to the cuff pressure algometry device was placed on the left lower leg at the level of the head of the m. gastrocnemius. A painful conditioned stimulus was administered via inflation to the level of 70% of the PTT [49]. Simultaneously, on the right lower leg, the first cuff was inflated by increasing pressure. The patient was instructed to rate the pain intensity via the electronic VAS and exclusively focus on the pain evoked by the cuff on the right leg and disregard the pain evoked by the cuff on the left leg. The CPM was defined as the difference between PDT with and without the conditioning stimulus.

Thermal stimulation

Heat evoked pain was induced by placing a 3 × 3 cm (9 cm^2) contact thermode (Medoc Advanced Medical Systems, Ramat Yishai, Israel) on an area of skin on the lower back 3 cm lateral from the processus spinosus between the L2 and the L4 vertebra. This placement was chosen in order to obtain an assessment of the thermal thresholds of the same spinal segments which would be affected by the subsequent surgical procedure. Each stimulus was started with a thermode temperature of 32 °C and tests were performed by raising the temperature by 0.5 °C/s, as reported in previous studies [51, 52]. The patient was instructed to press a button when she perceived the stimulation as warm (Warm Detection Threshold, (WDT)) and press the button again once the heat stimulation was perceived as pain (Heat Pain Threshold, (HPT)). The test was repeated and the mean WDT and HPT were calculated.

Surgical procedure

All surgical procedures were performed with Da Vinci™ Si robotic systems (Intuitive Surgical Inc., Sunnyvale, USA) and consisted of hysterectomy, bilateral salpingo-oophorectomy and removal of sentinel lymph nodes, which were mapped by intraoperative near-infrared fluorescence after injection of indocyanine-green dye in the cervix, according to the Memorial Sloan Kettering Cancer Center sentinel lymph node algorithm [53, 54].

In the postoperative setting, analgesic management for all patients consisted of Paracetamol (1,000 mg × 4 p.o.) and Naproxen (500 mg × 2, p.o.) for two weeks.

Multi-disciplinary tumor board meetings reviewed and FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) staged all cases postoperatively.

The questionnaire

A questionnaire developed by Brandsborg et al. [24] concerning chronic postoperative pain following hysterectomy on benign indication was modified at Center for Sensory-Motor Interaction, Department of Health Science and Technology, The Faculty of Medicine, Aalborg University, Aalborg, Denmark, and was controlled for validity in a pilot study amongst 10 patients. This modified version of the questionnaire has since been applied in two published studies [9, 55].

The questionnaire consisted of 32 questions in Danish language and contained questions related to the pre- and post-operative time period. The following variables were collected: presence of preoperative pelvic pain, acute postoperative pelvic pain, chronic postoperative pelvic pain, pain intensity ratings by a numeric rating scale (NRS), frequency and location of the pain, and lastly demographic data such as educational level and employment status. Table 1 contains the translated questions from the Danish questionnaire.

The questionnaire was mailed along with a prepaid return envelope to each patient six months after the surgical procedure. Non-responsive patients were contacted by telephone three weeks after receiving the mailed questionnaire and yet again after additional two weeks, if the patient did not respond. The returned questionnaires were gathered for data analysis. Chronic postoperative pain was defined as persistent, moderate to severe pain (mean VAS ≥ 3) on a daily basis six months after the surgical procedure [18, 41, 56].

Table 1: The questionnaire translated from Danish.

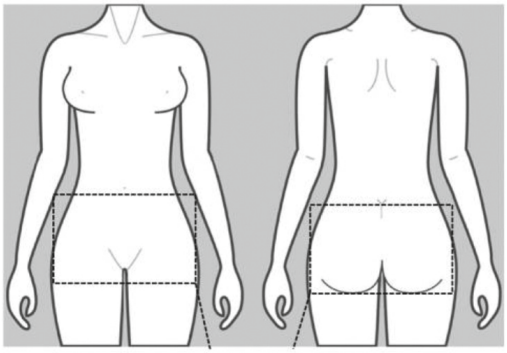
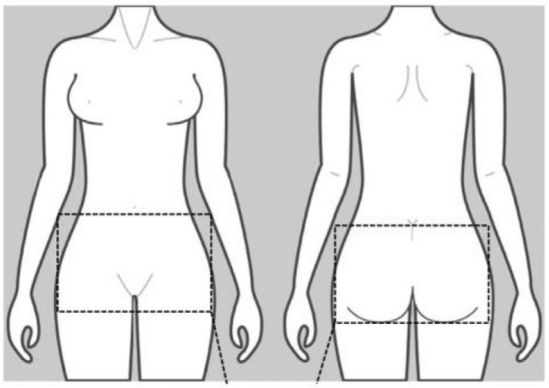
Question	*Answer*
1A - Did you have pain in the pelvic region (see image below) before the operation?	❑ Yes ❑ No (Go to question 7) ❑ Do not recall (Go to question 7)
1B - Mark on the image where you had pain before the operation.	
2 - How often did you have pelvic pain before the operation?	❑ 1-3 days a week ❑ 4-6 days a week ❑ Every day
3A - What was your daily level of pain before the operation? Circle your answer, 0 is no pain and 10 is worst pain imaginable.	0 1 2 3 4 5 6 7 8 9 10
3B - How severe was the pain when at worst? Circle your answer, 0 is no pain and 10 is worst pain imaginable.	0 1 2 3 4 5 6 7 8 9 10
4 - Did the pain before the operation disturb your sleep?	❑ Yes ❑ No ❑ Do not recall
5A - Did you feel pain in any of these situations before the operation?	Yes / No / Do not recall During running ❑ ❑ ❑ Wearing tight clothes ❑ ❑ ❑ During sexual intercourse ❑ ❑ ❑ During heavy lifting ❑ ❑ ❑ In other situations ❑ ❑ ❑
5B - If "Yes" to during sexual intercourse, did it affect your sex life?	❑ Yes ❑ No
6 - How much did the pain before the operation affect your daily life?	❑ Not at all ❑ To a low degree ❑ To a moderate degree ❑ To a high degree
7A - Did you have pain in any other location (e.g. headache, back pain, chest pain, neck pain)?	❑ Yes ❑ No (Go to question 8)
7B - Where was this pain located?	_____
7C - Did a medical doctor diagnose this pain?	❑ Yes (please specify:_____) ❑ No
The next questions concern the time *after* the operation. 8 - What was your level of pain the day after the operation? Circle your answer, 0 is no pain and 10 is worst pain imaginable.	0 1 2 3 4 5 6 7 8 9 10
9A - Have you had persistent / periodic pain during the last six months?	❑ Yes ❑ No (Go to question 14)
9B - How long after the operation did this pain start? 0 months indicate that the pain has been present since the operation.	____ months

Table 1: (continued)

9C - Mark on the image where your pain is located.	 Pelvic region
9D - How often do you have pain?	❑ 1-3 days a week ❑ 4-6 days a week ❑ Every day
10A - What is your daily level of pain? Circle your answer, 0 is no pain and 10 is worst pain imaginable.	0 1 2 3 4 5 6 7 8 9 10
10B - How severe is the pain when at worst? Circle your answer, 0 is no pain and 10 is worst pain imaginable.	0 1 2 3 4 5 6 7 8 9 10
11A - Do you feel *increased* pain in any of these situations?	Yes / No / Do not recall During running ❑ ❑ ❑ Wearing tight clothes ❑ ❑ ❑ During sexual intercourse ❑ ❑ ❑ During heavy lifting ❑ ❑ ❑ In other situations ❑ ❑ ❑
11B - If "Yes" to during sexual intercourse, does it affect your sex life?	❑ Yes ❑ No
12 - Has the pain disturbed your sleep during the last six months?	❑ Yes ❑ No
13A - Have you had pain in any other location (e.g. headache, back pain, chest pain, neck pain) during the last six months?	❑ Yes ❑ No (Go to question 15)
13B - Where is this pain located?	_____
13C - Did a medical doctor diagnose this pain?	❑ Yes (please specify:_____) ❑ No
14A - What is your employment status?	❑ Full-time job ❑ Early retired ❑ Stay-at-home work ❑ Part-time job ❑ Retired ❑ Other ❑ Unemployed ❑ Student
14B - What is your educational level?	❑ Elementary school ❑ Bachelor's degree ❑ High school ❑ Master's degree ❑ Vocational school ❑ PhD ❑ Higher education (2-3 years) ❑ Other
14C - What is your age?	____ years
14D - What is your hight?	____ cm
14E - What is your weight?	____ kg
14F - How many children have you given birth to?	____ children ____ number of vaginal deliveries ____ number of caesarean deliveries

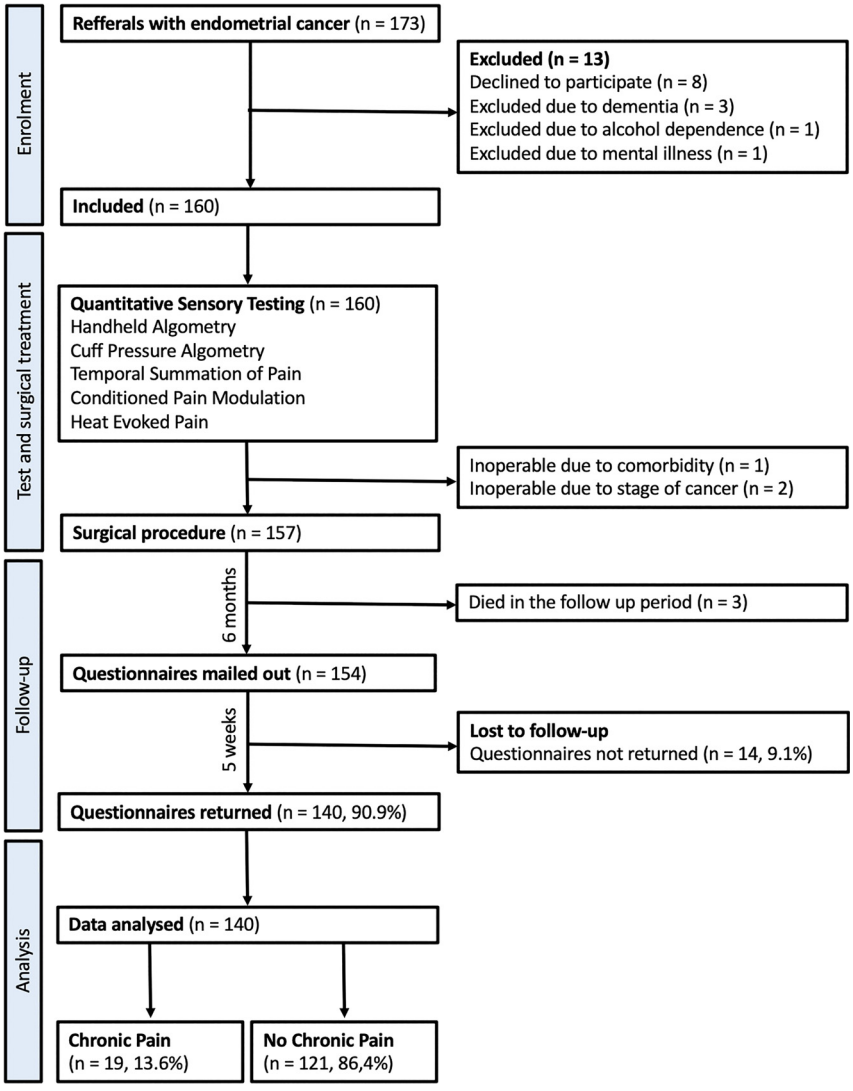


Figure 1: Flow chart of the study.

Review of medical records

The medical records of all eligible patients were reviewed for details concerning Body Mass Index (BMI) at the time of surgery (kg/m^2), duration of surgery (minutes), the blood loss during surgery (mL), parity, number of caesarean sections if any and histopathologic diagnose and stage of cancer. The review of medical records furthermore disclosed if any exclusion criteria had been met (e.g., subsequent surgery or dementia).

Statistical analysis

All study parameters were analyzed with independent samples *t*-test between the two subgroups with and without chronic postoperative

Table 2: Demographic characteristics of the subgrouped patients with and without chronic postoperative pain. Results are displayed as Mean ± SD for continuous variables and as proportions with corresponding frequencies for categorical variables. *Statistically significant difference between groups (p<0.05). Body Mass Index (BMI), Visual Analog Scale (VAS).

Study Parameter	Chronic pain (n=19)	No Chronic Pain (n=121)	p-Value
Age (years)	64.2 ± 10.0	66.4 ± 8.9	0.321
BMI (kg/m^2)	26.2 ± 7.3	29.9 ± 6.7	0.032*
Preoperative pelvic pain (%)	11/19 (57.9%)	21/121 (17.4%)	0.001*
Blood loss during surgery (mL)	64.7 ± 47.6	76.9 ± 79.7	0.521
Duration of surgery (min)	60.3 ± 22.1	64.7 ± 25.5	0.480
Level of acute postoperative pain (VAS)	5.8 ± 2.0	3.1 ± 2.7	0.001*

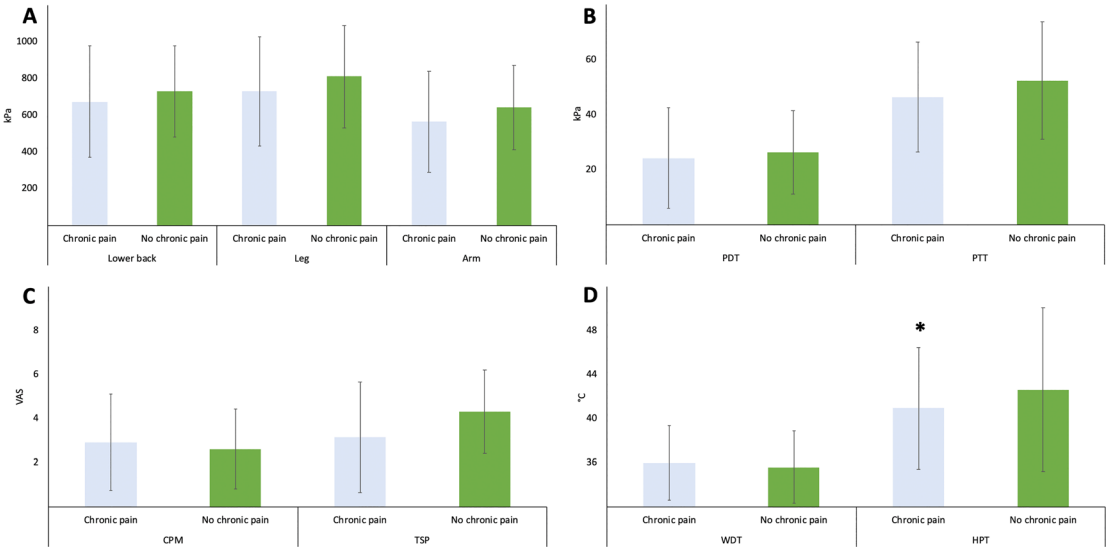


Figure 2: Preoperative Quantitative Sensory Testing of patients with (gray) and without (green) chronic postoperative pain. Results are displayed as Mean ± SD, except results from the Thermal Stimulation which are displayed as Mean and Range. (A) Handheld Algometry. Pressure Pain Thresholds (PPT) at three locations. (B) Cuff pressure algometry. Pain Detection Thresholds (PDT) and Pain Tolerance Thresholds (PTT). (C) Conditioned Pain Modulation (CPM) and Temporal Summation of Pain (TSP). (D) Thermal Stimulation. Warm Detection Thresholds (WDT) and Heat Pain Thresholds (HPT). *Statistically significant difference between groups ($p<0.05$).

Table 3: Binary logistic regression model with three predictive factors for development of chronic postoperative pain. The model has a Nagelkerke R^2 value of 0.251, indicating the model's goodness-of-fit between 0 and 1, i. e., 25.1% of the difference in one variable can be explained by the difference in a second variable, when predicting chronic postoperative pain. Results are displayed as Odds Ratio (OR) and the 95% Confidence Interval. Body Mass Index (BMI).

Study parameter	OR	95% CI
Heat Pain Threshold	0.86	0.72–1.02
BMI	0.92	0.85–1.00
Preoperative pelvic pain	6.62	2.26–19.44

pain. Results are displayed as Mean ± standard deviation (SD) for continuous variables - except results from the Thermal Stimulation which are displayed as Mean, Quartiles and Range – and as proportions with corresponding frequencies for categorical variables. $p \leq 0.05$ was considered statistically significant. A binary logistic regression model was established using the preoperative parameters and results displayed as Odds Ratios (OR) and the 95% Confidence Intervals. The statistical analysis was performed using IBM SPSS Statistics software for Mac OS, Version 26.0 (IBM Corp., Armonk, New York, USA).

Results

A total of 173 consecutive patients were diagnosed with endometrial cancer and scheduled for robot-assisted laparoscopic hysterectomy and bilateral salpingo-oophorectomy in the study period (Figure 1).

Thirteen patients either declined to participate or were excluded. The remaining 160 patients were included and QST tests performed prior to surgery. Three included patients were inoperable due to comorbidity or stage of cancer and three other patients died during the six months follow-up. A total of 154 questionnaires were mailed out and one-hundred and forty (90.9%) were returned within five weeks. A non-responder analysis with independent samples *t*-test between responders (n=140) and non-responders (n=14) did not show any significant difference in age, BMI, duration of surgery or blood loss.

The prevalence of chronic postoperative pain was 13.6% (95% CI 8.4–20.4%) equivalent to 19 patients which were grouped as "Chronic Pain". The remaining 121 patients were grouped as "No Chronic Pain" in the further analysis. An independent samples *t*-test demonstrated that the patients with chronic pain had significantly lower BMI (26.2 kg/m^2 (95% CI 22.8–28.4) vs. 29.9 kg/m^2 (95% CI 28.6–31.0), p=0.032), had a higher prevalence of preoperative pelvic pain (57.9 vs. 17.4%, p<0.001) and a higher level of acute postoperative pain (5.8 VAS (95% CI 4.8–6.8) vs. 3.1 VAS (95% CI 2.7–3.6), p<0.001) when compared to patients without chronic pain (Table 2). No differences in the distribution of histopathologic diagnose and stage of cancer was found between the

"Chronic Pain" and "No Chronic Pain" groups (data not shown).

Quantitative sensory testing

Handheld algometry

No significant differences in PPT were demonstrated between the two groups ($P_{lower\ back}$=0.377, P_{leg}=0.252 and P_{arm}=0.178) (Figure 2A).

Pressure pain detection and tolerance thresholds

No significant differences in PDT or PTT were demonstrated between the two groups (P_{PDT}=0.591 and P_{PTT}=0.255) (Figure 2B).

Temporal summation of pain

No significant difference in TSP was demonstrated between the two groups (P_{TSP}=0.300) (Figure 2C).

Conditioned pain modulation

No significant difference in CPM was demonstrated between the two groups (P_{CPM}=0.921) (Figure 2C).

Thermal stimulation

Significantly lower HPT were observed in the "Chronic pain" group compared with the "No chronic pain" group (40.9 °C, quartiles 38.5; 40.5; 42.25, range 11.0 vs. 42.6 °C, quartiles 39.9; 43.0; 44.9, range 14.9, P_{HPT}=0.043). No significant differences in WDT were demonstrated (P_{WDT}=0.204) (Figure 2D).

Logistic regression analysis

A binary logistic regression analysis using the preoperative study parameters HPT, BMI, and presence of preoperative pelvic pain showed preoperative pelvic pain to be the only significant, independent predictive risk factor of chronic postoperative pain (OR=6.62, 95% CI 2.26–19.44) (table 3). Additionally, the analysis indicated a trend towards HPT (OR=0.86, 95% CI 0.72–1.02) and BMI (OR=0.92, 95% CI 0.85 – 1.00) as independent factors (i.e., a high HPT and a high BMI reduces the risk of chronic postoperative pain). The regression model had a Nagelkerke R^2 value of 0.251, i.e., 25.1% of the difference in one variable could be explained by the difference in a second variable, when predicting chronic postoperative pain.

Discussion

Prevalence of chronic postoperative pain

This study showed a prevalence of chronic postoperative pain after robot-assisted laparoscopic hysterectomy of 13.6% (95% CI 8.4–20.4%), which is in agreement with a previously published, retrospective study that found a prevalence of 14.9% utilizing the same questionnaire [9]. Using the same definition of chronic postoperative pain (persistent, moderate to severe pain (mean VAS≥3) on a daily basis six months after the surgical procedure), Sng et al. found a prevalence of 15.7% in a prospective cohort study of women who underwent abdominal or laparoscopic hysterectomy for benign conditions [18]. Brandsborg et al. found that 17.0% had postoperative pelvic pain (with an intensity of VAS≥3) four months after vaginal, abdominal, or laparoscopic hysterectomy on benign indication, while Pokkinen et al. found a prevalence of 26.0% when including any persistent pelvic pain (NRS>0), six months after vaginal or laparoscopic hysterectomy on benign indication [17, 56]. Overall, these findings align with the results of the present study.

Preoperative risk factors

The results demonstrated preoperative pelvic pain to be a significant, independent predictive risk factor of chronic postoperative pain (OR=6.62, 95% CI 2.26–19.44) which aligns with previous studies of hysterectomy [9, 14, 18, 55]. This association between preoperative pain and development of chronic postoperative pain is well described in the literature across different types of surgery, e.g., inguinal hernia repair [12, 57], caesarean section [58], mastectomy [59], and postamputation phantom pain [60]. The underlying etiology for this association has not been fully understood, although the maladaptive neuroplastic mechanisms involving peripheral- and central sensitization are believed to contribute [1, 2, 61].

As shown, patients with chronic postoperative pain had a lower BMI when compared to patients without chronic postoperative pain (26.2 kg/m^2 vs. 29.9 kg/m^2). Even though this association did not prove strong enough in a logistic regression model (OR=0.92, 95% CI 0.85–1.00) the finding may still seem counterintuitive, seeing that multiple studies have shown obesity to induce a persistent,

low-grade, inflammatory response with elevated levels of tumor necrosis factor α, interleukin-6 and C-reactive protein [62–64]. These inflammatory mediators have previously been shown to lower the excitatory threshold of nerve-endings, thus increasing the peripheral pain sensitivity [1, 65, 66]. The associations between obesity and chronic pain have since been demonstrated in several conditions, e.g., multisite pain, neck- and shoulder pain, osteoarthritis, and abdominal pain [67–72]. In the present study, however, it is important to note, that both groups have BMI levels classified as overweight (in the range from 25.0 to 29.9 kg/m^2) according to the definitions by The World Health Organization [73]. Equivalent to obesity, smoking also induces a systemic, low-grade inflammatory state [74, 75]. Studies have also shown an association between smoking and chronic pain conditions, including chronic postoperative pain after hysterectomy [17, 76, 77]. In the present study, however, smoking status was not obtained.

Preoperative profiling by QST

As the only QST parameter in this study, HPT was found to be significantly lower in the chronic postoperative pain group compared to the non-chronic postoperative pain group (40.9 °C versus 42.6 °C). Both mean values, however, ranged within the normal span of HPT and the association did not prove strong enough in a logistic regression model for decreased HPT to be established as an independent risk factor. Consequently, we must conclude that the QST parameters evaluated in this study could not predict chronic postoperative pain after robot-assisted laparoscopic hysterectomy for endometrial cancer.

In contrast to the present study, previously published papers on chronic postoperative pain after arthroscopic knee surgery, thoracotomy, and herniotomy found a predictive capability for HPT and other thermal thresholds [32, 33, 41]. The wavering outcome of QST studies was addressed in a systematic review by Sangesland et al. in 2017 [28]. Here the authors concluded that the majority of QST modalities showed no consistent association with postoperative pain, but suprathreshold heat pain and temporal summation of pressure pain were the two QST modalities which showed the most consistent association [28]. When focusing solely on QST and gynecologic pelvic pain, other studies have made similar findings: In postoperative pain after caesarean section, Granot et al. found suprathreshold heat pain to be a significant predictor [78], while Pan et al. found HPT to be a significant predictor [34]. Likewise, Grundström et al. found lower thresholds for heat, cold, and pressure pain in patients with persistent pelvic pain and suspected endometriosis [79].

Cutaneous allodynia is often seen in dermatomes related to a structure with visceral pain (termed viscerosomatic convergence) or as cross-sensitization between two visceral structures (viscero-visceral convergence) [80, 81]. Jarrell et al. tested 61 patients scheduled for gynecologic laparoscopy on non-malignant indications and found abdominal cutaneous allodynia to be a predictor of postoperative pain [82], while Arendt-Nielsen et al. showed that cervical distension in patients with dysmenorrhea evoked larger areas of referred pain and higher pain ratings than in healthy controls, thereby suggesting central sensitization had occurred [11].

Only a few other QST studies on hysterectomy have been conducted. Brandsborg et al. examined various modalities including abdominal- and vaginal pressure pain detection thresholds among 90 patients scheduled for hysterectomy due to leiomyomas and/or menorrhagia and found that 51% had preoperative pain and 17% had postoperative pelvic pain [56]. Brandsborg furthermore showed that the patients with preoperative pain more often had degrees of allodynia and hyperalgesia than patients without pain, and that preoperative abdominal pressure pain detection thresholds did not correlate with acute or chronic postoperative pain, while vaginal pressure pain detection thresholds correlated to acute postoperative pain, but not chronic postoperative pain.

Limitations

The study limitations are primarily in regard to potential information bias, where recall bias in the questionnaire response should be regarded as a potential liability. The definition of chronic postoperative pain utilized in this study was persistent, moderate to severe pain (mean VAS≥3) on a daily basis six months after the surgical procedure, based on definitions in previously published studies [18, 41, 56]. The lack of an internationally recognized, consensus based definition for chronic postoperative pain is an inherent constraint to the research community, seeing that various definitions are utilized (VAS>0, 4 months after surgery; VAS>3, 2 months after surgery; VAS≥4, 12 months after surgery etc.,) [14, 19, 83]. This general

limitation should be kept in mind, when comparing the results of studies using varying definitions of chronic postoperative pain.

In the present study we found no difference in the distribution of histopathologic diagnose and stage of endometrial cancer between groups, thereby minimizing the risk of confounding due to cancer related pain. Other types of confounding, like pain susceptibility due to psychological traits, cannot be disregarded as this study did not evaluate the psychological state of the participants. Finally, the enrollment of participants was conducted at a single center, which could reduce the generalizability of the results.

Conclusions

This relatively large prospective study with a high responder rate (>90%) showed that preoperative QST profiling could not predict chronic postoperative pain, despite demonstrating preoperative heat pain hyperalgesia in patients that would develop chronic postoperative pain. Preoperative pelvic pain was found to be a significant, independent predictive risk factor of chronic postoperative pain after robot-assisted laparoscopic hysterectomy for endometrial cancer.

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Ethical approval: The research complies with all the national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by The North Denmark Region Committee on Health Research Ethics (N-20150028) and The Danish Data Protection Agency (2008-58-0028).

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