Pain Medicine

Pain Medicine 2014; 15: 857–864
Wiley Periodicals, Inc.

Thermal Quantitative Sensory Testing to Predict Postoperative Pain Outcomes Following Gynecologic Surgery

Shireen Ahmad, MD, Gildasio S. De Oliveira Jr., MD, MSCI, Jane M. Bialek, BS, and Robert J. McCarthy, PhD

Department of Anesthesiology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA

Reprint requests to: Robert J. McCarthy, PhD, Department of Anesthesiology, Feinberg School of Medicine, 251 East Huron Street, F5–704 Chicago, IL 60611, USA. Tel: 312-695-4976; Fax: 312-472-3590; E-mail: r-mccarthy@northwestern.edu.

Disclosures: Financial support for this study was provided by the Department of Anesthsiology. This study was presented at the International Anesthesia Research Society 2013 Annual meeting, San Diego, CA, USA: May 5–7, 2013.

Abstract

Objective. To evaluate the relationship of preoperative thermal quantitative sensory testing (QST) values with postoperative pain and opiate consumption in opiate-naïve patients following gynecologic surgery.

Design. Single blind observational study.

Settings. Surgical center of an academic medical center.

Methods. QST was performed preoperatively on 124 opioid-naïve patients. Pain outcomes were assessed on arrival to the post-anesthesia care unit and at 6 hourly intervals for 24 hours. Subjects were reclassified to three groups: Group 1 had a heat pain threshold above and a cold pain threshold below the median; Group 2 had either a heat pain threshold below or a cold pain threshold above the median; Group 3 had a heat pain threshold below and a cold pain threshold above the median. The primary outcome measure was the 24-hour morphine consumption.

Results. One hundred twenty subjects were evaluated. Median (interquartile range) warm and cold pain thresholds were 44.8 (42.4–46.9)°C and 10.5 (3.2–19.0)°C, respectively. Heat pain thresholds demonstrated a negative (rho = –0.23, $P = 0.01$) and cold thresholds a positive correlation (rho = 0.21, $P = 0.02$) with 24-hour morphine consumption. Median morphine consumption was 19 (2–33) mg ($P = 0.004$) equivalents greater in subjects (N = 46) with heat pain thresholds <45°C and cold pain thresholds >10°C than subjects with heat pain thresholds >45°C and cold pain thresholds <10°C.

Discussion. Reduced tolerance to both heat and cold thermal pain stimulus was associated with increased postoperative analgesic requirements. Combined responses to multiple pain modalities may be more useful than a single stimulus paradigm.

Key Words. Opioids; Postoperative Pain

Introduction

Pain is the most frequently reported postoperative symptom and in spite of an increased understanding of the physiology of pain mechanisms and advances in analgesic modalities, effective pain management continues to be a major health care challenge worldwide [1,2]. In addition to being a source of patient dissatisfaction, inadequate postoperative pain relief has been linked to the development of surgical wound infections, cardiac and pulmonary complications, and chronic pain conditions [3–10]. The large interpatient variability in the response to the postoperative nociceptive stimulus represents a major impediment to optimal postoperative analgesic therapy [11–16]. The ability to identify patients who are likely to develop severe postoperative pain can lead to an individualized and therefore more effective pain management strategy for surgical patients. In addition, it can avoid

unnecessary treatments in low-risk patients, thereby minimizing drug-related adverse side effects.

The use of pain psychophysics to risk stratify pain outcomes of surgical patients has been attempted by previous investigators with variable results [17–21]. Among the different modalities, thermal sensory testing has been the most utilized method. However, most prior studies have tested the relationship between a single testing paradigm and differences in pain scores and have not demonstrated a relationship between sensory testing and postoperative opioid analgesic consumption [22]. Because differences in pain scores may reflect poor postoperative management, opioid/analgesic consumption is considered a more robust postoperative pain outcome [23,24]. In addition, postoperative opioid consumption but not pain scores has been associated with poor quality of postsurgical recovery [25].

This prospective cohort study was undertaken to evaluate the relationship of preoperative thermal quantitative sensory testing (QST) values with postoperative opiate consumption and pain in opioid-naïve patients following abdominal hysterectomy or myomectomy surgery. We hypothesized that the 24-hour cumulative opioid consumption would be different in subjects with QST threshold values above and below the median values for the entire group.

Methods

The study was approved by Institutional Review Board of Northwestern University, and signed informed consent was obtained from all subjects. Patients who were scheduled to undergo abdominal myomectomy or hysterectomy, and who met the inclusion criteria were invited to participate in the study. Patients with a history of anxiety or depression, alcohol or substance abuse, and a history of chronic pain or current analgesic use preoperatively were excluded.

Thermal QST was performed preoperatively in all subjects using the TSA-II NeuroSensory Analyzer (Medoc Advanced Medical Systems, Durham, NC, USA). Prior to initiation of the testing, subjects received detailed explanation of the process. The QST was performed by the same investigator (SA) in a quiet room where the temperature ranged between 20 and 22°F. The standard 30×30 mm^2 thermode was applied to the volar aspect of the dominant forearm. The rate of temperature rise and fall change was 1.5°C/s, and the device was programmed to stop the heating when the temperature reached the upper limit (default is 50°C) and the cooling when the temperature reached 0°C. The stimuli increased or decreased from a basal temperature of 32°C until the end point was perceived, at which moment the stimulus was halted by the subject activating a button. For the warm and cold sensation modalities, the subject activated the button as soon as she felt a temperature change, and for the pain modalities, the subject pressed the button when the pain threshold was reached. The thermode temperature returned to baseline at 1°C/s following warm and cold sensation testing and at 10°C/s following heat and cold pain threshold testing. Clusters of four stimuli were given, in the sequence of cold sensation, warm sensation, cold pain threshold, and heat pain threshold. The minimum interstimulus interval during warm and cold sensation testing was 4 and 10 seconds during heat and cold pain testing. The mean value and standard deviation of each four stimuli were recorded.

Preoperative baseline pain was evaluated using a visual analog scale from 0 to 100 mm. Subjects received a general anesthetic with standard monitoring including noninvasive blood pressure monitoring, electrocardiography, pulse oximetry, capnography, and bispectral index (BIS) monitoring. All subjects received 2 mg of midazolam for premedication. A remifentanil infusion was initiated at 0.2 μg/kg/min. (ideal body weight) prior to induction and titrated to maintain the blood pressure and heart rate within 20% of preoperative values. General anesthesia was induced with 2 mg/kg of propofol and tracheal intubation was facilitated with either 0.5 mg/kg of succinylcholine or 0.5 mg/kg of rocuronium, at the discretion of the anesthesiologist. Additional doses of rocuronium were administered to maintain the train of four at 2/4 twitches. Anesthesia was maintained with desflurane or sevoflurane, air and oxygen 0.5 L/min. The depth of anesthesia was maintained at a BIS™ (XP version 3.0, Aspect Medical, Inc., Norwood, MA, USA) value between 40 and 60. The remifentanil infusion was discontinued 20–30 minutes prior to the end of surgery and morphine 400 μg/kg. (dosing body weight = ideal body weight + 0.4 × [actual weight—ideal body weight]) was administered. All subjects received ondansetron 4 mg prior to the end of surgery, for nausea prophylaxis and neuromuscular blockade were reversed with neostigmine and glycopyrrolate. Forced air warming blankets (Bair Hugger® Arizant Healthcare, Inc., Eden Prairie, MN, USA) and intravenous fluid warmers (Hotline® Level 1 Technologies, Inc., Rockland, MA, USA) were used in all subjects.

The level of sedation on arrival to the post-anesthesia care unit (PACU) was determined using the Ramsey Sedation Scale [26]. Pain was assessed upon arrival to the PACU and at 6-hour intervals for 24 hours using the numeric rating scale for pain (NRS: 0 = no pain, 10 = worst pain). Pain outcomes (24-hour opioid consumption and pain scores) were collected by a research assistant blinded to subjects preoperative QST values (JMB). Analgesia (i.v. morphine) was administered by the PACU personnel to achieve an NRS ≤4 and by patient-controlled analgesia (PCA) for the first 24 hours after surgery. The PCA pump (Abbott APM™, Abbott Laboratories, Chicago, IL, USA) was programmed for a bolus of 2 mg of morphine and a lockout of 10 minutes. Fifteen subjects received oral acetaminophen, and 20 subjects received ibuprofen for postoperative fever. Subjects tolerating oral intake within the first 24 hours were transitioned to oral nonsteroidal analgesics alone or in combination with oral opioid analgesics. The total of all opioid analgesics consumed during that period was recorded and converted to i.v. morphine

equivalents (morEq) in milligrams [27]. Other data collected included subjects' demographics and surgical characteristics, intraoperative opioids consumption, acetaminophen and ibuprofen use, pruritus, and the incidence of postoperative nausea and/or vomiting.

Statistical Analysis

A sample size analysis determined that 120 subjects would be required to be studied. This number would result in 60 subjects stratified at the median heat, or cold pain threshold would achieve 80% power to detect a difference in cumulative analgesic consumption of 10 mg morEq and a standard deviation of 20 mg in the first 24 hours after surgery using a two-tailed Mann–Whitney test and an alpha equal to 0.05. A 10-mg morphine difference in opioid consumption has been associated with better quality of recovery scores in subjects undergoing abdominal hysterectomy [23]. The sample size calculation was made using PASS version 11.0.10 release date August 9, 2012 (NCSS, LLC, Kaysville, UT, USA).

The primary outcome measure was the 24-hour morphine consumption. To assess for an interaction between heat and cold thermal pain thresholds, subjects were reclassified into three groups (Fig 1). Group 1 subjects demonstrated heat and cold pain thresholds above and below the median values, respectively. Group 2 subjects demonstrated either a heat pain threshold below the median or cold pain threshold above the median values. Group 3 subject a heat pain threshold below the median and a cold pain threshold above the median value. Cumulative opioid consumption, pain scores at PACU admission and pain burden for 24 hours postoperatively were compared among these three groups using the Kruskal–Wallis test. Post-hoc comparisons were made using Dunn's test corrected for six comparisons. Pain burden was defined as the area under the numeric rating score for pain for the first 24 hours calculated using the trapezoidal method. Intraoperative opioid use, post-anesthesia care admission pain and sedation scores, 24-hour morphine consumption, and pain and sedation scores at admission were also compared at the median value of hot and cold pain threshold values using the Mann–Whitney *U* test. The time to first analgesic request was compared at the median threshold using the log-rank test. The incidence of postoperative nausea and/or vomiting was compared at the median threshold using Fisher's exact test. All reported *P* values are two-tailed. The criterion for rejection of the null hypothesis was a two-tailed $P \leq 0.05$. Statistical analysis was performed R version 3.0.2, release date 9/25/2013 (The R Foundation for Statistical Computing, Vienna, Austria).

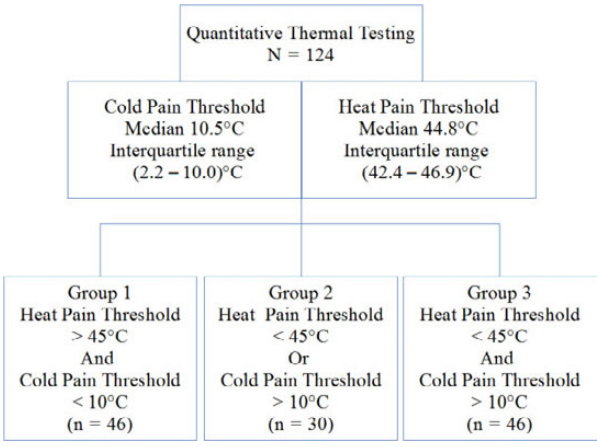

Figure 1 Study flow diagram. 124 subjects had quantitative sensory testing performed prior to surgery. Based on median heat and cold pain threshold values in the tested subjects, groups were allocated at the median response cutoff values. Group 1 subjects demonstrated heat and cold pain thresholds above and below the cutoff values, respectively. Group 2 subjects demonstrated either a heat pain threshold below the cutoff or cold pain threshold above the cutoff values. Group 3 subjects had heat pain thresholds below the cutoff and a cold pain threshold above the cutoff value.

Results

One hundred sixty-one subjects scheduled to undergo abdominal hysterectomy or myomectomy were approached. Thirty-seven did not meet entry criteria (history of anxiety or depression, alcohol or substance abuse, history of chronic pain, or current analgesic use). One hundred twenty-four subjects gave informed consent and were enrolled in this study. Four subjects were excluded from the final analysis. One subject experienced severe intraoperative hemorrhage and required postoperative ventilator support; another patient was found to have cancer and underwent staging surgery. One subject's surgery was converted to laparoscopy after she consented to participate in the study, and a forth subject developed marked tremors postoperatively and was switched to a non-opioid analgesic.

Subject characteristics are shown in Table 1. The median (interquartile range [IQR]) warm and cold pain thresholds were 44.8 (42.4–46.9)°C and 10.5 (3.2–19.0)°C, respectively. There was no difference in thermal threshold among subjects stratified by race or type of procedure. There was no association between cool and warm sensation threshold with age or body mass index (BMI). Age did not correlate with cold and heat pain thresholds; however, cold pain thresholds were positively correlated with BMI (rho = 0.21, $P = 0.02$), and heat pain thresholds were inversely correlated with BMI (rho = –0.29, $P = 0.004$). When stratified at a BMI of 30, there was no difference in 24-hour morphine consumption in subjects with a BMI < 30 kg/m^2, 56 (35–85) mg compared with subjects with a BMI > 30 kg/m^2, 53 (36–76) mg.

Table 1 Subject characteristics

Age (years)	42 (38–48)
Race (n, %)	
Caucasian	45 (37)
African American	62 (52)
Hispanic	10 (8)
Asian	3 (3)
BMI (kg/m^2)	29 (24–33)
ASA physical status	
1	27 (23)
2	93 (77)
Preoperative VAS (mm)	0 (0–0.5)
Procedure	
Abdominal hysterectomy	76 (63)
Abdominal myomectomy	44 (37)
Surgery duration (min)	134 (108–163)
Cool sensation threshold (°C)	30 (29–31)
Cold pain threshold (°C)	10.5 (3.2–19)
Warm sensation threshold (°C)	34.5 (34–35)
Heat pain threshold (°C)	45 (42–47)

ASA = American Society of Anesthesiologists; BMI, body mass index; VAS = visual analog scale.

Intraoperative and postoperative outcomes stratified at median thermal pain cutoff thresholds are shown in Table 2. Heat pain thresholds demonstrated a negative correlation (rho = –0.23, $P = 0.01$) and cold thresholds had a positive correlation (rho = 0.21, $P = 0.02$) with 24-hour morphine consumption. The median difference (97.5% confidence interval) in 24-hour morphine consumption for subjects with a cold threshold below 10°C was –15 (–2 to –29) mg ($P = 0.01$) less than for subjects with a cold threshold above 10°C. Subjects with heat pain thresholds above 45°C had median differences in 24-hour morphine consumptions of –13(–1 to –26) mg ($P = 0.01$) less than subjects with heat pain thresholds below 45°C. There were no differences in preoperative pain scores, intraoperative remifentanil utilization, PACU admission pain scores, PACU morphine administration, time to first analgesic request, or 24 pain burden when stratified at the median of the cold or heat threshold values. There were no differences in opioid-related side effects among groups.

Subjects who demonstrated heat pain thresholds below the median and cold pain threshold above the median values had greater 24-hour morphine consumption than

Table 2 Intraoperative and postoperative outcomes stratified at median thermal pain thresholds

	Cold pain threshold			Heat pain threshold		
	<10°C N = 59	≥10°C N = 61	*P*	<45°C N = 59	≥45°C N = 61	*P*
Surgical duration (min)	132 (124–141)	137 (121–141)	0.25	127 (117–137)	138 (132–148)	0.10
Intraoperative remifentanil infusion (μg/kg/min)	0.14 (0.11–0.17)	0.15 (0.11–0.19)	0.46	0.15 (0.11–0.19)	0.14 (0.11–0.17)	0.20
Intraoperative BIS™ index	46 (43–49)	47 (44–50)	0.54	47 (44–49)	46 (43–49)	0.64
Intraoperative morphine (mg)	26 (24–30)	28 (24–30)	0.21	28 (24–30)	26 (24–30)	0.63
PACU admission pain score (NRS 0–10)	6 (4–8)	6 (4–8)	0.71	6 (4–8)	5 (4–7)	0.05
PACU admission sedation score	2 (2–3)	2 (2–3)	0.53	2 (2–3)	2 (2–3)	0.06
PACU morphine administered (mg)	10 (6–21)	14 (8–25)	0.59	14 (8–22)	10 (6–22)	0.12
Time to first analgesic request (min)	88 (73–103)	81 (72–89)	0.29	82 (74–89)	88 (73–103)	0.66
Pain burden for 24 hours (Units*hour)	27 (24–36)	30 (24–36)	0.99	33 (27–36)	24 (21–33)	0.15
Opioid consumption in 24 hours (i.v. morphine equivalents)	43 (30–72)	63 (40–89)	0.01	60 (41–85)	42 (28–76)	0.01
Acetaminophen consumption in 24 hours	650 (325–900)	650 (325–650)	0.54	650 (325–65)	650 (325–650)	0.60
Ibuprofen consumption in 24 hours	600 (600–600)	600 (600–600)	0.32	600 (600–600)	600 (600–600)	0.22
Nausea/vomiting in 24 hours (N, %)	20 (34)	16 (26)	0.24	15 (25)	21 (36)	0.23
Pruritus in 24 hours (N, %)	4 (7)	6 (9)	0.39	3 (5)	7 (12)	0.15

Data presented as median (interquartile range).
BIS = bispectral index; PACU = post-anesthesia care unit; NRS = numeric rating score (0 = no pain, 10 = worst pain).

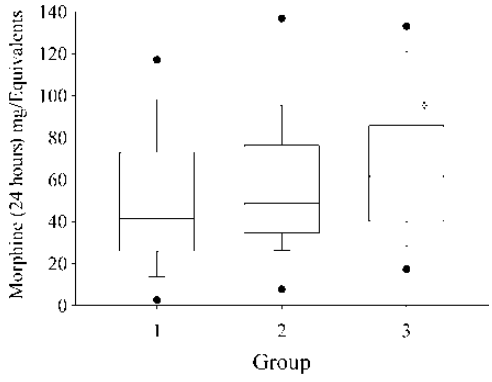

Figure 2 Morphine consumption (24 hours) mg equivalents among quantitative sensory testing groups stratified at a heat pain threshold of 45°C and cold pain threshold of 10°C. Group 1 subjects (N = 44) demonstrated heat and cold pain thresholds above and below the cutoff values, respectively. Group 2 subjects (N = 30) demonstrated either a heat pain threshold below the cutoff or cold pain threshold above the cutoff values. Group 3 subjects (N = 46) had heat pain thresholds below the cutoff and a cold pain threshold above the cutoff value. Group 3 subjects had a median (95% confidence interval) difference in 24-hour morphine consumption of 19 (7–33) mg equivalents ($P = 0.004$) compared with Group 1 subjects and 13 (0–28) mg equivalents compared with group 2 subjects ($P = 0.05$).

subjects who demonstrated heat and cold pain thresholds above and below the median values as well as subjects who demonstrated either a heat pain threshold below the median or cold pain threshold above the median values (Fig. 2). Median morphine consumption was 19 (2–33) mg ($P = 0.004$) equivalents greater in subjects (N = 46) with heat pain thresholds <45°C and cold pain thresholds >10°C than subjects with heat pain thresholds >45°C and cold pain thresholds <10°C. There were no differences in the pain scores on PACU admission or pain burden for 24 hours among the groups.

Discussion

The important finding of this study is the demonstration of a significant association between preoperative thermal QST and postoperative opioid consumption. In our study, the median cold pain threshold was 10°C, and the median heat pain threshold was 45°C. These values are similar to the reported thresholds in normal individuals, cold threshold 10°C and heat threshold 47.1 ± 2°C [28,29]. When subjects were stratified at the median value for cold or heat pain thresholds prior to surgery, we observed a significant difference in the 24-hour morphine consumption.

An additional important finding was increased 24-hour morphine consumption when the hot pain threshold was below 45°C and the cold pain threshold was above 10°C compared with subjects who demonstrated neither heat or cold pain thresholds above and below the median values as well as subjects who demonstrated either a heat pain threshold below the median or cold pain threshold above the median values. No prior study has reported the beneficial role of assessing both heat and cold pain thresholds to detect postoperative opioid consumption. Our findings suggest that evaluation of the response to both cold and heat pain thresholds may be a better predictor of analgesic use that the use of either stimulus alone. A recent review of studies evaluating QST and analgesic needs suggested that multiparadigm approaches to testing should be evaluated rather than single static pain assessments [22].

Previous studies have used pain psychophysics for risk stratification of pain outcomes in surgical patients receiving neuraxial anesthesia [18,19]. In a study of 58 women scheduled for caesarean delivery under epidural anesthesia, Granot et al. found that a supra-threshold 48°C thermal stimulus but not the pain threshold was associated with postoperative visual analog scores [18]. Preoperative pain thresholds in the aforementioned study were similar to those in the current study 44.2 ± 2.6°C, but no assessment of the association between pain thresholds and opioid analgesic consumption was reported. Pan et al. evaluated thermal pain thresholds as part of a multifactorial assessment of predictors of post-caesarean section pain in 34 parturients who received epidural anesthesia and found that thermal pain thresholds and patient expectation were predictive of resting pain, while thermal pain thresholds and the State Trait Anxiety Inventory were predictive of recovery room analgesic consumption [19]. Differences in the findings of the aforementioned studies in post-caesarean delivery subjects and the current study may relate to the use of neuraxial anesthesia and use of postoperative multimodal analgesia.

Studies have also evaluated the thermal pain responses following general anesthesia [20,21]. Similar to our findings, in a study of 59 patients that underwent laparoscopic tubal ligation, Rudin et al. demonstrated that preoperative heat pain responses were able to predict up to 43% of the variance in postoperative pain, but the investigators did not evaluate the possible association with opioid consumption [20]. In another study of 20 patients undergoing total knee arthroplasty, Martinez et al. demonstrated that postoperative opioid consumption correlated with preoperative heat hyperalgesia, but not thermal or mechanical pain thresholds [21]. In the latter study, the preoperative thermal sensory values likely reflected an inflammatory process with hyperalgesia in the operative site (knee) and therefore may predominantly reflect the degree of preoperative injury. In contrast, we were able to demonstrate the

ability of preoperative thermal sensory characteristics to predict postoperative opioid consumption in analgesic-naïve subjects at the presentation for surgery.

In the review of studies evaluating QST methods, Grosen et al. suggested a primary limitation of prior studies of sensory testing in surgical patients was that opioid consumption was not a primary outcome [22]. Most prior studies evaluated pain scores following surgery, and differences in pain scores may reflect poor postoperative management and opioids/analgesic consumption is frequently considered a more robust postoperative pain outcome [22]. In addition, postoperative opioid consumption but not pain scores have been associated with poor quality of postsurgical recovery [30,31].

Our subjects received a standardized anesthetic with a loading dose of morphine 20–30 minutes prior to the end of surgery to optimize analgesia [32–35]. Although a trend toward an increase in opioid-related adverse effects has been reported with the use of a loading dose, this was not observed in our study. There was no difference in the level of sedation or incidence of postoperative nausea, and vomiting or pruritus when stratified at the median values of heat and cold pain thresholds or when examined in the three groups of subjects representing the interaction of the QST responses despite differences in 24-hour morphine consumption. We also limited our study population to premenopausal women who were undergoing gynecologic surgery for nonmalignant causes in order to control for confounding factors such as age, gender, and type and duration of surgery that could affect pain burden and opioid analgesic consumption.

Our findings have important clinical implications as we have demonstrated that thermal QST can be used to stratify patients based on their predicted postoperative opioid consumption. QST is easy to perform, and assessments take only a few minutes to complete in the preoperative period. Based on our findings, patients with a predicted high postoperative opioid requirements (cold pain threshold >10°C and heat pain thresholds <45°C) could be managed using more aggressive multimodal analgesic strategies including non-opioid analgesics and dexamethasone in order to optimize postsurgical recovery [12]. In contrast, subjects with high heat pain thresholds >45°C, low cold pain thresholds <10°C would be expected to have lower opioid requirements and could receive less aggressive postoperative opioid therapy in order to minimize adverse side effects [13,14].

Our study is only valid when interpreted within the context of its limitations. We studied subjects that did not report preoperative pain that has been shown to be associated with an increase of up to 50% in postoperative opioid consumption. Nonetheless, we believe that characterization of an opioid-naïve subjects' response to thermal stimulus and the association with postoperative analgesic consumption allows generalizable of our findings to other surgical populations. We did not assess preoperative anxiety levels that have been found to be an important factor in predicting postoperative analgesic use; however, the impact of anxiety is controversial and appears to be a more important factor for predicting early postsurgical pain levels rather than 24-hour opioid consumption [36–39]. In addition, we excluded subjects with a diagnosis of anxiety or depression in order to minimize confounding effects. We did not evaluate the response to supra-threshold stimulus, which may have greater sensitivity to differentiate outcomes than thermal pain thresholds as assessed in this study. Finally, our study was underpowered to examine the interaction among subjects with responses to both heat and cold stimulus in the upper half of the normal range with those with a threshold response below the upper half to either heat or cold stimulus.

In conclusion, our study demonstrates that preoperative QST thermal thresholds in subjects without pre-existing pain prior to surgery is a predictor of postoperative analgesic requirements and may be useful for identify patients with increased opioid requirements. Thermal QST is a simple, non-noxious test, and the information gleaned from the testing might be useful for stratification of subjects based on their relative opioid requirement in order to optimize postoperative pain management.

References

1 Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg 2003;97:534–40.

2 Benhamou D, Berti M, Brodner G, et al. Postoperative Analgesic Therapy Observational Survey (PATHOS): A practice pattern study in 7 central/ southern European countries. Pain 2008;136:134–41.

3 Myles PS, Williams DL, Hendrata M, Anderson H, Weeks AM. Patient satisfaction after anesthesia and surgery: Results of a prospective survey of 10 811 patients. Br J Anaesth 2000;84:6–10.

4 Schumann R, Shikora S, Weiss JM, et al. A comparison of multimodal perioperative analgesia to epidural pain management after gastric bypass surgery. Anesth Analg 2003;96:469–804.

5 Gloth FM III. Principles of perioperative pain management in older adults. Clin Geriatr Med 2001;17:553–73.

6 Walder B, Schafer M, Henzi I, Tramer MR. Efficacy and safety of patient-controlled opioid analgesia for acute postoperative pain: A quantitative systematic review. Acta Anaesthesiol Scand 2001;45:795–804.

7 Tsui SL, Law S, Folk M, et al. Postoperative analgesia reduces mortality and morbidity after esophagectomy. Am J Surg 1997;173:472–8.

8 Kehlet H, Holte K. Effect of postoperative analgesia on surgical outcome. Br J Anaesth 2001;87:62–72.

9 Wu CL, Raja SN. Treatment of acute postoperative pain. Lancet 2011;377(9784):2215–25.

10 Buvanendran A. Chronic postsurgical pain: Are we closer to understanding the puzzle? Anesth Analg 2012;115:231–2.

11 Lynch EP, Lazor MA, Gellis JE, et al. Patient experience of pain after elective noncardiac surgery. Anesth Analg 1997;85:17–23.

12 Ip HY, Abrishami A, Peng PW, Wong J, Chung F. Predictors of postoperative pain and analgesic consumption: A qualitative systematic review. Anesthesiology 2009;111:657–77.

13 Gourlay GK, Willis RS, Lamberty J. A double-blind comparison of the efficacy of methadone and morphine in post-operative pain control. Anesthesiology 1986;64:322–7.

14 Lotsch J, Zimmermann M, Darimont J, et al. Does the A118G polymorphism at the μ-opioid receptor gene protect against morphine–6-glucoronide toxicity? Anesthesiology 2002;97:814–9.

15 Mamie C, Rebsamen MC, Morris MA, Morabia A. First evidence of a polygenic susceptibility to pain in a pediatric cohort. Anesth Analg 2013;116:170–7.

16 Lee A, O'Loughlin E, Roberts LJ. A double-blinded randomized evaluation of alfentanil and morphine versus fentanyl: Analgesia and sleep trial (DREAMFAST). Br J Anaesth 2013;110:293–8.

17 Granot M. Can we predict persistent postoperative pain by testing preoperative experimental pain? Curr Opin Anaesthesiol 2009;22:425–30.

18 Granot M, Lowenstein L, Yarnitsky D, Tamir A, Zimmer EZ. Postcesarean section pain prediction by preoperative experimental pain assessment. Anesthesiology 2003;98:1422–6.

19 Pan PH, Coghill R, Houle TT, et al. Multifactorial preoperaticve predictors for postcesarean section pain and analgesic requirement. Anesthesiology 2006;104:417–25.

20 Rudin A, Wolner-Hanssen P, Hellbom M, Werner MU. Prediction of post-operative pain after laparoscopic tubal ligation procedure. Acta Anaesthesiol Scand 2008;52:938–45.

21 Martinez V, Fletcher D, Bouhassira D, Sessler DI, Chauvin M. The evolution of primary hyperalgesia in orthopedic surgery: Quantitative sensory testing and clinical evaluation before and after total knee arthroplasty. Anesth Analg 2007;105:815–21.

22 Grosen K, Fischer IWD, Olesen AE, Drewes AM. Can quantitative sensory testing predict responses to analgesic treatment? Eur J Pain 2013;17:1267–80.

23 Catro-Alves LJ, De Azevedo VL, De Freitas Braga TF, Goncalves AC, De Oliveira GS Jr. The effect of neuraxial versus general anesthesia techniques on postoperative quality of recovery and analgesia after abdominal hysterectomy: A prospective, randomized, controlled trial. Anesth Analg 2011;113:1480–6.

24 De Oliveira GS Jr, Agarwal D, Benzon HT. Perioperative single dose ketorolac to prevent postoperative pain: A meta-analysis of randomized trials. Anesth Analg 2012;114:424–33.

25 De Oliveira GS Jr, Fitzgerald P, Streicher LF, Marcus RJ, McCarthy RJ. Systemic lidocaine to improve postoperative quality of recovery after ambulatory laparoscopic surgery. Anesth Analg 2012;115:262–7.

26 Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br Med J 1974;2:656–9.

27 Macintyre PE, Ready LB. Pharmacology of Opioids. Acute Pain Management. A Practical Guide, 2nd edition. Philadelphia: WB Saunders; 2001:15–49.

28 Neziri AY, Scaramozzino P, Andersen OK, et al. Reference values of mechanical and thermal pain tests in a pain-free population. Eur J Pain 2011;15:376–83.

29 Croze S, Duclaux R. Thermal pain in humans: Influence of the rate of stimulation. Brain Res 1978;157:418–21.

30 De Oliveira GS Jr, Fitzgerald PC, Marcus RJ, Ahmad S, McCarthy RJ. A dose-ranging study of the effect of transversus abdominis block on postoperative quality of recovery and analgesia after outpatient laparoscopy. Anesth Analg 2011;113:1218–25.

31 De Oliveira GS Jr, Ahmad S, Fitzgerald PC, et al. Dose ranging study on the effect of preoperative dexamethasone on postoperative quality of recovery and opioid consumption after ambulatory gynaecological surgery. Br J Anaesth 2011;107:362–71.

32 Upton RN, Semple TJ, Macintyre PE. Pharmacokinetic optimization of opioid treatment in acute pain therapy. Clin Pharmacokinet 1997;33:225–44.

33 Mazoit JX, Butscher K, Samii K. Morphine in postoperative patients: pharmacokinetics and pharmacodynamics of metabolites. Anesth Analg 2007; 105:70–8.

34 Bounes V, Charpentier S, Houze-Cerfon CH, Bellard C, Ducassć JL. Is there an ideal morphine dose for

prehospital treatment of severe acute pain? A randomized, double-blind comparison of 2 doses. Am J Emerg Med 2008;26:148–54.

35 Aubrun F, Amour J, Rosenthal D, Coriat P, Riou B. Effects of a loading dose of morphine before intravenous morphine titration for postoperative pain relief. A randomized, double blind placebo-controlled study. Br J Anaesth 2007;98:124–30.

36 Scott LE, Clum GA, Peoples JB. Preoperative predictors of postoperative pain. Pain 1983;15:283–93.

37 Taenzer P, Melzack R, Jeans ME. Influence of psychological factors on postoperative pain, mood and analgesic requirements. Pain 1986;24:331–42.

38 Hansson P, Ekblom A, Thomsson M, Fjellner B. Pain development and consumption of analgesics after oral surgery in relation to personality characteristics. Pain 1989;37:271–7.

39 Jamison RN, Taft K, O'Hara JP, Ferrante FM. Psychosocial and pharmacologic predictors of satisfaction with intravenous patient-controlled analgesia. Anesth Analg 1993;77:121–5.