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Preoperative Pain Sensitivity and Its Correlation with Postoperative Pain and Analgesic Consumption

A Qualitative Systematic Review

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ABSTRACT

Pain perception to minor physical stimuli has been hypothesized to be related to subsequent pain ratings after surgery. The objective of this systematic review was to evaluate the correlation between preoperative pain sensitivity and postoperative pain intensity. After a literature search of MEDLINE, EMBASE, and meeting abstracts, we identified 15 studies (n = 948 patients) with univariate and/or multivariate analysis on the topic. In these studies, three types of pain stimuli were applied: thermal, pressure, and electrical pain. The intensity of suprathreshold heat pain (*i.e.*, pain beyond patient threshold) was most consistently shown to correlate with postoperative pain. The most common limitation of the included studies was the method of statistical analysis and lack of multivariate analysis. More research is required to establish the correlation of other pain sensitivity variables with postoperative pain outcomes.

TREATMENT of postoperative pain continues to be an ongoing challenge, despite the use of multimodal analgesic techniques. If not managed effectively, postoperative pain can lead to prolonged rehabilitation, poor surgical outcomes, and increased risk of cardiovascular and pulmonary complications.[1–4] Acute postoperative pain also may be an important predictor of persistent pain after major surgical procedures.[5]

Pain is a multifaceted phenomenon that consists of physiological, emotional, and behavioral components, and it is influenced by genetic factors.[6,7] Individual variability in any of these factors can lead to different pain experiences, as well as variable response to pain-management therapies. Therefore, identification of patients at risk of severe postoperative pain will allow more individualized and effective pain management. This approach will also prevent unnecessary treatment of low-risk patients and thus reduce the risk of potential adverse effects of postoperative analgesic medications.

In this regard, a systematic review of 48 studies showed that preoperative pain, age, anxiety, and type of surgery were independently correlated with postoperative pain and/or analgesic consumption.[8] The coefficient of determination (R^2) of the predictive models of postoperative pain was less than 54%, leaving approximately half of the variability unexplained by the tested variables. Therefore, other variables exist that contribute to the complexity of the postoperative pain outcomes.

Previous experimental and some human studies suggest that preoperative pain sensitivity may correlate with postsurgical clinical pain.[9–11] Pain perception to physical stimuli has been hypothesized to predict subsequent pain ratings after surgery.[10] Therefore, those patients who can tolerate more pain preoperatively will report a lower postoperative pain score and may require less analgesia.

The utility and optimal modality for testing pain sensitivity for predicting acute post surgical pain is unclear. Quantitative assessment of pain sensitivity has been reliably used in other clinical pain research (*e.g.*, on patients with neuropathic pain).[12,13] In this method, different pain modalities (thermal, pressure, or chemical) are applied to different tissues (skin, muscles, and viscera), and the responses are assessed to determine pain threshold and other related parameters.[12] If preoperative pain sensitivity testing predicts postoperative pain intensity, this method may be used to identify patients who will require more intensive pain management postoperatively.

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Table 1. Methodological Quality of the Studies

	Lautenbacher *et al.*[16]	Weissman-Fogel *et al.*[28]	Aasvang *et al.*[20]	Lundblad *et al.*[25]	Rudin *et al.*[27]	Yarnitsky *et al.*[18]	Martinez *et al.*[30]
Sampling							
The sampling frame or recruitment described (*e.g.,* setting, time, and location)?	+	+	+	+	+	+	+
Exclusion/inclusion criteria strictly outlined?	+	+	+	−	+	−	+
The important basic characteristics of the sample reported?	+	+	+	+	−	+	+
Measurements							
Clear definition or description of the predictive factors?	+	+	+	+	+	+	+
The predictive factors measured by valid and reliable instruments?	+	+	+	+	+	+	+
Clear definition or description of the outcomes?	+	+	+	+	+	+	+
The outcomes measured by valid and reliable instruments?	+	+	+	+	+	+	+
Postoperative measurement blinded from the preoperative data?	?	?	+	?	?	+	?
Analysis							
Multivariate analysis was used to adjust for all potential confounders?	+	+	−	+	+	+	−
If multivariate analysis, overfitting of the data avoided?	?	?	N/A	?	+	?	N/A
If multivariate analysis, multicollinearity avoided?	+	?	N/A	?	+	?	N/A
If multivariate analysis, the model prospectively validated?	?	?	N/A	?	?	?	N/A
Follow up							
Complete data for at least 80% of the initial study sample size?	+	+	+	+	−	+	+
Reasons for loss to follow-up provided?	N/A	N/A	+	N/A	+	N/A	N/A
The basic characteristics of those who lost to follow-up reported?	N/A	N/A	−	N/A	−	N/A	N/A

+ = yes; − = no; ? = unclear; N/A = not applicable.

The purpose of this systematic review is to identify and summarize the modalities used in the preoperative assessment of pain sensitivity and to evaluate the correlation with postoperative pain intensity, analgesic consumption, and the occurrence of persistent postsurgical pain.

Materials and Methods

Search Strategy

The databases EMBASE (1980–November 2009), MEDLINE (1966–November 2009), and the Cochrane

Table 1. Continued

Nielsen *et al.*[26]	Strulov *et al.*[29]	Pan *et al.*[11]	Hsu *et al.*[21]	Werner *et al.*[10]	Granot *et al.*[9]	Wilder-Smith *et al.*[19]	Bisgaard *et al.*[23]
+	+	+	+	+	+	+	+
+	−	+	+	−	−	+	+
+	−	+	+	−	−	+	+
+	+	+	+	+	+	+	+
+	+	+	+	+	+	+	+
+	+	+	+	+	+	+	+
+	+	+	+	+	+	+	+
+	?	?	?	?	?	?	?
−	+	+	+	−	−	−	+
N/A	?	?	?	N/A	N/A	N/A	?
N/A	?	+	?	N/A	N/A	N/A	?
N/A	?	?	?	N/A	N/A	N/A	?
+	+	+	+	+	?	?	+
+	N/A	N/A	N/A	N/A	N/A	N/A	+
−	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (Issue 4, 2009) were searched to retrieve articles on the topic. The following keywords were used in the search: quantitative sensory test, preoperative, perioperative, postoperative, postsurgical, postoperative pain, threshold, anesthesia, analgesia, postprocedure, algometer, pain matcher, and thermal sensory analysis. Furthermore, the following subheadings were explored: perioperative/postoperative/intraoperative/reoperative care, surgical procedures, anesthesia, anesthesiology, pain threshold, pain measurement, physical/electrical stimulation, cold/hot temperature, and pain. We also reviewed the abstracts of the following meetings: Canadian Anesthesiologists' Society (2000–2009), American Society of Anesthesiologists (2000–2009), and International Anesthesia Research Society (2000–2009). A manual search of the reference lists from the selected articles was conducted to identify additional trials.

Selection Criteria

The search results were evaluated by two independent reviewers to find the eligible articles for inclusion. Any disagreements between the authors were resolved by discussion or by consulting with the senior author. In the first phase of the review, obviously irrelevant articles were excluded by reviewing the title of the search results. In the next phase, the abstract and/or full-text articles were evaluated to determine whether they met the eligibility criteria. All observational studies with univariate and/or multivariate analysis were eligible for inclusion if they studied the correlation between preoperative pain sensitivity parameters and postoperative pain outcomes (*i.e.*, acute postoperative pain intensity, analgesic consumption, and chronic postoperative pain existence or intensity). Moreover, the included studies must have met these criteria: human trials, adult patients 18 yr or older, and published in English.

Quality Assessment of the Studies

Two independent reviewers assessed quality by using the criteria shown in table 1, and any disagreements were resolved by discussion. If a resolution could not be reached, the opinions of the senior authors were sought. The practical guideline of evaluation of the quality of prognosis studies was used for appraisal of the included studies.[14] The assessment was based on four categories: sampling, measurement, statistical analysis, and follow-up (table 1). We did not adopt a scoring system because it is not necessarily a scientific approach.[14] We evaluated each of the categories separately in every study. Each category was composed of different questions that could be answered "yes," "no," "unclear," or "not applicable." If all the applicable questions in a category were answered "yes," the category was considered fully met. If the category had half or more than half the questions answered "yes," the study was considered partly met, and if less than half of the questions were answered "yes," the category was considered unsure. Finally, the category was considered not met if all the related questions were answered as "no."

Data Extraction, Data Analysis, and Conclusion Synthesis

Data extraction was performed by two reviewers and validated by the senior author. The following data were extracted

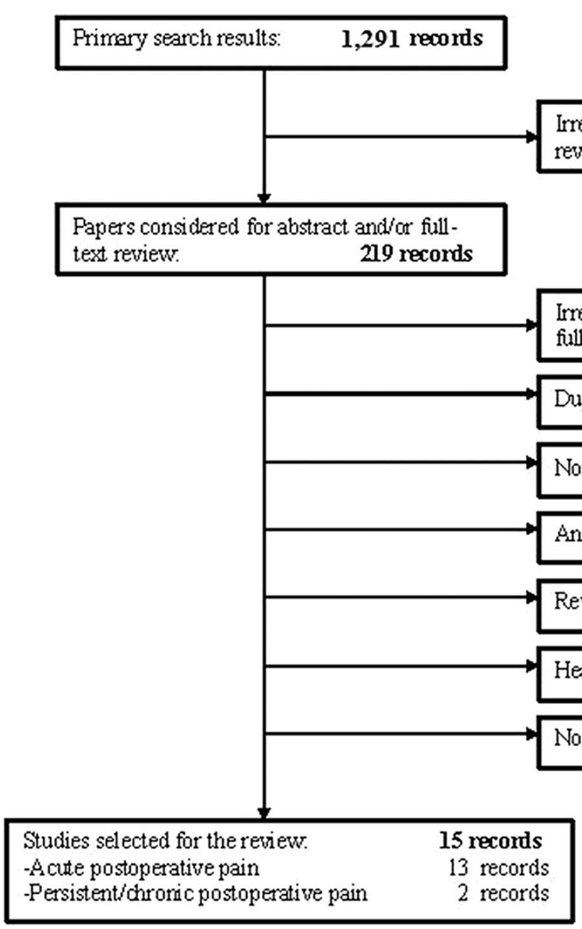

Fig. 1. Flowchart of the literature search and study selection.

from each study: sample size, type of surgery, patient demographic data, measures of predictive preoperative factors, type of pain stimulus and instruments used for preoperative pain sensitivity, the methods of pain sensitivity testing, outcome measures, time course of the assessment, type of statistical methods (univariate *vs.* multivariate analysis), coefficient of regression (β), the squared multiple correlation (R^2) of the regression models, coefficient of correlation (r) in the bivariate linear regression analysis, and the respective P values. The review included two primary outcomes: (1) postoperative pain intensity, which includes acute postoperative pain and/or chronic or persisting pain as defined in each study; and (2) the amount of postoperative analgesic consumption. Each article was assessed to verify whether the preoperative pain sensitivity parameters were significantly (P value less than 0.05) correlated with the postoperative outcomes of the study and to determine the direction of the correlation (+, direct correlation; −, reverse correlation). The results are presented in summary tables that are used for descriptive analysis and conclusion synthesis. Meta-analysis of the results (*e.g.*, pooling of the correlation coefficients) was not feasible because of obvious clinical inconsistency among the studies in terms of their design (*e.g.*, type of pain stimulus or statistical analysis).

Measures of Preoperative Pain Sensitivity

Pain threshold is considered the level of the stimulus at which the participants perceived the first painful sensation (*i.e.*, the nonpainful stimulus changed into a painful stimulus). *Pain tolerance* is considered the level of stimulation that is perceived by the participants as intolerable pain. *Intensity of suprathreshold pain* is the amount of pain that a patient perceives after a stimulus with intensity higher than the patient's pain threshold. *Temporal summation of pain* is a dynamic measure of pain sensitivity that reflects the central sensitization of pain after repetitive painful stimulation and is calculated as the difference between the pain score evoked by a single stimulus and the pain score evoked by trains of several stimuli delivered later.[15,16] Another dynamic pain measure is *diffuse noxious inhibitory control*, which reflects the pain-inhibits-pain phenomenon and is defined as pain reduction during exposure to another painful stimulus (conditioning stimulus) at a remote body area (*e.g.*, immersion of the other hand in hot water).[17,18]

Table 2. Study Characteristics

Study	Country	Sample Size	M/F	Age, yr (Range)	ASA (I/II/III)	Surgery Type
Lautenbacher *et al.*[16]	Germany	54	54/0	18 ± 4	—	Major elective thoracic surgery
Weissman-Fogel *et al.*[28]	Israel	84	49/35	62 ± 13	—	Major elective thoracic surgery
Aasvang *et al.*[20]	Denmark	165	165/0	59 (21–85)	—	Primary unilateral hernial surgery
Lundblad *et al.*[25]	Sweden	69	34/35	68 (40–80)	—	Total knee replacement
Rudin *et al.*[27]	Sweden	59	0/59	38 (35–41)	—	Laparoscopic tubal ligation
Yarnitsky *et al.*[18]	Israel	62	38/24	62 (19–86)	—	Major elective thoracic surgery
Martinez *et al.*[30]	France	20	1/19	69 ± 2	—	Total knee replacement
Nielsen *et al.*[26]	Denmark	45	0/45	35 (32–37)	I	Elective cesarean section
Strulov *et al.*[29]	Israel	47	0/47	—	—	Elective cesarean section
Pan *et al.*[11]	USA	34	0/34	—	I or II	Elective cesarean section
Hsu *et al.*[21]	Taiwan	40	0/40	41 ± 6	I or II	Lower abdominal gynecologic surgery
Werner *et al.*[10]	Denmark	20	14/6	28 (24–33)	—	Knee arthroscopic surgery
Granot *et al.*[9]	Israel	58	0/58	—	—	Elective cesarean section
Wilder-Smith *et al.*[19]	Switzerland	41	31/10	46 (21–64)	I or II	Elective disc herniation surgery
Bisgaard *et al.*[23]	Denmark	150	21/129	41 (20–79)	120/28/2	Laparoscopic cholecystectomy

ASA = American Society of Anesthesiologists class; F = female; M = male.

Table 3. Summary of the Methods of Variable Measurements in the Included Studies

	Preop Pain Assessment				Other Preop Outcome	Postop Pain Assessment	
Study	Stimulus	Pain Measure	Tool	Site		Measure	Time
Lautenbacher *et al.*[16]	Pressure	Pain threshold	Algometer	Forearm/volar (R)	Anxiety depression somatization hypervigilance	Pain score	Day 1–7
	Thermal	Pain threshold	TSA	Forearm/volar (R)		Analgesic (PCEA) use	Day 1–4
	Thermal	Temporal summation	TSA	Forearm/volar (R)			
Weissman-Fogel *et al.*[28]	Thermal	Pain threshold	TSA	—	Anxiety pain catastrophizing	Pain score	Day 1,5
	Thermal	Suprathreshold pain	TSA	Hand/Thenar (D)			
	Thermal	Temporal summation	Pathway system	Forearm/volar (D)			
	Pressure	Temporal summation	Von Frey hairs	Forearm/volar (D)			
	Pressure	Suprathreshold pain	Von Frey hairs	Forearm/volar (D)			
Aasvang *et al.*[20]	Electrical	Pain threshold	Pain Matcher	1st and 2nd finger	—	Pain score	Day 1–7 (daily)
	Electrical	Pain tolerance	Pain Matcher	1st and 2nd finger			
Lundblad *et al.*[25]	Electrical	Pain threshold	Pain Matcher	1st and 2nd finger (R)	—	Pain score	After 18 months
Rudin *et al.*[27]	Thermal	Pain threshold	MSA Thermotest	Calf/medial side (ND)	Anxiety	Pain score	Day 0–10 (daily)
	Thermal	Suprathreshold pain	MSA Thermotest	Calf/medial side (ND)			
Yarnitsky *et al.*[18]	Thermal	Pain threshold	TSA	Forearm/volar (D)	—	Pain score	After 29 weeks
	Thermal	DNIC	TSA	Forearm/volar (D)			
	Thermal	Suprathreshold pain	TSA	Forearm/volar (D)			
Martinez *et al.*[30]	Thermal	Pain threshold	MSA Thermotest	Knee/patella (OS)	—	Pain score	Day 0,1,4
	Thermal	Suprathreshold pain	MSA Thermotest	Knee/patella (OS)		Analgesic (PCA) use	Day 1,2
	Pressure	Pain threshold	Von Frey hairs	Knee/patella (OS)			
Nielsen *et al.*[26]	Electrical	Pain threshold	Pain Matcher	1st and 2nd finger	—	Pain score	Day 0–2 (daily)
Strulov *et al.*[29]	Thermal	Pain threshold	TSA	Forearm/volar (ND)	Pain catastrophizing	Pain score	Day 1,2
	Thermal	Suprathreshold pain	TSA	Forearm/volar (ND)		Analgesic use	Day1
Pan *et al.*[11]	Thermal	Pain threshold	TSA	Forearm/volar (D), back	Anxiety	Pain score	Day 1
	Thermal	Suprathreshold pain	TSA	Forearm/volar (D), back		Analgesic (PCA) use	PACU, Day 0
Hsu *et al.*[21]	Pressure	Pain threshold	Algometer	3rd finger pulp (R)	Anxiety	Pain score	PACU, Day 1
	Pressure	Tolerance threshold	Algometer	3rd finger pulp (R)		Analgesic (PCA) use	PACU, Day 1

(*continued*)

Table 3. Continued

Study	Preop Pain Assessment				Other Preop Outcome	Postop Pain Assessment	
	Stimulus	Pain Measure	Tool	Site		Measure	Time
Werner *et al.*[10]	Thermal	Pain threshold	—	Calf/medial side (NOS)	—	Pain score	Day 0–10 (daily)
	Pressure	Pain threshold	Von Frey hairs	Calf/medial side (NOS)			
Granot *et al.*[9]	Thermal	Pain threshold	TSA	Forearm/volar (ND)	—	Pain score	Day 1
	Thermal	Suprathreshold pain	TSA	Forearm/volar (ND)			
Wilder-Smith *et al.*[19]	Electrical	Pain threshold	Biometer	Back, leg, arm (OS)	—	Pain score	Day 0,1,5
	Electrical	Pain tolerance	Biometer	Back, leg, arm (OS)		Analgesic use	Day 0,1
Bisgaard *et al.*[23]	Thermal	Pain threshold	ice water	Hand (ND)	Neuroticism, pain expectation	Pain score	Day 0–7 (daily)

Hypervigilance refers to repetitive and autonomic prioritization of pain.
D = dominant side; DNIC = diffuse noxious inhibitory control; MSA = manual sensory analyzer; ND = nondominant; NOS = nonoperating side; OS = operating side; PACU = postanesthesia care unit; PCA = patient-controlled analgesia; PCEA = patient-controlled epidural analgesia; postop = postoperative; preop = preoperative; R = right; TSA = thermal sensory analyzer side.

Results

Literature Search and Study Characteristics

The search strategy resulted in an initial yield of 1,291 citations. After reviewing the titles and the abstract of the studies, 1,072 and 145 records were found irrelevant, respectively. Subsequently, 59 studies were excluded for various reasons, including animal studies, duplicate reports of the same study in different journals, studies published in the non-English language, a narrative review article,[15] a study on healthy volunteers not undergoing surgery,[17] and a study without the postoperative pain outcomes (fig. 1).[19] Finally, 15 studies (n = 948 patients) were included in the analysis of this systematic review.

Six studies originated from Scandinavia, three from the rest of Europe, four from Israel, one from the United States, and one from Asia. The studies were published from 2001 to 2009. The characteristics of all the included studies are shown in table 2. The studies were variable in terms of sample size, type of surgery, patient demographics, and type of instruments used to measure the variables. The mean sample size was 54 with a range of 20–165 patients. The most common type of surgery was gynecological procedures followed by thoracic orthopedic surgery and laparoscopic abdominal surgery. The average age of the patients ranged from 18 to 69 yr (table 2).

Methodologic Quality of the Studies

The details of the quality assessment of each study can be found in table 1. Only two studies (13.3% of all the included studies) partially or fully met each category of the quality assessment.[11,18] The remaining studies had at least one category of the quality assessment considered unsure or not met. In terms of *sampling*, 12 studies fully or partially met the criteria and 3 studies were considered unsure. Regarding the validity of the *measurements*, three studies fully met the quality criteria, whereas the remaining studies partially met these criteria because they did not clearly report whether the preoperative measurements were blinded from the postoperative assessment. The most common limitation among all the included studies was in the *analysis* category because none of the studies fully met its criteria (table 1). This was due to the lack of multivariate analysis, insufficient measures to avoid collinearity or overfitting, and the lack of external validation of the multiple regression models. Finally, in terms of *follow-up* completeness, 12 studies fully or partially met the criteria, and the remaining studies were considered unsure. Because of insufficient raw data from the included studies, it was not possible to perform the sensitivity analysis to determine the effect of this quality assessment on the synthesis of the final conclusion.

Preoperative Assessments of Pain Sensitivity

The timing of the preoperative pain assessment was reported in 14 of 15 included studies. The preoperative pain evaluations were performed 1–4 weeks before surgery in three studies[10,11,20] or 1–3 days before surgery in nine studies. In two studies, the assessments were carried out on the day of surgery either at the preoperative holding area[21] or in the operating theater.[22] Three types of pain stimuli were applied: thermal (heat and cold) in 10 studies, pressure in 5 studies, and electrical pain in 4 studies. Several studies examined more than one type of pain stimulus such that the total number may exceed the total number of the included studies.

Thermal Pain

Thermal pain, which was used in 10 studies, was the most common stimulus applied to evaluate pain sensitivity. Thermal stimuli were delivered by use of computerized thermal stimulators into different anatomical places, such as the forearm, calf, hands, or over the knee in patients undergoing knee replacement surgery (table 3). In most studies, the thermal pain threshold was determined by application of a baseline temperature (*e.g.*, 32°C), which was then gradually increased or decreased. Werner *et al.*[10] assessed pain threshold within the area of a first-degree burn injury, which was induced on the calf for the study purposes. In the study by Bisgaard *et al.*,[23] patients were asked to immerse the nondominant hand into ice water (0–1°C) to measure cold pain threshold.

Pressure Pain

Pressure stimulus, which was used in five studies, was the second most common type of pain stimulation. Pressure stimuli were delivered by use of a handheld pressure applier or a series of calibrated rigid filaments (von Frey hairs). These hairs are made from nylon filaments of varying diameters and are used to apply a precise force over the skin (*i.e.*, point pressure) for pressure pain analysis.[24] The pressure stimulation was applied over the forearm, fingers, and knee or within the area of a first-degree burn on the calf (table 3).

Electrical Pain

Electrical stimulus was the least common type of pain stimulation, and it was used in four studies (26.6% of all the included studies).[20,22,25,26] Electrical stimuli were delivered by use of an electrical stimulation device (table 3). These instruments provided constant current stimulations, despite the variable skin resistance. The electrical stimuli were applied over the fingers, thighs, arms, or the back next to the planned surgical incision.

Other Preoperative Measures

Anxiety, pain catastrophizing, and other psychological measures were among the most common variables evaluated before surgery in the included studies (table 3). Preoperative anxiety was assessed using the State-Trait Anxiety Inventory and was shown to significantly correlate with postoperative pain in five studies.[11,16,21,27,28] Pain catastrophizing was examined in three studies[16,28,29] by use of the Pain Catastrophizing Scale, which contains questions about inability to inhibit pain-related thoughts, magnification of pain situations, helplessness, and expectations of negative outcomes. These studies showed a significant correlation between the Pain Catastrophizing Scale and the intensity of postoperative pain. In addition to preoperative anxiety and pain cata-

Table 4. Preoperative Pain Sensitivity Variables and Their Correlation with Acute Postoperative Pain

Preoperative Variables	Type of Analysis	Lautenbacher *et al.*[16]	Weissman-Fogel *et al.*[28]	Aasvang *et al.*[20]	Rudin *et al.*[27]	Martinez *et al.*[30]	Nielsen *et al.*[26]	Strulov *et al.*[29]
Heat pain threshold	U	+	−	—	0	0	—	0
	M	+	0	—	0	—	—	0
Cold pain threshold	U	0	—	—	—	—	—	—
	M	0	—	—	—	—	—	—
Suprathreshold heat pain	U	—	0	—	+	0	—	+
	M	—	0	—	+	—	—	+
Temporal summation of heat pain	U	0	0	—	—	—	—	—
	M	0	0	—	—	—	—	—
Pressure pain threshold	U	0	—	—	—	0	—	—
	M	0	—	—	—	—	—	—
Pressure pain tolerance	U	—	—	—	—	—	—	—
	M	—	—	—	—	—	—	—
Suprathreshold pressure pain	U	—	+	—	—	—	—	—
	M	—	+	—	—	—	—	—
Temporal summation of pressure pain	U	—	+	—	—	—	—	—
	M	—	+	—	—	—	—	—
Electrical pain threshold	U	—	—	0	—	—	−	—
	M	—	—	—	—	—	—	—
Electrical pain tolerance	U	—	—	0	—	—	—	—
	M	—	—	—	—	—	—	—

Please refer to the text for exact definition of the preoperative parameters.

— = no analysis on the relevant parameters; M = multivariate analysis; U = univariate analysis; + = positive correlation; − = negative correlation; 0 = no significant correlation (significance level; $P < 0.05$).

strophizing, Lautenbacher *et al.*[16] also proposed pain hypervigilance, a strong attentional bias toward pain, as an important predictor of postoperative pain, which could explain approximately 17% of variation in the intensity of postoperative pain.

Correlation between Preoperative Variables and Postoperative Pain Outcomes

Postoperative Pain Intensity. Acute postoperative pain was evaluated in 13 studies. Chronic postoperative pain was assessed in two studies. The assessment time was variable among the studies, ranging from the day of surgery, when the patient was in the postanesthesia care unit, to 2–10 days after surgery. In 61.5% (8 of 13) of the studies in this group, multiple regression analysis was used to evaluate the independent correlation between preoperative variables and postoperative pain intensity. The summary of the results of both multivariate and univariate analysis is shown in table 4.

In univariate analyses, heat pain threshold (eight studies), suprathreshold heat pain (six studies), pressure pain threshold (four studies), and electrical pain threshold (three studies) were among the most common variables assessed in the included studies (table 4). Of these variables, only suprathreshold heat pain was consistently shown to have significant correlation with the intensity of postoperative pain as reported in four studies. The coefficient of correlation (r) for this variable ranged from 0.37 to 0.49 (all P values less than 0.05).

In multivariate analyses, the most commonly studied variables were heat pain threshold (five studies) and suprathreshold heat pain (four studies). Suprathreshold heat pain was shown to have positive correlation with postoperative pain intensity in 75% of the studies. The coefficient of regression (β) and the squared multiple correlation (R^2) ranged from 0.30 to 0.41 and from 0.17 to 0.59, respectively (all P values less than 0.05).

Chronic postoperative pain was examined in two studies. Yarnitsky *et al.*[18] evaluated the development of chronic post-thoracotomy pain at 29 weeks after surgery. This study showed that diffuse noxious inhibitory control was significantly related to pain as shown with both multivariate and univariate analysis. The logistic regression analysis showed that a 10-point reduction in the score of heat pain during exposure to another painful stimulus could decrease the risk of developing chronic pain by 52% (odds ratio = 0.52; 95% CI = 0.33–0.77; P = 0.0024). Lundbald *et al.*[25] showed that electrical pain threshold was significantly related to chronic pain 18 months after knee replacement surgery. The

Table 4. Continued

Pan *et al.*[11]	Hsu *et al.*[21]	Werner *et al.*[10]	Granot *et al.*[9]	Wilder-Smith *et al.*[19]	Bisgaard *et al.*[23]	Summary: No. of Studies	Any Correlation +	Any Correlation −	No Correlation
−	—	0	0	—	—	8	1	2	5
−	—	—	—	—	—	5	1	1	3
—	—	—	—	—	+	2	1	0	1
—	—	—	—	—	+	2	1	0	1
+	—	—	+	—	—	6	4	0	2
+	—	—	—	—	—	4	3	0	1
—	—	—	—	—	—	2	0	0	2
—	—	—	—	—	—	2	0	0	2
—	−	0	—	—	—	4	0	1	3
—	0	—	—	—	—	2	0	0	2
—	−	—	—	—	—	1	0	1	0
—	−	—	—	—	—	1	0	1	0
—	—	—	—	—	—	1	1	0	0
—	—	—	—	—	—	1	1	0	0
—	—	—	—	—	—	1	1	0	0
—	—	—	—	—	—	1	1	0	0
—	—	—	—	0	—	3	0	1	2
—	—	—	—	—	—	0	0	0	0
—	—	—	—	0	—	2	0	0	2
—	—	—	—	—	—	0	0	0	0

Table 5. Preoperative Pain Sensitivity Variables and Their Correlation with Postoperative Analgesic Consumption

							Summary			
								Any Correlation		
Preoperative Parameters	Type of Analysis	Lautenbacher *et al.*[16]	Martinez *et al.*[30]	Strulov *et al.*[29]	Pan *et al.*[11]	Hsu *et al.*[21]	No. of Studies	+	−	No Correlation
Heat pain threshold	U	0	0	0	−	—	4	0	1	3
	M	0	—	0	−	—	3	0	1	2
Cold pain threshold	U	0	—	—	—	—	1	0	0	1
	M	0	—	—	—	—	1	0	0	1
Suprathreshold heat pain	U	—	+	0	+	—	3	2	0	1
	M	—	—	0	0	—	2	0	0	2
Temporal summation of heat pain	U	0	—	—	—	—	1	0	0	1
	M	0	—	—	—	—	1	0	0	1
Pressure pain threshold	U	0	0	—	—	0	3	0	0	3
	M	0	—	—	—	0	2	0	0	2
Pressure pain tolerance	U	—	—	—	—	−	1	0	1	0
	M	—	—	—	—	−	1	0	1	0

Please refer to the text for exact definition of the preoperative parameters.

— = no analysis on the relevant parameters; M = multivariate analysis; U = univariate analysis; + = positive correlation; − = negative correlation; 0 = no significant correlation (significance level; $P < 0.05$).

lower the threshold preoperatively, the higher the risk of developing chronic pain (odds ratio = 9.2; 95% CI = 1.69–50.1; $P = 0.01$).

Postoperative Analgesic Consumption. The amount of postoperative analgesic consumption was reported as an outcome in five studies. The outcomes reported included the following: postoperative use of intravenous morphine using patient-controlled analgesia in three studies (table 3), postoperative use of oral opioid and nonopioid analgesics,[29] and postoperative use of patient-controlled epidural analgesia.[16] The assessment period was from the postanesthesia care unit to 1–5 days after surgery. The summary of the results of both multivariate and univariate analysis is shown in table 5.

In univariate analyses, heat pain threshold (four studies), suprathreshold heat pain (three studies), and pressure pain threshold (three studies) were among the most common variables assessed in the included studies (table 5). Similar to the results of multivariate analysis, only suprathreshold heat pain was relatively associated with consistent findings in the studies. Two of the three studies on this factor showed that there was a positive correlation between the suprathreshold heat pain and the amount of postoperative analgesic consumption. The coefficient of correlation (r) for this variable was 0.48 and 0.63 (all P values less than 0.05) as reported by Pan *et al.*[11] and Martinez *et al.*,[30] respectively.

Multivariate analysis was performed in only two studies. In these studies, suprathreshold heat pain failed to correlate with postoperative analgesic requirements. Heat pain threshold and pressure pain tolerance, each studied separately (*i.e.*, Pan *et al.*[11] and Hsu *et al.*,[21] respectively), were the only factors found to be related to postoperative analgesic use in both multivariate and univariate analyses. Both factors had negative correlation with the amount of analgesics used after surgery (table 5). The coefficient of regression (β) and the squared multiple correlation (R^2) ranged from −0.049 to −0.24 and from 0.27 to 0.46, respectively (all P values were less than or equal to 0.01). Other factors were not related to postoperative analgesic consumption.

Discussion

This systematic review includes 15 clinical studies on preoperative pain sensitivity testing and its correlation with postoperative pain outcomes. Thermal, pressure, and electrical stimuli were used in the included studies to measure various types of pain sensitivity variables. The techniques used in the preoperative assessments were reviewed and summarized in detail. An important finding of this systematic review was that the response to suprathreshold heat pain could consistently predict postoperative pain outcomes, whereas no significant correlation was consistently found between heat pain threshold and postoperative pain. Suprathreshold heat pain was shown to have a positive correlation with postoperative pain. A definite conclusion could not be drawn regarding the correlation between other preoperative pain measures and postoperative pain because they were either associated with conflicting results (*e.g.*, pain threshold) or analyzed only in individual studies (*e.g.*, pain tolerance and temporal summation).

Pain threshold reveals the transition point between painful and nonpainful sensations but does not necessarily represent the patient's experience of a clinically painful situation. Suprathreshold painful stimuli, which are at a level between pain threshold and tolerance, may more closely mimic the pain experience caused by surgical trauma. Therefore, it may be suggested that although pain threshold, suprathreshold pain, and pain tolerance are all considered *static* measures of pain sensitivity,[15] they refer to different points in our experience of pain and have different prognostic values in predicting the subsequent clinical pain. Similar to the results of this review, experimental genetic studies in mice showed that suprathreshold, not the baseline pain threshold, had the best correlation with postoperative pain, possibly because only the former is thought to activate central pain modulatory systems or is genetically linked to hypersensitivity.[31]

It also should be noted that these findings were observed mainly in the studies on healthy female patients undergoing elective cesarean section or gynecologic procedures.[9,27,29] On the other hand, studies of mixed-gender populations[28] or of patients with preoperative pathologic pain[30] failed to show the superiority of suprathreshold pain over the pain threshold for predicting postoperative pain intensity. This discrepancy may be related to the following factors:

Female sex may be a confounding factor that is related to both postoperative pain outcomes and preoperative pain sensitivity parameters. A meta-analysis of the results of studies on postsurgical pain predictors showed that female sex is moderately related to postoperative pain severity.[8] In addition, a meta-analysis of studies on experimental pain sensitivity showed that there was a weak but statistically significant correlation between sex and thermal pain threshold (*i.e.*, the male subjects' mean pain threshold was higher than female subjects).[32] In our review, approximately half of the studies were gender-specific surgery (men or women), so the effect of gender could not be analyzed in these studies.

Pain threshold has been shown to be increased in pregnant humans. In this regard, Carvalho *et al.*[33] showed that heat pain tolerance was significantly increased in pregnant women before and after delivery compared with nonpregnant control subjects. The exact mechanism of this phenomenon has not yet been established in human studies, but animal studies showed that activation of the endorphin system and increased circulating estrogen and progesterone may cause pregnancy-induced nociceptive changes.[34–36]

Pathologic chronic pain can also modulate our response to an experimental painful stimulus. In this regard, Martinez *et al.*[30] showed that during preoperative assessments, the responses to the suprathreshold heat stimuli were significantly increased on the operative knee compared with the intact knee. Therefore, there is some degree of hyperalgesia in the affected knee, mainly as a result of peripheral nerve sensitization caused by inflammatory mediators, such as prostaglandins and other cytokines.[30]

The confounding effect of emotional factors such as preoperative anxiety and pain catastrophizing on preoperative pain sensitivity, as well as postoperative pain values, has not been fully evaluated among the included studies. The assessment of pain sensitivity may not reflect the complex emotional and psychological postoperative pain experience. Anxiety and psychological stress were found to be predictors of postoperative pain and analgesic consumption, respectively.[8] In addition, the impact of anxiety or nervousness on pain threshold has been shown in human and animal studies.[37–39] Therefore, emotional factors may affect the results of correlational studies on postoperative pain, and the results need to be adjusted using multivariate analysis. This was carried out in less than half of the included studies. However, our results show that suprathreshold heat pain is an independent predictor of postoperative pain.

The results of this systematic review should be interpreted considering the following limitations of the review and the included studies. The significant heterogeneity of the included studies precluded a meta-analysis of the results (*i.e.*, pooling of the regression coefficients) (table 3). The methodologic quality of the studies showed that the majority had only univariate analysis rather than multivariate analysis (*i.e.*, the analysis of multiple variables simultaneously). Therefore, the results of these studies could have been affected by other confounding factors, such as demographics or emotional factors. In the studies with multivariate analysis, major problems such as unblinded measurements, as well as lack of external validation of the regression models, were noticed. In addition, two of the three studies with a positive correlation between preoperative suprathreshold heat pain and postoperative pain outcome[27,29] have a number of uncertain factors, specifically relating to multivariate analysis but, to some extent, even sampling. Because there are very few studies with adequate methodologic quality, sensitivity analysis to evaluate the effect of the validity on the conclusion could not be carried out in this review. Therefore, the conclusion is based on the results of the studies with different quality.

None of the included studies mentioned whether they were statistically powered to eliminate the risk of type II error in their analysis. Therefore, the *no correlation* findings in the studies (table 4 and 5) may not mean that there is no relationship between the study variable but may be due to a relatively small sample size or other factors that could affect the precision of a correlational study. Finally, low predictability values of the existing multivariate models on preoperative pain sensitivity parameters ($R^2 = 0.17–0.59$ for postoperative pain and 0.27–0.46 for postoperative analgesic consumption) may indicate that there are other potentially important predictors that have not been measured and/or analyzed in the included studies.

The generalizability of the results of this review should be carried out cautiously considering the following factors. A major percentage of the studies were from Western countries, and there is only one article from Asia. Only a few studies reported the American Society of Anesthesiologists' classification; thus a general assessment of the patient's medical condition cannot be made from the studies. The perioperative pain sensitivity was studied at various time intervals up to 4 weeks before planned surgery and up to 7 days postoperatively. In the studies that showed a significant correlation between suprathreshold heat pain and postoperative pain outcomes, the preoperative assessment was performed 1–3 days before surgery and postoperative assessment was done 1–2 days after surgery (table 3 and 4). Therefore, these results do not necessarily apply to the longer assessment periods.

In conclusion, the results of this systematic review suggest that high levels of pain intensity evoked by a suprathreshold heat stimulus were most consistently associated with higher postoperative pain. These results, however, apply only to female patients, because this correlation was not found in studies including male patients. Therefore, suprathreshold heat pain can be suggested as an important predictor of postoperative pain in female patients. More research is required to establish the correlation of other pain sensitivity variables with postoperative clinical pain and to evaluate the effect of sex differences on these correlations. In addition, the correlation between pain sensitivity and other predictors of postoperative pain (*e.g.*, anxiety) need to be assessed with multivariate analysis.

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ANESTHESIOLOGY REFLECTIONS

Annie Oakley Guns Down "Cocaine Libel"

From 6 to 15 yr of age, sharpshooter Phoebe "Annie" Mosey (1860–1926) sniped at rural Ohio's wild game with such accurate "headshots" that her proceeds paid off her widowed mother's mortgage. Avoiding Annie's stage surname of Oakley (a family name from a Cincinnati suburb), "Buffalo Bill" Cody billed her from 1885 to 1901 on his "Wild West Show" as Sitting Bull's adopted daughter, "Little Sure Shot." Later, after newspapers sensationalized a Chicago actress' confusing claim of abusing cocaine as "Any Oakley," the real Annie gunned down 54 of her 55 legal opponents in libel suits. Ironically, a 66-yr-old Annie Oakley would die . . . not from a gunshot . . . but from the lack of a shot—lack of a simple vitamin B-12 injection to reverse the fatal course of her pernicious anemia. (Copyright © the American Society of Anesthesiologists, Inc. This image also appears in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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