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Prediction of Postoperative Pain

A Systematic Review of Predictive Experimental Pain Studies

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ABSTRACT

Quantitative testing of a patient's basal pain perception before surgery has the potential to be of clinical value if it can accurately predict the magnitude of pain and requirement of analgesics after surgery. This review includes 14 studies that have investigated the correlation between preoperative responses to experimental pain stimuli and clinical postoperative pain and demonstrates that the preoperative pain tests may predict 4–54% of the variance in postoperative pain experience depending on the stimulation methods and the test paradigm used. The predictive strength is much higher than previously reported for single factor analyses of demographics and psychologic factors. In addition, some of these studies indicate that an increase in preoperative pain sensitivity is associated with a high probability of development of sustained postsurgical pain.

RECENT surveys indicate that postoperative pain still remains inadequately treated.[1–4] In addition, it has been estimated that up to 5% of individuals undergoing surgery will develop severe persisting pain leading to chronic physical disability and psychosocial distress.[5,6] In a number of studies, preexisting pain and high-intensity postoperative pain have been the predictors of development of persisting pain after surgery.[7–12]

The research in postoperative pain management has for more than two decades centered on delivery methods, pharmacotherapy with new drugs or combination of older drugs, and organizational aspects.[13,14] Despite extensive resources used on patient-controlled analgesia, spinal drug delivery methods, coanalgesics, multimodal analgesia, guidelines for acute pain management, and implementation of acute pain services, the results, in terms of an improved outcome after major surgery, seem unexpectedly modest.[15,16]

Therefore, the postoperative pain research has recently focused on investigating pharmacologic and psychophysiologic explanations for the insufficient pain relief, that is, an inadequate response to analgesics[17] or an increased response to pain.[18] Implementation of relevant preoperative screening methods may facilitate more aggressive pain therapies specifically targeted at individuals at a high risk of experiencing severe postoperative pain, which may translate to an improvement in postoperative rehabilitation and a reduction in short- and long-term morbidity.

This article is a review of studies investigating the correlation between responses to preoperatively applied experimental pain stimuli and clinical postoperative pain.[19–32]

Materials and Methods

Literature Search

Strategy. Ten of the studies included in this review were known to the authors before the start of the review. Reference lists in the included articles were reviewed for related articles. To cross-track studies, a citation search for each of these articles was made (ISI Web of Knowledge[SM]). The original articles were as of July 1, 2009 cited a total of 220 times (median 6 [interquartile range,

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Table 1. Surgical Procedures, Demographics, and Preoperative Tests

Study	Surgical Procedure	N	F:M	Age (yr)	Preoparative Pain Stimulus	Psychophysiologic Variable	Preoperative Pain Ratings	Psychologic Variable
Gynecological and obstetrical surgery								
Hsu *et al.*[23]	Abdominal hysterectomy or myomectomy	40	F	41* (±6)	Pressure	PPT, tolerance†	None	STAI-S
Granot *et al.*[20]	Cesarean section	58	F	NR	Heat	HPT, HSTP	VAS	
Wilder-Smith *et al.*[21]	Cesarean section	120	F	30‡ (27–32)	Electrical	EDT, EPT, ESTP	VRS	
Pan *et al.*[24]	Cesarean section	34	F	NR	Heat	HPT, HSTP	VAS	STAI, expectations
Strulov *et al.*[25]	Cesarean section	45	F	33* (±5)	Heat	HPT, HSTP	VAS (phasic) COVAS (tonic)	PCS preoperative/ postoperative
Nielsen *et al.*[26]	Cesarean section	39	F	35§ (32–37)	Electrical	EDT, EPT	Arbitrary units	
Rudin *et al.*[28]	Laparoscopic tubal ligation	59	F	38‡‡ (35–41)	Heat	WDT, HPT, HSTP	VAS	STAI, HADS, vulnerability
Abdominal surgery								
Aasvang *et al.*[31]	Groin hernia repair	162	M	59§ (21–85)	Electrical	EDT, EPT, EPTo	Arbitrary units	
Bisgaard *et al.*[19]	Laparoscopic cholecystectomy	150	129:21	41§ (20–79)	Cold	CPPTo	VAS	Vulnerability
Thoracic surgery								
Yarnitsky *et al.*[29]	Thoracotomy	62	24:38	62* (±14)	Heat	HPT, HSTP, DNIC	NPS	
Weissman-Fogel *et al.*[32]	Thoracotomy	84	35:49	62* (±13)	Heat	HPT, HSTP, HTS, MPT, MSTP, MTS	NPS	STAI, PCS
Knee surgery								
Werner *et al.*[22]	ACL	20	6:14	28‡ (24–33)	QST‖ Inflammatory injury#	WDT, HPT, HSTP, SHA	VAS	
Martinez *et al.*[27]	TKA	20	19:1	69* (±2)	QST**	CDT, CPT, WDT, HPT, HSTP, MPT	VAS	
Lundblad *et al.*[30]	TKA	69	35:34	68†† (40–80)	Electrical	EDT, EPT	VAS	

* Mean (±SD). † Before/after 2 μg/kg fentanyl. ‡ Mean (95% confidence interval). § Median (range). ‖ Warmth, heat, and punctuate. # 47°C, 7 min, 12.5 cm.^{2} ** Cold, cool, warmth, heat, and punctuate. †† Mean (range). ‡‡ Median (interquartile range).

ACL = knee arthroscopic repair of anterior cruciate ligament; CDT = cool detection threshold; COVAS = Computerized Visual Analogue Scale; CPPTo = cold pressor pain tolerance; CPT = cold pain threshold; DNIC = diffuse noxious inhibitory control; EDT = electrical detection threshold; EPT = electrical pain threshold; EPTo = electrical pain threshold; ESTP = electrical suprathreshold pain percept; F = female; HADS = Hospital Anxiety Depression Scale; HPT = heat pain threshold; HSTP = heat suprathreshold pain percept; HTS = heat temporal summation; M = male; MPT = mechanical pain threshold (von Frey); MSTP = mechanical suprathreshold pain percept (von Frey); MTS = mechanical temporal summation; NPS = Numerical Pain Scale; NR = not reported; PCS = Pain Catastrophizing Scale; PPT = pressure pain threshold; QST = quantitative sensory testing; SHA = secondary hyperalgesia area; STAI-S = State-Trait Anxiety Inventory-State; TKA = total knee arthroplasty; TPI = total pain intensity; VAS = Visual Analogue Scale; VRS = Verbal Rating Scale; WDT = warmth detection threshold.

3–21]), and these references were examined manually. Finally a PubMed, EMBASE, CINHAL, and Cochrane database search was performed between the years 1966 and 2009 using the MeSH terms postoperative pain, predictive value of tests, and pain measurement.

Quality Assessment. Nineteen quality domains[33] reflecting study population, study attrition, prognostic factor measurement, outcome measurement, confounding factors, and analysis were analyzed (appendix). Each domain was evaluated using a dichotomized quality score of 0 or 1. A global quality assessment score was obtained by simple summation of the scores, thus the global assessment score for each study was between 0 and 19 points. Initial assessments of all studies were made independently by the authors. In case of a difference in assessors' scores of more than or equal to 3 points, a reevaluation was made and a consensus was reached.

Results

Literature Search

Fifteen studies with preoperative pain testing were identified.[19–32,34] One study correlated preoperative data with intraoperative pain assessments during transrectal biopsy of the prostate and did not fill the inclusion criteria, and therefore, it was excluded.[34]

Quality Assessment

The median (interquartile range) of the global quality assessment scores (0–19) of the studies was 16 (14–17).

Physical Status

In five of the studies,[19,21,23,24,26] patients were classified according to the American Society of Anesthesiologists classification system as status I–III. The demographical data are presented in table 1.

Preoperative Pain Evaluation

In six of the studies,[19,22,24,27,28,30] the presence of preoperative pain was reported. In one study,[28] the patients were asked to indicate the presence of preoperative pain, but in the remaining studies, only pain localized to the area of surgery was investigated. In the knee surgery studies, the duration of pain[27,30] and the skin temperature and knee circumferences[27] were reported. In two thoracotomy

Table 2. Anesthesia, Postoperative Analgesia, and Pain Assessment

Study	Anesthesia	Postoperative Analgesia	Analgesia (prn/Enforced)	Postop Follow-up	No. Pain Assessments	Postoperative Pain Intensity	Postoperative Pain Assessment
Gynecological and obstetrical surgery							
Hsu *et al.*[23]	Gen	O* (PCA)	prn	1 d	2	VAS/NRS	R
Granot *et al.*[20]	Reg	NSAID*/O*	prn	12 h	1	VAS	R, D
Wilder-Smith *et al.*[21]	Reg	NSAID/T/O*	Enforced 1 day	1 d	11	VRS (5 points)	R, D
Pan *et al.*[24]	Reg	NSAID/O* (PCA)	prn	1 d	1	VAS	R, D
Strulov *et al.*[25]	Reg	NSAID*/O*	prn	2 d	NR	VAS	R
Nielsen *et al.*[26]	Reg	P/NSAID/O	Enforced 1.5 days	1.5 d	4	VAS	R, D
Rudin *et al.*[28]	Gen	P*/NSAID*/O*	prn	10 d	13	VAS, SF-MPQ (day 10)	R, D
Abdominal surgery							
Aasvang *et al.*[31]	Gen + Reg	P/NSAID/T*	prn	7 d	13	NRS (10 points)	D
Bisgaard *et al.*[19]	Gen	P/NSAID/O*	Enforced 4 days	7 d	8	VAS/VRS	R
Thoracic surgery							
Yarnitsky *et al.*[29]	Gen + EDA	EDA/NSAID*/O*/T*	prn	29 (± 17) wk	3	NPS (100 points)	R, D†
Weissman-Fogel *et al.*[32]	Gen + EDA	EDA/NSAID*/O*/T*	prn	5 d	2	NPS (100 points)	R, D
Knee surgery							
Werner *et al.*[22]	Gen	P/NSAID	Enforced 7 days	10 d	14	VAS	R, D
Martinez *et al.*[27]	Gen	P/Ne/O* (PCA)	prn	4 mo	15	VAS	R, D
Lundblad *et al.*[30]	NR	NSAID/Reg	NR	18 mo	1	VAS	R, D‡

* Rescue. † Acute and chronic. ‡ Only chronic.

D = dynamic; EDA = epidural analgesia; Gen = general; Ne = nefopam (monoaminergic antagonist, NMDA antagonist); NPS = Numerical Pain Scale; NR = not reported; NRS = Numerical Rating Scale; NSAID = nonsteroidal antiinflammatory drugs; O = opioid; P = paracetamol; PCA = patient-controlled anesthesia; R = rest; Reg = regional; SF-MPQ = short-form McGill Pain Questionnaire; T = tramadol; VAS = Visual Analogue Scale; VRS = Verbal Rating Scale.

studies, individuals with pain[29] or with thoracic pain,[32] respectively, were excluded.

Preoperative Pain Stimulation Methods

Quantitative sensory testing (QST),[35] defined as quantifiable mechanical (pressure, punctuate, vibratory, and light touch), thermal (cold pain, cool, warm, and heat pain) or electrical stimuli, was used in nearly all the studies. (In neurologic literature, QST usually refers only to testing with light touch, vibratory, and thermal stimulation.[36,37]) The experimental stimulation methods were the cold-pressor test,[19] heat immersion test,[29] brief phasic[20,24,27,28,32] or tonic heat stimulation,[25] cutaneous electrical stimulation,[21,26,30,31] pressure algometry,[23] punctate mechanical stimulation,[27,32] and induction of an inflammatory injury (table 1).[22] Contact thermodes were used in eight studies,[20,22,24,25,27–29,32] hand immersion in cold or hot water in two studies,[19,29] electrical stimulation with surface electrodes in four studies,[21,26,30,31] pressure algometry with digital pinching in one study,[23] and punctuate stimulation with monofilaments in two studies.[27,32]

Pain intensity during the preoperative stimulation procedure was assessed with a Visual Analog Scale (VAS) or Numerical Rating Scales (Verbal Rating Scale and Numerical Pain Scale [table 1]). The additional pain assessments were with the short-form McGill Pain Questionnaire[19,28] or nonvalidated questionnaires.[22,24]

Preoperative Psychometric Evaluations

In six studies,[19,23–25,28,32,] the assessments of psychologic vulnerability,[19,28] anxiety and depression (State Trait Anxiety Inventory and Hospital Anxiety Depression Scale),[23,28,32] and pain catastrophizing (Pain Catastrophizing Scale)[25,32] supplemented the experimental pain testing (table 1).

Surgical Procedure, Anesthesia, and Postoperative Analgesia

Data concerning the surgical procedure, and anesthesia and postoperative analgesia are outlined in tables 1 and 2, respectively. Epidural analgesia with bupivacaine and fentanyl was used in two studies.[29,32] Systemic analgesia was with paracetamol, nonsteroidal antiinflammatory drugs, nefopam (centrally acting inhibitor of serotonin, dopamine, and norepinephrine reuptake), and opioids. In most of the studies, a combination therapy was used except for one study that used opioid monotherapy.[23] In all studies except two,[23,27] nonsteroidal antiinflammatory drugs were used. In four studies,[19,21,22,26] postoperative around-the-clock analgesia with fixed doses was prescribed, with a duration of medication from 1 to 7 days. In the remaining studies, analgesics were prescribed as a rescue medication.[20,23–25,27–29,31,32]

Postoperative Pain Assessments

In all studies except one,[31] resting pain scores were reported, and in 10 studies, dynamic pain scores were also reported[20–22,24,26–29,31,32] (table 2). Pain localization was specified in eight studies.[19–21,24–27-30] In two studies, patients were asked either to indicate incisional, deep, evoked, referred, and/or overall pain,[19] or to indicate pain localizations on an anatomic chart daily for 10 days after surgery.[28] Two studies investigated sustained pain in the

Table 3. Outcome Variables, Predictors, Nonpredictors, and Correlation

Study	Outcome Variables	Predictors	Nonpredictors	Correlation	Contribution (%)
Gynecological and obstetrical surgery					
Hsu *et al.*[23]	AP	STAI-S, PPTo	—	R^2 = 0.27–0.39	27–39
	RA*	PPTo†	STAI-S	R^2 = 0.46	46
Granot *et al.*[20]	AP	HSTP	HPT	r^2 = 0.10–0.54	10–54
Wilder-Smith *et al.*[21]	AP	EDT,EPT, ESTP	—	r^2 = 0.04–0.07‡	4–7
Pan *et al.*[24]	AP	HPT, HSTP, expectation, BP	Preoperative pain, STAI	R^2 = 0.20–0.28	20–28
	RA§	HPT, preoperative pain, STAI	HSTP, expectation, BP	R^2 = 0.22–0.27	22–27
Strulov *et al.*[25]	AP	HSTP (tonic), PCS	HPT, HSTP (phasic)	R^2 = 0.14–0.17	14–17
Nielsen *et al.*[26]	AP	EPT	EDT	ρ^2 = 0.27–0.42	27–42
Rudin *et al.*[28]	AP	HSTP, preoperative pain, STAI-T, vulnerability	WDT, HPT, HADS	R^2 = 0.29–0.43	29–43
	RA‖	HSTP	WDT, HPT, STAI-T, vulnerability, HADS	r^2 = 0.09	9
Abdominal surgery					
Aasvang *et al.*[31]	AP	Age	EDT, EPT, EPTo	ρ^2 = 0.06	6
Bisgaard *et al.*[19]	AP	CPPTo, age, vulnerability, preop. biliary symtoms	—	ρ^2 = 0.04–0.09#	4–9
Thoracic surgery					
Yarnitsky *et al.*[29]	CPP	DNIC	HPT, HSTP	OR = 0.52 (95% CI 0.33–0.77)**	?
	AP		HPT, HSTP	OR = 1.80 (95% CI 1.28–2.77)††	?
Weissman-Fogel *et al.*[32]	AP	MSTP, MTS	HPT, HSTP, HTS, MPT, STAI, PCS	R^2 = 0.20	20
Knee surgery					
Werner *et al.*[22]	AP	HSTP	WDT, HPT, SHA	ρ^2 = 0.32–0.42	32–42
Martinez *et al.*[27]	AP	Preoperative pain (dynamic)	CDT, CPT, WDT, HPT, HSPT, MPT	ρ^2 = 0.36	36
	RA*	HSTP	CDT, CPT, WDT, HPT, MPT, preoperative pain (dynamic)	ρ^2 = 0.40	40
Lundblad *et al.*[30]	CPP	Preoperative pain	EDT	OR = 6.48 (95% CI 1.32–31.96)	?
		EPT	EDT	OR = 9.19 (95% CI 1.69–50.07)	?

Contribution (%) means the percentage contribution for each variable to the variability of post-op pain.

* Postoperative morphine requirement/24 h. † Includes preoperative fentanyl-induced decrease in PPTo. ‡ Method for univariate analysis is not defined. § Intraoperative analgesics. ‖ Postoperative requirement of ibuprofen. # ρ^2 is not specified. ** DNIC efficiency predicting chronic postsurgical pain. †† Acute postoperative pain predicting chronic postsurgical pain.

AP = acute postoperative pain; BP = blood pressure; CPP = chronic postsurgical pain; CPPTo = cold pressor pain tolerance; DNIC = diffuse noxious inhibitory control; EDT = electrical detection threshold; EPT = electrical pain threshold; EPTo = electrical pain tolerance; ESTP = electrical suprathreshold pain; HADS = Hospital Anxiety Depression Scale; HPT = heat pain threshold; HSTP = heat suprathreshold pain; HTS = heat temporal summation; OR = odds ratio; MSTP = mechanical suprathreshold percept; MTS = mechanical temporal summation; PCS = Pain Catastrophizing Scale; PPT = pressure pain threshold; PPTo = pressure pain tolerance; rho (ρ) = Spearman's correlation coefficient (rho); r = Pearson's correlation coefficient; R = multiple regression coefficient; r^2/R^2 = coefficient of determination; RA = requirement of analgesics; SHA = secondary hyperalgesia area; STAI-S/T = State-Trait Anxiety Inventory-State/Trait; WDT = warmth detection threshold.

surgical area at 29 weeks and 18 months, respectively, after surgery.[29,30]

Statistical Methods

In all studies except one,[30] univariate analyses[19–29,31,32] were used to investigate the association between dependent variables, postoperative pain, or analgesic requirement and independent preoperative predictor variables (table 3). Univariate parametric analyses (Pearson's r) were used in six studies,[20,23,25,28,29,32] and nonparametric analyses (Spearman's rho [ρ]) were used in six studies.[19,22,24,26,27,31] In two studies, data distribution was evaluated for normality by the Kolmogorov-Smirnov test.[22,23] In eight studies,[19,23–25,28–30,32] the predictor variables were tested in a multiple linear regression analyses stepwise method, calculating the multiple regression coefficient (R), or in a logistic regression model calculating odds ratio in six studies[19,23–25,28,32] and two studies[29,30] (table 3).

Prediction of Postoperative Pain Intensity

The predictive variables for acute and chronic postoperative pain were investigated in 13 studies[19–29,31,32] and three studies,[27,29,30] respectively. The significant predictors for acute postoperative pain were found in 11 studies[19–28,32] and for chronic postoperative pain in two studies.[29,30] The psychologic factors significantly predicted postoperative pain intensity in five studies using univariate analyses[19,23–25,28] or using multiple regression models.[23–25,28]

Prediction of Postoperative Requirement of Analgesics

Four studies evaluated the predictive power of QST and psychometrics on requirement of analgesics.[23,24,27,28] In a pressure algometry study,[23] the preoperative pain tolerance after the intravenous administration of fentanyl (2 μg/kg) predicted 23% of variance in postoperative morphine requirement the first 24 h postoperatively. In the cesarean section studies, preoperative anxiety assessments (State Trait

Anxiety Inventory) predicted 22% of the variance in total analgesic requirement (assessed intraoperatively, at the postanesthesia care unit and 6 h postoperatively),[24] whereas preoperative pain catastrophizing (Pain Catastrophizing Scale),[25] response to phasic heat pain test,[25] and electrical pain thresholds[26] did not correlate with postoperative need of supplemental analgesics. In one of the knee studies, preoperative heat hyperalgesia at the inflammatory changed surgical area predicted 44% of the variance in postoperative morphine consumption by patient-controlled analgesia during the first 24 h.[27]

Discussion

The present review demonstrates that the preoperative pain tests may predict 4–54% of the variance in postoperative pain experience depending on the testing method and testing paradigm used (table 3). The predictive strength of these tests is much higher than previously reported for single factor analyses of demographics (age,[38,39] gender[40,41]) and psychologic factors (depression,[42–46] anxiety,[8,47–49] and vulnerability[18]). Indeed, the authors in the first experimental pain studies[19,20,22] indicated that the incentive to use a psychophysical testing paradigm was based on the previous unsuccessful attempts at getting adequate predictive power from psychometrically based tests. This was indirectly corroborated in the current study, because by adding psychologic variables (vulnerability,[19,28] anxiety,[23,28,32] depression,[28] and catastrophizing[25,32]) to the sensory variables in the multivariate regression analysis, the increase in predictive power of the model generally was modest or even absent. However, the variables may be dependent, and therefore, it is noteworthy that only one of the studies tested for interdependency of the variables.[28]

Quality Assessment

More than 2,500 new systematic reviews are indexed annually in PubMed.[50] Although elaborate reporting guidance exists for randomized controlled trials, the Consolidated Standards of Reporting Trials statements,[51] and for reporting of meta-analysis of randomized controlled trials,[52] the Quality of Reporting of Meta-analyses statement, a standard quality assessment method for systematic reviews of nonrandomized controlled trails has not until recently been available.[33,50] Therefore, quality appraisal is incomplete in most reviews of prediction studies.[33] We selected a number of relevant domains, used a simple quality score, and for each study, calculated a global quality assessment score to facilitate a quantitative comparison of the studies. The studies of this review achieved a high median score, but a high score does not necessarily *per se* imply a greater scientific value because most of the studies included in this review are small-scale studies of exploratory nature.

Preoperative Pain

Only four studies[19,27,28,30] reported the prevalence of preoperative pain, which has been considered a significant predictor of severe postoperative pain[5,48,53,54] and for development of chronic postsurgery pain.[5,7] The prevalence of chronic pain in Europe is 19%, which underscores the significance of the problem in the surgical population.[55] However, not all studies have observed a relationship between preoperative pain and development of chronic pain; in a recently published study, high-intensity postoperative pain, but not preoperative pain, was associated with the development of chronic pain and functional impairment 6 months after surgery.[11] Nevertheless, it has been hypothesized that severe preoperative pain is associated with a sustained nociceptive input that may lead to neuroplasticity changes in the central nervous system.[5,56] This sensitization, which may be enhanced by opioid treatment,[57] plays an important role in the exaggerated postoperative pain response seen in chronic pain patients.[29,57–60]

Preoperative Pain Stimulation Methods

In two knee studies, the QST assessments were made either in an experimentally induced burn injury contralateral to the surgery site[22,61] or in the inflammatory changed tissues at the surgery site.[27] This distinction could be important because surgery is associated with profound changes in the inflammatory and nociceptive system leading to pain and hyperalgesia, where abnormal persistence of the nervous system sensitization may lead to the development of chronic postsurgery pain.[62] It could be speculated that the preoperative QST assessments in the inflammatory changed tissues more accurately reflect and predict the postoperative state of the nociceptive system. In support of this is the fairly good predictive power, observed in these two studies,[22,27] explaining 36–43% of the variance in postoperative pain experience (table 3).

It is believed that suprathreshold noxious stimulation has a better predictive performance than pain thresholds in regard to experience of clinical pain and requirement of analgesics.[63,64] The current data corroborate this statement because in five[20,22,24,25,28] of six thermal QST studies (table 3), a better predictive power of suprathreshold stimulation was observed. Furthermore, in 11 of 12 studies, suprathreshold pain stimulation, either in a phasic[20,24,25,27,28,32] or tonic[19,21–23,25,29] stimulation mode, was used.

However, a number of interesting observations were made in the three of four studies that used transcutaneous electrical stimulation.[21,26,30] First, a highly significant correlation between electrical pain thresholds and postoperative pain ratings was observed (table 3). Second, in one of the studies, a high predictive power ($\rho^2 = 0.27–0.42$) was found.[26] Third, in a recent total knee replacement study, preoperative low electrical pain thresholds were associated with an increased risk of chronic pain 18 months after surgery.[30] These findings suggest that important differences may exist between stimulation modalities, that is, the electrical pain thresholds seem to have a much greater predictive potential than the mechanical or thermal pain thresholds. However, it should be noted that in the fourth of the electrical stimulation studies, in male groin hernia repair patients,[31] no significant predictive role for electrical pain thresholds

and tolerance thresholds was observed, which probably can be explained by gender-related differences.

In the electrical stimulation studies,[21,26,30,31] the gender distribution (females/males) was 50% (194/196), and for studies with positive predictive value, the gender distribution (females/males) was 85% (194/36). Females generally demonstrate lower electrical detection thresholds, electrical pain thresholds, and electrical tolerance levels than males.[65–67] This may indicate that perception of electrical stimulation is associated with higher levels of anxiety and greater level of discomfort in females compared with males.[66]

From a methodologic standpoint, it is remarkable that 67% (645/964) of the study population in the 14 studies in the current review was female and that 58% (559/964) of the study populations were included in single-gender studies (table 1). Although the heterogeneity of the studies in this review does not allow any gender-related comparisons, there are data that indicate a higher correlation between responses to experimental pain stimuli, and clinical pain and pain-treatment outcomes in females compared with males.[63,68]

Five studies included cesarean section patients corresponding to 31% (298/964) of the study population.[20,21,24–26] A majority of the parturients (53%) was investigated with electrical stimulation. The prevailing opinion has been that pregnancy is associated with an increased antinociception.[20] In a recent study,[69] however, the responses to mechanical and electrical noxious stimuli were tested immediately before and 4 days after elective cesarean section in 30 women and compared with a control group of nonpregnant women. No intragroup or between-group differences were observed, indicating that late pregnancy does not seem associated with an increased antinociception.

Preoperative Psychometric Evaluations and Age

As previously stated, psychologic factors do not seem as efficient predictors of intensity of postoperative pain as QST variables (table 3). This is interesting because a number of recent studies have reported that in particular preoperative anxiety,[47,70] but also depression,[44] neuroticism[71,72] and catastrophizing behavior[49] seem associated with the development of high-intensity postoperative pain[18] and may have a negative effect on surgical outcome.[73]

A significant inverse correlation between age and postoperative pain intensity was seen in the two largest studies,[19,31] including patients from 20 to 85 yr, a finding that is consistent with the previous studies.[43,74]

Surgical Procedures

The previous research has demonstrated that the surgical procedure and technique may influence the intensity and the duration of postoperative pain.[5,74] Therefore, an important limitation of this systematic review is that although 5 of 14 studies were on cesarean section, in the remaining studies, seven different surgical procedures were performed (table 1), indicating an important heterogeneity of data. It is not known whether the pain mechanisms or pain trajectory may differ between inflammatory, neuropathic, or visceral types of postoperative pain. The results from the elective cesarean section studies[20,21,24–26] suggest rather consistently that pain after this procedure can, in part, be predicted (table 3).

In the current review, two relatively minor surgical procedures were included, that is, laparoscopic tubal ligation[28] and open groin hernia repair.[31] Both studies indicate that even after minor tissue injury, a considerable number of patients experience movement-related acute pain of moderate to severe intensity. Unfortunately, because of the large interstudy variability in the assessments of postoperative pain and in the postoperative analgesia regimen, it is not possible to seek out differences in pain ratings between various procedures. Even in the cesarean section studies[20,21,24–26] with a standardized tissue injury, a major variability in pain ratings was evident.

In the large thoracotomy study,[29] focused on the development of chronic postsurgical pain, the patients were not fully characterized in terms of their concomitant oncological disease. The adjuvant treatments and the presence of metastases are confounding factors that may lead to an increased pain. Even short-term treatment with morphine has been demonstrated to be associated with diffuse noxious inhibitory control (DNIC)-interference[75] and development of tolerance and hyperalgesia, which may influence postoperative pain management.[76,77]

Prediction of Postoperative Pain Intensity and Development of Chronic Postsurgical Pain

The initial mean or median pain ratings (VAS, Verbal Rating Scale and Numerical Pain Scale [0–100]) were more than 45 in four studies during rest[19,23,25,27] and in seven studies during movement,[20,22,24,26,27,29,32] representing 29 and 26%, respectively, of the total study population. An association between intensity of acute postoperative pain and subsequent development of chronic pain has been demonstrated.[5,11,12] In a 1 yr, questionnaire-based follow-up[12] of the patients included in the large laparoscopic cholecystectomy study,[19] the sum of postoperative VAS during days 1–7 was a better predictor than maximum reported VAS, which may indicate that also the duration of postoperative pain may influence the development of chronic pain.[12]

In a number of predictive studies, the focus has recently shifted from acute postoperative pain and requirement of analgesics to development of chronic postsurgical pain.[11,12,29,30] In the 1-yr follow-up[12] of the laparoscopic cholecystectomy study,[19] 11% of the patients fulfilled criteria of chronic pain. The first preoperative QST study on development of chronic postoperative pain[30] included 69 patients with osteoarthritis undergoing total knee replacement surgery. The relationship between preoperative variables and postoperative assessments of pain at rest and during movement, 18 months after the surgical procedure, was studied by logistic regression analysis ($n = 63$). A VAS score (0–10) of 1 was used as the lower boundary for persistent postoperative pain at rest or during movement (!). Two preoperative variables, pain at rest and elec-

trical pain sensitivity, contributed significantly to the prediction of persistent pain with odds ratios of 6.48 (95% CI, 1.32–31.96) and 9.19 (1.69–50.07), respectively. The study did not report data on acute postoperative pain or give details on postoperative pain management.

The second QST study[29] investigated 62 patients undergoing anterolateral thoracotomy during a follow-up period of 29 weeks. This study used preoperative activation of the DNIC system induced by hand immersion in hot water (46.5°C) for 1 min as the "conditioning stimulus." Noxious test stimuli were 30 s heat stimuli calibrated individually for each patient (45°–47°C)[78] corresponding to a perceived pain intensity of 60 of 100 on a Numerical Pain Scale. These test stimuli were given before and after the DNIC-challenge, and the difference in Numerical Pain Scale values of the assessments represented "DNIC efficiency." Higher levels of DNIC efficiency was associated with an odds ratio of 0.52 (95% CI, 0.33–0.77), that is, predicting a nearly halved risk of developing chronic pain, whereas severe postoperative pain was associated with an odds ratio of 1.80 (1.28–2.77), predicting a nearly doubled risk of chronic pain development. Interestingly, DNIC efficiency *per se* did not correlate with the magnitude of acute postoperative pain. These results are in the vanguard of predictive postoperative research and seem applicable in a clinical setting, in particular if the high noxious intensity of the conditioning stimulus can be reduced.[79]

Prediction of Postoperative Requirement of Analgesics

These data indicate that during specific procedures (cesarean section, hysterectomy, knee surgery, and myomectomy), preoperative QST and State Trait Anxiety Inventory assessments may predict 22–44% of the postoperative analgesic requirement.[23–27] However, a composite calculation score based on rescue analgesic consumption and pain ratings (both before and after rescue) during a defined time period is probably much more appropriate to use, but unfortunately it is used rarely in clinical pain research.[80,81]

Clinical Implications

Although some authors in the current review stated a necessity for a multifactorial model combining psychosocial and psychophysical aspects of pain,[24,28] others pointed to the need for a simple and reliable prognostic assessment method of postoperative pain.[23,26] The application of sensory tests and psychometric questionnaires are in most cases a time consuming process,[82] and not clinically feasible at this time, although a simple electrical device was used in two of the studies.[26,31] Kalkman et *al.*[48] presented a multivariate model that included seven clinically relevant variables, all easily obtained during the preoperative evaluation, to predict the probability of severe pain at the first postoperative hour. The specificity and sensitivity of the model in predicting severe postoperative pain (Numerical Rating Scale ≥8 of 10) was 61 and 74%. The authors recently revised the model and improved its content and construct validity.[70,74] Unfortunately, this method has not been compared with preoperative QST assessments.

Conclusion

This review demonstrates that QST assessments may predict up to 54% of the variance in postoperative pain experience, particularly after cesarean section, and in development of persistent postsurgical pain. The predictive strength of the tests is much higher than previously reported for single factor analyses of demographics and psychologic factors.

The predictive ability of thermal methods requires stimuli of suprathreshold intensity, whereas for electrical methods, only stimuli at pain threshold intensity are needed. The data corroborate that there is a better correlation between electrical pain threshold and clinical pain, in females compared with males. The psychometric assessments do not seem to contribute to an increase in predictive power.

Future predictive studies will benefit from improved methodology, in regard to selection of surgical procedures, standardization of assessments, and increased clinical applicability of methods, and use of dynamic QST-assessments, such as DNIC efficiency[29] and temporal summation.[32]

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Appendix: Quality Assessment: Grading System[33]

Selected domains:

1. Study population described
2. Completeness of follow-up described
3. Completeness of follow-up adequate
4. Prognostic factors defined
5. Prognostic factors measured appropriately
6. Outcome defined
7. Outcome measured appropriately
8. Confounders defined and measured
9. Confounding accounted for
10. Analysis described
11. Analysis appropriate
12. Analysis provides sufficient presentation of data
13. Follow-up length appropriate
14. Follow-up length described
15. General appropriateness of outcome
16. Research question definition
17. Sample size adequate
18. Study design adequate
19. Evidence supporting conclusions

Grading is dichotomized yes (1) or no (0), and a simple summation of grades (0–19) gives global assessment score.

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