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Multifactorial Preoperative Predictors for Postcesarean Section Pain and Analgesic Requirement

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Background: **The study aimed to determine predictive factors for postcesarean pain and analgesia using an assessment of pain threshold and suprathreshold thermal stimuli as well as degree of somatization and anxiety.**

Methods: **Thirty-four healthy parturients scheduled for cesarean delivery under subarachnoid anesthesia were enrolled. Preoperative thermal pain threshold, intensity, and unpleasantness to heat stimuli applied to arm and lower back, State Trait Anxiety Inventory, and patient expectation for postoperative pain and need for analgesia were assessed. After surgery, overall, resting, and movement pain and analgesic consumption were recorded. Prediction of pain and analgesic use outcomes was made by principal component factor analysis, followed by stepwise linear regression.**

Results: **Resting pain was predicted by two factors, thermal pain and unpleasantness and patient expectation ($r^2 = 0.26$, $P < 0.01$), evoked pain by thermal pain threshold in the back ($r^2 = 0.20$, $P < 0.009$), composite pain by thermal pain and unpleasantness and preoperative blood pressure ($r^2 = 0.28$, $P < 0.008$), intraoperative analgesic need by preexisting pain ($r^2 = 0.22$, $P < 0.006$), recovery room analgesia by thermal pain threshold and State Trait Anxiety Inventory ($r^2 = 0.27$, $P < 0.01$), and total analgesic need by State Trait Anxiety Inventory ($r^2 = 0.22$, $P < 0.01$). These models predicted the upper twentieth percentile of composite pain scores and analgesic requirement with sensitivity of 0.71 to 0.80 and specificity of 0.76 to 0.80.**

Conclusions: **The authors' results suggest a meaningful combination of preoperative patient responses from physical and psychological tests yields a valid multifactorial predictive model for postoperative pain and analgesic requirement with significant improvements over individual predictive variables.**

INDIVIDUAL variability in severity of postoperative pain is influenced by multiple factors, including sensitivity to pain, psychological factors (*e.g.*, state of anxiety and somatization), age, and genetics.[1–4] Such factors are thought to drive both interpatient variability in the postoperative pain experience as well as requirements for analgesics after the same or similar surgical procedure.[1–3] Despite advancement in postoperative pain management, postoperative pain relief and patient satisfaction are still inadequate in some patients.[1–3] In addition, a high percentage of hospitalized patients continue to experience moderate to severe postoperative pain.[5] Recently, the Joint Commission on Accreditation of Healthcare Organization established standards for pain assessment and treatment in healthcare facilities with the goal to generate uniformly low pain scores of no more than 3 of 10 both at rest and with movement. Furthermore, improved pain relief may improve postoperative outcomes, whereas severe postoperative pain may lead to development of chronic pain.[6,7] The visual analog scale (VAS) has been validated for pain assessment, allowing a reliable and consistent measure and study of pain intensity and unpleasantness.[8,9] Accurate prediction of postoperative pain and/or analgesic requirement in an individual patient could lead to tailored methods to reduce severe postoperative pain and improve acute and chronic outcomes.

Previous studies have observed weak but statistically significant correlations between degree of postoperative pain and preoperative conditions, such as thermal or pressure pain threshold and tolerance, anxiety, expectation, and age.[1–4,10–12] Granot *et al.*[10] reported, for example, that postoperative VAS pain scores at rest and during activity were significantly correlated ($r = 0.4–0.5$) with preoperative pain scores to suprathreshold heat stimuli, whereas there was no such correlation with pain threshold to heat. Similarly, VAS pain on the first postoperative day is correlated with pressure pain tolerance ($r = -0.5$).[12] In addition to response to experimental pain, anxiety, somatization, and catastrophizing are predictive single factors of postoperative pain.[13]

Few previous studies have explored multiple psychological and physical responses to generate a multifactorial predictive model for postoperative pain. Similarly, prior experience, patient expectations, and VAS use rarely have been included together in such studies, and never in a comprehensive fashion. In addition, few previous studies have examined predictive factors for analgesic drug use, yet this is a particularly interesting outcome, because it is largely controlled by the patients in the postoperative period and because opioid drug dose correlates with bothersome side effects.[14,15] Finally, chronic nociception can result in altered response to

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experimental pain stimuli in affected dermatomes, including low thoracic and upper lumbar dermatomes at term pregnancy,[16] yet previous studies have performed experimental pain testing before cesarean section in the arm, distant from these dermatomes.[10–12] The purpose of the current study was to determine factors that predict postoperative pain and analgesic drug use after cesarean section using a far-ranging assessment of pain threshold and response to suprathreshold thermal stimuli in both cervical and lumbar dermatomes as well as degree of somatization and anxiety.

Materials and Methods

Study Population

With approval from institutional review boards (Wake Forest University and Forsyth Medical Center, Winston-Salem, NC), written informed consent was obtained from 34 healthy American Society of Anesthesiology Class I–II parturients at normal term pregnancy and who were scheduled for elective cesarean section under subarachnoid anesthesia. Patients with a history of psychiatric disease, preeclamptic or hypertensive disease, hearing deficits, alcohol or drug abuse, chronic opioid or nonsteroidal antiinflammatory drug use, or weight over 250 lbs and non-English speaking parturients were excluded.

Preoperative Assessment Preparation

Preoperative testing was performed within 2 weeks before the cesarean section in a quiet room. Patients received a detailed explanation of each testing procedure and were trained in the use of the VAS to report pain intensity and unpleasantness (one end indicating no pain or not at all unpleasant and the other end indicating the most intense pain imaginable or the most unpleasant imaginable) using a radio analogy.

Assessment of Emotional and Psychological State

All patients completed the State Trait and Anxiety Inventory (STAI), a validated tool that measures trait (20 questions) and state (20 questions) anxiety. Patients also completed a questionnaire assessing their views about use of medications, preoperative anxiety, baseline pain, unpleasantness during pregnancy, their expectations of surgical and postsurgical pain, and their expected amount of postoperative pain medication needed.

Assessment of Audio Sensitivity

The patients rated the intensity (loudness) of a series of audio tones using the mechanical VAS. This trained the patients in using the scale to report intensity of stimuli and to evaluate the patient's scale use ability.

Assessment of Thermal Pain Sensitivity and Threshold

Thermal stimuli were administered to the ventral surface of the dominant forearm and then to the lower back with a Thermal Sensory Analyzer (Model TSA II; Medoc Inc., Ramat Yishai, Israel) *via* a 16 x 16-mm Peltier contact thermode. Each thermal testing trial was separated by approximately 2 min and at a separate site to avoid sensitization or adaptation.

Thermal Pain Threshold Temperature

Thermal pain threshold was determined by methods of limit. The thermode was applied to the ventral surface of the dominant forearm or the lower back and the temperature was increased at 1°C/s from 35 to 50°C. Patients were asked to indicate the transition point at which the nonpainful warm sensation changed into a painful heat sensation by pressing a button, and the simultaneous thermode temperature was recorded electronically. This test was repeated successively six times and the mean threshold temperature was calculated.

Suprathreshold Thermal Pain Intensity and Unpleasantness

Stimulus responses for noxious heat stimuli were performed by applying phasic heat stimuli at eight different temperatures (35, 43, 44, 45, 46, 47, 48, and 49°C). Each stimulus started at the level of 35°C and increased at a rate of 1°C/s. After reaching the destination temperature, the stimulus remained for 5 s at that temperature, and then it rapidly decreased back to baseline at a rate of 8°C/s. The interstimulus interval between successive stimuli was 30 s. The various temperature stimuli were administered first to the ventral surface of the dominant forearm and then the lower back each four times, with the first time in ascending temperature, the second and third times in random order of temperature, and the fourth time in descending order of temperature. Patients were asked to report the level of perceived pain intensity and unpleasantness, respectively, by means of the VAS.

Protocol for Cesarean Anesthetic and Postoperative Pain Management

On the day of surgery while in the preoperative holding area, vital signs, anxiety score using VAS (limits of "not anxious at all" and "the most anxious imaginable"), and fetal heart rate were obtained. After intravenous infusion of 1 l lactated Ringer's solution, a 27- or 25-gauge Whitacre spinal needle was inserted at the L3–L4 or L4–L5 interspace with patients in sitting position, and 11.25 mg hyperbaric 0.75% bupivacaine and 20 μg fentanyl were administered intrathecally. Intravenous morphine or fentanyl was administered as needed in the case of intraoperative discomfort, but no anxiolytics were administered during surgery during the study period.

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After surgery, patients received either 50 mg rofecoxib or 800 mg ibuprofen orally shortly after arrival in the recovery room and intravenous morphine at 2- to 4-mg bolus increments as needed in the recovery room for verbal pain score of more than 3 of 10 and/or at patient request for pain. Ibuprofen 800 mg was administered every 8 h, whereas rofecoxib was administered once during the first postoperative 24 h. Patients were discharged from the recovery room to the ward with a verbal numeric pain score of 3 or less of 10. On arrival on the ward, intravenous patient-controlled analgesia (PCA) was initiated using a 3-mg morphine loading dose a 1-mg demand dose, with an 8-min lock out and a maximum limit of 8 mg/h. PCA settings could be increased to a maximum hourly limit of 16 mg if the initial settings were inadequate for postoperative pain control.

Cesarean Section and Postcesarean Section Pain Assessment

Sensory level to pin-prick testing was obtained just before skin incision, at the end of surgery, and 2 h after injection of subarachnoid anesthetic. Duration of surgery (from incision to end of surgery procedure), duration of anesthetic (time from subarachnoid anesthetic injection to time when sensory blockade level receded to a T10 or lower level), time to first request for supplement analgesia, amount of supplement analgesia required during surgery and after surgery in the recovery room, and in the first 6 and 18 to 24 postoperative hours were recorded. On the morning of the first postoperative day (20 to 24 h after surgery), patients rated the intensity of pain at the surgical wound by means of the VAS, both at rest and during activity (changing from supine to sitting up at bedside: evoked pain). Patients also rated the overall level of pain since surgery, effectiveness of PCA pain relief, overall postoperative pain control satisfaction, and overall satisfaction with the cesarean surgery experience, each using the VAS.

Statistical Analysis

Statistical analyses were conducted using SPSS software version 13.0 (SPSS Inc., Chicago, IL). Descriptive statistics were calculated for all variables (*i.e.*, mean, SD, median, and range) as appropriate. Because the medication outcome variables were positively skewed, a nonparametric Spearman correlation was used to examine the relationship between predictive factors and outcome variables. For all analyses, α was set at 0.05 for statistical significance.

To examine if predictors could be reduced into meaningful subsets based on their relationship to each other, principal component factor analysis with varimax rotation was used. Factor analysis often is used as a data reduction technique or as a method to mathematically identify meaningful subgroups of items. Care was taken to create a solution of item groups (factors) that were very similar to each other, but relatively uncorrelated. Because factor analysis is typically conducted on much larger samples than that of the current exploratory study, a minimally acceptable factor loading of 0.80 or more was used to better ensure the stability of identified factors. Predictors were combined to form factor scores by summing the individual items in the factor. Reliability estimates of the factors were conducted using Cronbach α.

To examine if groups of predictors (factors) could be used in conjunction to improve prediction of each outcome variable (pain and medication use), multiple regression analyses were used. A model-building strategy was used that attempted to account for the greatest amount of variance in the outcome variable while considering only factors that were statistically significant (or likely to be statistically significant with a larger sample). Any variable that was independently correlated with the outcome variable was entered into the equation, but was removed if not statistically significant when considered with the other predictors. In essence, this strategy aims at maximizing the adjusted r^2 value, or variance accounted for by the model if applied to a different sample. This conservative strategy resulted in parsimonious regression models that are likely to be replicated.

Finally, to index the predictive ability of the regression models and for clinical applicability, a receiver operating characteristic curve was used to estimate sensitivity and specificity of the models' ability to predict the upper twentieth percentile of individuals' pain and medication use. The optimal cutoff value of the prediction equation was chosen such that sensitivity and specificity were as high as possible, while still remaining balanced.

Results

The 34 parturients enrolled in this study had a mean (SD) body weight of 90 (19) kg, height of 161 (8) cm, and a median (range) parity of 1 (1–3). The mean (SD) cesarean surgery duration was 45 (14) min. There was a large interindividual variability in the results of all preoperative thermal pain tests as well as the ranges of postoperative pain scores and analgesic requirement. Complete descriptive statistics for predictor and outcome variables are provided in table 1.

Preoperative Assessment

The mean (SD) thermal pain threshold on the arm and back were 47 (3)°C and 47 (2)°C, respectively. The mean (SD) VAS pain intensity and unpleasantness to the 49°C stimulus were 33 (27) and 33 (29) for the arm, respectively, and 22 (24) and 25 (28) for the back, respectively. The mean (SD) pain threshold temperature for the arm and the back were 47.5 (3.1)°C and 47.3 (2.3)°C, respectively.

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Table 1. Descriptive Statistics of Main Predictor Variables and Outcome Variables

	n	Range	Mean	SD
Predictor variables				
Pregnancy history				
Overall pain during pregnancy*	34	0–90	41	25
Overall unpleasantness while pregnant*	34	0–100	47	33
Patient's expectation				
Expectation on analgesic required*	34	80–100	59	29
Expectation on postoperative pain*	34	70–100	57	24
Day of surgery status				
Systolic blood pressure (mmHg)	34	95–144	123	12
Diastolic blood pressure (mmHg)	34	55–105	78	10
Heart rate (beats/min)	34	71–118	93	12
Preoperative anxiety VAS	30	0–100	53	35
Surgical duration (min)	32	26–87	45	14
Preoperative experimental testing				
Audio: audio intensity VAS	32	15–100	73	26
Suprathreshold thermal stimuli at 49°C				
Arm pain VAS	34	0–93	33	27
Arm unpleasantness VAS	34	0–91	33	28
Back pain VAS	32	0–80	22	23
Back unpleasantness VAS	32	0–100	25	27
Arm threshold temperature (°C)	32	38–50	48	3.1
Back threshold temperature (°C)	32	40–50	47	2.3
STAI and anxiety testing				
State anxiety	32	20–59	36	10
Trait anxiety	34	22–56	36	8.3
Training anxiety	34	0–100	57	36
Outcome variables				
Analgesic outcomes (mg morphine equivalent)				
Intraoperative analgesia	34	0–23	2.9	5.4
RR analgesia	33	0–54	18.8	15.0
PCA analgesia first 6 h	32	4–25	13.8	7.2
Total analgesia (sum of above three)	32	4–81	36.1	18.7
Pain outcomes (VAS)				
Resting pain	34	0–70	20	20
Evoked pain	34	2–100	50	28
Overall pain	34	5–98	46	24
Composite pain score†	34	7–220	116	61

* Visual analog scale score. † Sum of resting, evoked, and overall pain VAS score.

PCA = patient-controlled analgesia; RR = recovery room; STAI = State Trait and Anxiety Inventory; VAS = visual analog scale (0–100).

Postcesarean Section Pain Assessment and Analgesic Requirement

The mean (SD) VAS were 20 (20), 50 (28), and 46 (24) for postcesarean section resting pain, evoked pain, and overall pain, respectively. The mean (SD) analgesic requirements were 2.9 (5.4), 18.8 (15.0), 13.8 (7.2), and 36.1 (18.7) mg morphine equivalents for intraoperative, recovery room, first 6 h of intravenous PCA consumption on the ward, and total analgesic required for the three periods above combined, respectively.

Predictive Model Using Factor Analysis

Tables 2 and 3 display the results of the principal component factor analysis. The analysis resulted in six relatively orthogonal (uncorrelated) newly formed predictive factors (groups) that accounted for 90% of the total observed variances in predictors. It is of note that the STAI was moderately to highly correlated with many of the factors and was removed from the factor solution and used as a separate predictor category (although not orthogonal to the others). The usefulness of these factors then was examined in regression models for predicting the outcome measures in postoperative pain and analgesic requirement. Each factor was given a name consistent with its several independent measured component variables and its clinical relevance as appropriate (table 2).

The reliability estimates (Cronbach α) of the individual components forming each predictor factor (group) are shown in table 3. An α of 0.8 or more was used as an acceptable reliability to include the component in the corresponding factor (group) for final regression analyses. Because two factors (thermal pain threshold, intraoperative factors) did not meet that criterion, the single item most highly related to those factors was considered independently for the purposes of regression analyses.

The outcome measures were:

- Postoperative Pain. The outcome variables were the VAS (0–100) scores on postoperative resting pain, evoked pain, and overall pain rating and a calculated

Table 2. The Six Predictive Factors (Groups) and Their Corresponding Component Predictor Variables

Factor Number	Factor Name	Description
Factor 1	Pain and unpleasantness	This consisted of thermal pain intensity and unpleasantness ratings (measured as VAS of 0–100) when heat stimuli of 49°C applied on the arm and on the back.
Factor 2	Preoperative blood pressure	This consisted of systolic and diastolic blood pressure measured before surgery in the holding area on the day of surgery.
Factor 3	Preexisting pain	This consisted of patients' VAS (0–100) rating of their overall pain and overall unpleasantness during pregnancy.
Factor 4	Expectation	This consisted of patients' VAS (0–100) rating of their expected postcesarean section pain and amount of pain medicine needed.
Factor 5	Thermal pain threshold	This consisted of the threshold temperatures when thermal stimuli applied on the arm and on the back.
Factor 6	Intraoperative factor	This consisted of duration of surgery and the sensory blockade level at time of incision.

VAS = visual analog scale.

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Table 3. Final Principal Components Solution of Predictor Variables (with Varimax Rotation), with Reliability Estimates

Predictor Variable	Pain and Unpleasantness	Blood Pressure	Preexisting Pain	Expectation	Thermal Pain Threshold	Intraoperative Factors
Arm pain	**0.93**	0.10	0.13	0.09	−0.08	0.11
Arm unpleasantness	**0.94**	0.02	0.18	0.14	−0.04	0.16
Back pain	**0.96**	0.08	0.08	0.05	−0.11	−0.02
Back unpleasantness	**0.94**	−0.02	0.06	0.07	−0.04	−0.03
Systolic pressure	−0.01	**0.89**	0.18	−0.11	0.05	0.02
Diastolic pressure	0.19	**0.90**	−0.01	−0.16	0.01	0.09
Overall pregnancy pain	0.30	−0.03	**0.88**	0.09	0.07	0.12
Overall pregnancy unpleasantness	0.01	0.23	**0.89**	0.17	−0.06	−0.03
Expected pain medicine	0.15	−0.10	0.36	**0.87**	0.01	−0.01
Expected cesarean pain	0.14	−0.19	−0.01	**0.89**	−0.13	0.15
Arm threshold temperature	−0.64	−0.31	0.10	−0.08	**0.59**	−0.06
Back threshold temperature	−0.21	0.16	−0.05	−0.06	**0.91**	−0.03
Surgical duration	0.00	−0.14	−0.03	−0.19	0.12	**−0.88**
Sensory anesthetic level	0.29	−0.08	0.09	−0.15	0.51	**0.61**
Cronbach α*	0.94	0.83	0.83	0.80	0.69	0.03

Boldface values indicate the factor loadings that defined the characterization of the factor.

* An α of 0.80 or more was set to include the components in the predictive factor (group). If less than 0.8, then the individual component with the higher reliability was used for that predictive factor.

composite pain score, which was the sum of the three VAS scores for resting, evoked, and overall pain rating.

- Analgesic Requirement. The outcome variables were the milligrams of morphine equivalents required for analgesia during intraoperative period, recovery room period, and the first 6 h of PCA in the ward and the total analgesia required that was the sum of analgesia consumed during the above three periods.

Spearman Correlations between Pain and Analgesic Outcome Variables and Individual Predictor Factors

The Spearman correlation between the pain outcome variables and each individual predictor factor (group) is shown in table 4. Table 5 shows the Spearman correlation between each individual predictor factor (group) and the analgesic outcome variables. It is of interest to note that evoked pain and resting pain were best predicted by different predictor factors (groups). Similarly, intraoperative analgesia and recovery room analgesia also were best predicted by different predictor factors.

Final Predictive Model with Multiple Regression Analysis

Final predictive model with multiple regression analysis for pain outcomes and analgesic outcomes are shown in tables 6 and 7, respectively. Two predictive factors (pain and unpleasantness and expectation) provided the best predictive model for resting pain ($r^2 = 0.26$, $P < 0.01$). Thermal pain threshold in the back area alone provided the best predictive model for evoked pain ($r^2 = 0.20$, $P < 0.009$), whereas two factors (pain and

Table 4. Spearman Correlations between Pain Outcomes and Individual Predictor Factors (Groups)

Predictor Factor Variables*	Resting Pain†	Evoked Pain‡	Overall Pain§	Composite Pain Score‖
1. Pain and unpleasantness	0.45#	0.40**	0.30	0.39
2. Blood pressure	−0.27	−0.09	−0.22	−0.33
3. Preexisting pain	0.13	0.22	0.25	0.21
4. Expectation	0.41**	0.26	0.24	0.34**
5. Thermal pain threshold	−0.036**	−0.42**	−0.14	−0.30
Back threshold (alone)	−0.32	−0.41**	−0.10	−0.37**
6. Intraoperative factor	−0.21	0.02	−0.14	−0.24
Surgical duration (alone)	−0.09	0.13	−0.02	−0.02
7. State Trait Anxiety Inventory	0.30	0.21	0.25	0.31

* Predictor factor variables are as defined previously in text. † Resting pain is the visual analog score (0–100) for the intensity of pain at rest at 20 to 24 h after surgery. ‡ Evoked pain is the visual analog score (0–100) for the intensity of pain when changing position from supine to sitting up or standing at 20 to 24 h after surgery. § Overall pain is the visual analog score (0–100) for the overall level of pain since surgery when asked at 20 to 24h after surgery. ‖ Composite pain score is the sum of the above three visual analog scores. # $P < 0.01$. ** $P < 0.05$.

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Table 5. Spearman Correlations between Analgesic Outcome Variables and Individual Predictor Factors (Groups)

Predictor Factor Variables*	Intraoperative†	Recovery Room‡	PCA§	Total Analgesia‖
1. Pain and unpleasantness	−0.16	0.48#	0.34	0.43**
2. Blood pressure	0.10	−0.02	0.00	−0.01
3. Preexisting pain	0.46	0.11	0.22	0.34
4. Expectation	−0.08	−0.03	0.15	0.14
5. Thermal pain threshold	0.15	−0.43**	−0.05	−0.27
Back threshold (alone)	0.00	−0.41**	−0.08	−0.31
6. Intraoperative factor	0.12	0.04	−0.02	0.01
Surgical duration (alone)	0.01	−0.06	−0.04	−0.02
7. State Trait Anxiety Inventory	0.27	0.39**	0.33	0.40**

* Predictor factor variables are as defined previously in text. † Intraoperative analgesia supplement required (in milligrams of morphine equivalent). ‡ Recovery room analgesia required (in milligrams of morphine equivalent). § The first 6 h of intravenous patient-controlled analgesia required in the ward (in milligrams of morphine equivalent). ‖ Total analgesia is the sum of analgesia (in milligrams of morphine equivalent) of the above three (†‡§) periods. # $P < 0.01$. ** $P < 0.05$.

PCA = patient-controlled analgesia.

unpleasantness and blood pressure) fitted the best predictive model for the composite pain score ($r^2 = 0.28$, $P < 0.008$); fig. 1 and table 6).

For predicting analgesic requirement, the factor of preexisting pain alone provided the best predictive model for intraoperative analgesic need ($r^2 = 0.22$, $P < 0.006$), whereas two factors (thermal pain threshold and STAI) fitted best for recovery room analgesia ($r^2 = 0.27$, $P < 0.01$) and STAI total score alone for the predictive model of total analgesic need ($r^2 = 0.22$, $P < 0.01$; fig. 2 and table 7).

When dichotomizing the pain (composite pain score) outcome to predict the upper twentieth percentile of individuals' pain using a receiver operating characteristic curve, this multifactorial predictive model yielded an optimal sensitivity of 0.71 and specificity of 0.76 in predicting the composite pain score outcome. Similarly for total analgesic requirement, the predictive model yielded a sensitivity of 0.80 and a specificity of 0.80.

Discussion

These results suggest that factor analysis with a thoughtful combination of predictors yields a model with significant improvements over single variables in predicting pain and analgesic requirement outcomes after cesarean section. Thermal pain sensitivity study is an accepted method for experimental pain assessment.[17,18] Granot *et al.* [10] reported postoperative pain VAS score at rest and during activity to be significantly correlated ($r = 0.4 - 0.5$) with preoperative pain VAS score on the arm to thermal stimuli, especially at 48°C, but failure of thermal pain threshold to correlate with postoperative pain. Our results with thermal testing in the arm are consistent with those findings, but we enlarge on them by concurrent measurement of heat pain responses to the lower back. Bajaj *et al.*[16] reported hypoalgesia in late pregnancy to be generalized in women with pelvic pain, but localized to presumed referred pain sites in the lower back and sacrum in women without pelvic pain. The authors suggest that descending noxious inhibition may be activated in late pregnancy and is probably more intense and generally activated in women with pelvic pain but only segmentally activated in women without pain. Our data did not find preexisting pain during pregnancy to be a strong predictor factor for postoperative pain. However, the thermal pain threshold in the lower

Table 6. Multiple Regression Analyses for Each Pain Outcome (Final Model)

						Model			
Pain Outcome	Predictors	b	β	t	*P* Value	F	*P* Value	r^2	Adjusted r^2
Resting pain						5.1	0.01	0.26	0.21
	Pain and unpleasantness	0.7	0.32	1.95	0.06				
	Expectation	1.5	0.35	2.2	0.04*				
Evoked pain						7.7	0.009†	0.20	0.18
	Back threshold	−5.4	−0.45	2.8	0.009				
"Overall" pain	No predictors met criteria								
Composite pain score‡						5.7	0.008†	0.28	0.23
	Pain and unpleasantness	2.5	0.42	2.7	0.01*				
	Blood pressure	−1.1	−0.37	2.3	0.03*				

* $P < 0.05$. † $P < 0.01$. ‡ Reliability of composite pain score $\alpha = 0.79$. Composite pain score is the sum of the visual analog scores of resting, evoked and overall pain.

b = unstandardized regression coefficient; β = standardized regression coefficient; F = F statistic, which evaluates the model; r^2 = variance in pain outcome accounted for by the predictors; t = t statistic, which evaluates the predictor.

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Table 7. Multiple Regression Analyses for Each Analgesic Use Outcome (Final Model)

Analgesic Outcome	Predictors	b	β	t	*P* Value	Model F	Model *P* Value	Model r^2	Model Adjusted r^2
Intraoperative analgesia*						8.8	0.006#	0.22	0.19
	Preexisting pain	0.46	0.46	3.0	0.006#				
Recovery room analgesia†						4.9	0.016	0.27	0.22
	Thermal pain threshold	−0.80	−0.24	1.4	0.18				
	State Trait Anxiety Inventory	0.36	0.40	2.2	0.030.19‖				
PCA‡	No predictors met criteria								
Total analgesia§						7.1	0.01#	0.22	0.19
	State Trait Anxiety Inventory	0.52	0.46	2.8	0.01#				

* Intraoperative analgesia supplement required (in milligrams of morphine equivalents). † Recovery room analgesia required (in milligrams of morphine equivalents). ‡ First 6 hours of intravenous patient controlled analgesia required in the ward (in milligrams of morphine equivalents). § Total analgesia is the sum of analgesia (in milligrams of morphine equivalents) of the above three (†‡§) periods. ‖ $P < 0.05$. # $P < 0.01$.

b = unstandardized regression coefficient; β = standardized regression coefficient; F = F statistic, which evaluates the model; PCA = patient-controlled analgesia; r^2 = variance in pain outcome accounted for by the predictors; t = t statistic, which evaluates the predictor.

back near the dermatomes of the surgical wound interestingly was the most important predictive factor for evoked pain and for recovery room analgesia requirement after cesarean section, consistent with variability in homosegmental inhibition at term pregnancy as a determinant for postinjury pain.

In contrast to evoked pain after cesarean section, the degree of pain at rest was predicted by two other factors: pain and unpleasantness and patient expectation. This may suggest that the mechanisms of resting and evoked pain are different and that psychological aspects may play a significantly greater role in resting pain than evoked pain. It is conceivable that different treatments or combinations of treatments may be more appropriate to control resting pain as compared with evoked pain.

Surgery and postoperative recovery evoke significant physiologic and psychological reactions. Jamison *et al.*[19] found significant correlations between stress and postoperative analgesic usage, whereas Hansson *et al.*[20] did

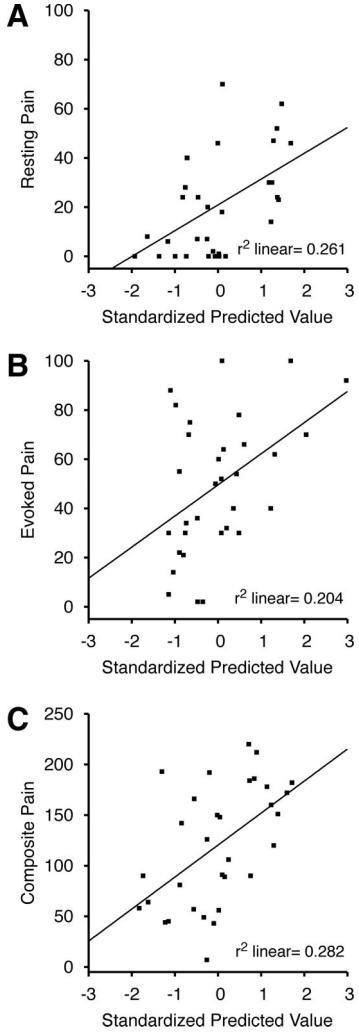

Fig. 1. Graphs showing the standardized predictive value of linear composite of predictors *versus* postoperative visual analog scale pain scores for (*A*) resting, (*B*) evoked, and (*C*) composite pain.

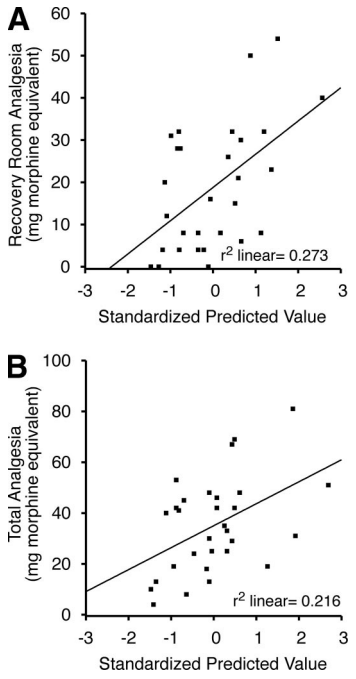

Fig. 2. Graphs showing the standardized predictive value of the linear composite of predictors *versus* postoperative analgesia outcomes for (*A*) recovery room analgesia and (*B*) total analgesia.

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not. These conflicting results and those of others on stress and postoperative pain and analgesic drug use may reflect in part interstudy differences in patient gender, surgical procedures, and presence or absence of pregnancy.[19–23] Cesarean section is a unique surgery, accompanied by the significant hormonal and emotional changes associated with pregnancy, arrival of the newborn with attendant care responsibilities, expectation to recover rapidly, and sleep deprivation resulting from maternal neonatal interactions. Patients' expectations and their pain experience during pregnancy or with previous surgery also may impact postoperative pain experience. For example, preoperative expectation of pain is correlated with postoperative pain intensity in nonpregnant patients.[22] Expectations powerfully modulate both subjective reports of acute pain and pain-induced brain activity through mechanisms likely involving the prefrontal cortex, anterior cingulated cortex, and the anterior insular cortex.[24] In our study, regression analysis also identified preoperative expectation to be a key component to predict resting pain but not evoked pain.

Both pain and analgesic drug use vary widely after surgery, and these share a complex relationship. Aubrun *et al.*,[14] in a study of 3,045 patients, reported the relationship between postoperative pain and morphine requirements was not linear and was best described as sigmoidal. Therefore, predictors for postoperative analgesic requirement may be different from those for postoperative pain intensity. Our results are consistent with this presumption. Furthermore, the key predictive factor for postoperative analgesia requirement may differ even for different stages of recovery or activity. For example, preexisting pain during pregnancy was the key predictive factor for intraoperative analgesic drug use in the current study, whereas thermal pain threshold and STAI were key factors predicting analgesic drug use in the recovery room, and STAI was the key predictor for total analgesic drug use. Hsu *et al.*[12] reported a significant correlation between postoperative analgesic requirements and the effect of a probe dose of fentanyl on experimental pressure pain tolerance. It is conceivable that such pharmacodynamic predictors could further improve our multifactorial model.

Postoperative systemic opioid analgesia consumption varied widely with a significant interindividual variability. Macintyre and Jaarvis[4] reported a 10-fold difference in postoperative morphine consumption, which also is consistent with findings in our study. It is not known whether this large interindividual variability in response to systemic opioids also exists for other forms of analgesia or multimodal analgesia. Therefore, application of regression analysis with meaningful subsets of variables to predict postoperative pain and analgesic requirement may be useful in individualizing analgesic methods and identifying patients at higher risk for severe postoperative pain and high analgesic requirement who may then benefit from more intensive therapy (be it higher dose or multimodal analgesia) to reduce variability in postoperative pain and further improve comfort and quality of care.

There are a number of limitations in our exploratory study other than the small sample size. The unanticipated withdrawal of rofecoxib by Merck during our study period led us to switch to the use of 50 mg rofecoxib once to 800 mg ibuprofen every 8 h during the first 24 h after surgery. These two regimens generally are considered to have similar analgesic effects during the study period.[25] We also allowed opioid analgesic supplement during surgery when needed or requested by patients for pain and discomfort. Even though the average amount of discretional supplemental opioid used during surgery was small (2.9 mg of morphine equivalents), this may make the recovery room analgesic need difficult to interpret. However, denial of opioid analgesic supplement when needed or when requested for pain and discomfort would not represent normal good practice and may make the study enrollment more difficult or may even be deemed unethical. Instead, in the design of our study, we included the total analgesic use (intraoperative, recovery room, and ward intravenous PCA use) as one of the main outcome measure that would have taken the intraoperative supplement analgesic use into consideration. The pain scores assessed on postoperative day 1 should also not be affected significantly by the small amount of intraoperative opioid supplement. Even with a relatively small sample size in this exploratory study, statistical significance in predictive power and correlations were observed, as well as clinical relevance. However, results of this study must be applied with caution within the limitations of the study, and also a significant part of the variability in the outcomes measured still cannot be predicted fully by our existing multifactorial predictive model. Further research is needed to determine a more complete multifactorial prediction model for postoperative pain and analgesic required.

In conclusion, our results suggest that a multifactorial predictive model with factor analysis, using a meaningful combination of patients' responses to thermal sensitivity tests and to psychological questionnaires, provides a reliable method in predicting postoperative pain and analgesic requirement outcomes after cesarean section. Furthermore, different predictors may be useful for predicting different types of postoperative pain and analgesic requirement. These findings may have important clinical implications to help identify patients at risk for postoperative hyperalgesia who may then benefit from tailored treatment to improve outcomes and quality of care.

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