Original Article

Pre-operative pain sensitivity: A prediction of post-operative outcome in the obstetric population

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Abstract

Context: Experimental assessments can determine pain threshold and tolerance, which mirror sensitivity to pain. This, in turn, influences the post-operative experience.

Aims: The study intended to evaluate whether the pre-operative pressure and electrical pain tests can predict pain and opioid requirement following cesarean delivery.

Settings and Design: Research was conducted on females scheduled for cesarean section at a tertiary care hospital of the state. Twenty women were enrolled, after obtaining written informed consent.

Materials and Methods: Pain assessment was performed on the eve of cesarean sections using three devices: PainMatcher® determined electrical pain threshold while the algometers PainTest™ FPN100 (manual) and PainTest™ FPX 25 (digital) evaluated pressure pain threshold and tolerance. Post-operative pain relief included intravenous morphine administered by patient-controlled analgesia, diclofenac (100 mg, every 12 h, rectally, enforced) and paracetamol (1000 mg, every 4-6 h, orally, on patient request). Pain scores were reported on numerical rating scales at specified time intervals.

Statistical Analysis Used: Correlational and regression statistics were computed using IBM SPSS Statistics 21 software (IBM Corporation, USA).

Results: A significant correlation was observed between morphine requirement and: (1) electrical pain threshold (r = –0.45, P = 0.025), (2) pressure pain threshold (r = –0.41 P = 0.036) and (3) pressure pain tolerance (r = –0.44, P = 0.026) measured by the digital algometer. The parsimonious regression model for morphine requirement consisted of electrical pain threshold (r^2 = 0.20, P = 0.049). The dose of morphine consumed within 48 h of surgery decreases by 0.9 mg for every unit increment in electrical pain threshold.

Conclusions: The predictive power of pain sensitivity assessments, particularly electrical pain threshold, may portend post-cesarean outcomes, including opioid requirements.

Key words: Analgesia, anesthesia, cesarean section, obstetrical, pain threshold, patient-controlled, post-operative pain

Introduction

Pain is a major concern for surgical patients. Albeit medical advances and development of new treatment modalities, post-operative pain management of these patients may still present a challenge. Disregard of individual variability is a chief contributor to inadequate pain relief. The search for a 'gold standard' is trivial[1] given that pain is a personal, multidimensional experience.

Numerous experimental stimulation models for testing pain sensitivity have been studied, with the goal of predicting acute post-surgical pain.[2-11] Electrical pain threshold appears to have superior predictive power, compared with thermal and mechanical assessment.[12] Its potential in estimating the expected opioid drug use, particularly when this is largely controlled by patient in the post-operative period, is definitely worth establishing.

In a previous publication,[13] an inverse correlation was observed between pre-operative electrical pain threshold and

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pressure pain tolerance and pain scores recorded post-cesarean section, as well as a relationship between the electrical pain threshold and post-operative paracetamol consumption. In the original research, opioid administration was enforced post-surgery. This study was designed to evaluate the efficacy of different pain predictive tools to predict post-operative pain and opioid requirements following cesarean delivery.

Materials and Methods

The validated study design has been published earlier in more detail,[13] but will be described briefly.

Healthy women at 36+ weeks' gestation, scheduled to undergo elective lower segment cesarean section were eligible for inclusion. Enrollment was restricted to patients having no obstetric complications or implanted electrical devices. Subjects were individually briefed about the non-invasive experimental procedures that the study entailed. Following approval by the University Research Ethics Committee, 20 patients who fulfilled the criteria and agreed to participate, were consecutively recruited after giving signed informed consent.

The day before the elective section, experimental pain assessment was performed using an electrical stimulation unit – PainMatcher® (Cefar Medical AB, Lund, Sweden) and two pressure algometers-manual PainTest™ FPN 100 and digital PainTest™ FPX 25 (Wagner Instruments, Greenwich, USA).

PainMatcher® generates electrical impulses with progressively increasing intensity corresponding to steps on a 0-99 scale. The electrical charge per second is minimal, does not cause tissue damage and can be instantly interrupted by the subject.[6] To estimate electrical pain threshold, each patient pressed the electrode contact area with the thumb and index finger until the stimulus became painful. Triplicate testing was performed and the mean value calculated.

For pressure pain assessment, the 1 cm^2 probe of both algometers, one after the other, was applied, with gradually increasing pressure, to the soft-tissue of the third finger. The pressure corresponding to the patient's pain threshold (first painful sensation perceived) and pain tolerance (maximum pain that could be endured) was recorded in each case.

Surgery and anesthesia

Cesarean sections were performed under spinal or general anesthesia. The intraoperative protocol was left unchanged.[13] Post-operatively, paracetamol 1000 mg and diclofenac 100 mg were administered per rectum before patient's transfer to an obstetric ward.

Post-operative analgesia and pain assessment

Post-surgery pain management included diclofenac (100 mg, every 12 h, rectally, regularly enforced) and paracetamol (1000 mg, every 4-6 h, orally, as needed). For the administration of opioids, a patient-controlled analgesia (PCA) pump was provided, loaded with a syringe containing 1 mg/ml morphine in 0.9% normal saline. It was programmed to deliver 1 mg intravenous morphine with a lockout interval of 5 min and a 4 h limit of 48 mg. In the immediate post-operative setting, respiratory rate, sedation scores, blood pressure and heart rate, were monitored hourly. Post-operative pain at rest, at 6, 12, 24 and 48 h following cesarean section was recorded using a 0 to 10 numerical rating scale (NRS).

Statistical analysis

Variables were reviewed using standard descriptive statistics including mean, standard deviation (SD) and range. Normality of the data distribution was evaluated by the Shapiro-Wilk test and parametric statistics were applied. To explore the relationship between predictors and outcome variables, correlation coefficients were calculated with the Pearson correlation test (which measures the strength of a relationship between two continuous variables having a metric scale) and the one-way analysis of variance (ANOVA) (which compares mean scores between two or more independent groups). The latter was also used when comparing data from the two population samples. A $P < 0.050$ was considered significant. Linear regression analysis with stepwise selection was used to determine the independent factors (e.g., anesthesia) and/or covariates (e.g., electrical pain threshold) that were predictive for the dependent variable-morphine consumption within 48 h of surgery. In building a parsimonious model, variables were removed if not statistically significant in accounting for outcome variance. The model was tested for collinearity, reported as tolerance and variance inflation factor (VIF). In accordance with published data,[14] a VIF higher than five and a reciprocal tolerance value lower than 0.20 were deemed indicative of collinearity. Analyses were performed using IBM SPSS Statistics 21 software (IBM Corporation, USA).

Results

The 20 women enrolled in this study had a mean age of 29.6 ± 5.4 years and a mean gestation of 38 weeks ± 5 days. In most cases, surgical procedure involved spinal anesthesia and exteriorization of the uterus for repair (17 and 15, respectively). The majority of patients (14) were undergoing cesarean section for the 1st time.

Pre-operative assessment

Similar pressure pain threshold and tolerance results were obtained with both algometers used. The median

PainMatcher® threshold was 15.83, with an approximate seven-fold difference in the responses. Of note, there were six patients with an electrical pain threshold of less than 10 and four with a threshold greater than 20. Further descriptive statistics for all pre-operative tests performed are shown in Table 1.

Post-operative assessment

The mean (±SD) NRS pain scores for post-cesarean section pain at 6, 12, 24 and 48 h, were 5.30 (±2.56), 5.55 (±2.50), 4.45 (±2.04), 3.60 (±1.79), respectively. The mean ± SD morphine requirement was 17.55 ± 15.41 mg. Distribution analysis is presented in Table 2. The mean dose of paracetamol consumed within 48 h of surgery was 8300 ± 1866.61 mg.

Pre-operative variables and post-operative outcomes

Electrical pain threshold, measured pre-operatively by PainMatcher®, correlated significantly with the NRS pain score reported 6 h post-surgery ($r = -0.48$, $P = 0.016$). A significant negative relationship was noted between morphine consumption and: Electrical pain threshold ($r = -0.45$, $P = 0.025$; Figure 1), PainTest™ FPX 25 pressure pain threshold ($r = -0.41$, $P = 0.036$) and tolerance ($r = -0.44$, $P = 0.026$).

Table 1: Descriptive statistics of pre-operative assessments

Preoperative variable	Minimum	Maximum	Mean	Standard deviation
Electrical pain threshold	4.33	32.33	15.13	7.60
Digital* pressure pain threshold	1560	3840	3074.30	690.17
Digital* pressure pain tolerance	2520	5460	4252.25	856.77
Manual† pressure pain threshold	1875	4350	3223.00	699.37
Manual† pressure pain tolerance	2625	6001	4373.20	866.08

*n=20, *Pressure in mmHg as measured by FPX25 digital algometer, †Pressure in mmHg as measured by FPN100 manual algometer*

Table 2: Distribution of patients according to NRS pain scores and morphine consumption

NRS pain score	0-2	3-5	6-8	9-10
At 6 h	4	4	11	1
At 12 h	5	2	13	0
At 24 h	4	10	6	0
At 48 h	6	10	4	0
Morphine consumption mg in 48 hr	**0-12**	**13-25**	**26-38**	**39-50**
	9	4	5	2

n=20, NRS=Numerical rating scale

Predictive model

The preliminary model included the following variables: Parity, site of uterine repair, previous cesarean sections, breastfeeding, type of anesthesia, age, electrical pain threshold, pressure pain threshold and tolerance measured by PainTest™ FPX 25 and pressure pain tolerance and threshold measured by PainTest™ FPN 100. For all variables entered, collinearity statistics showed that tolerance was greater than 0.2 and VIF less than 5, thus, there is no indication that any variable was excluded from the regression equation because of a strong relationship with another variable in the analysis. The most statistically significant fit for post-operative morphine consumption within 48 h of surgery was provided by electrical pain threshold, measured by PainMatcher® ($r^2 = 0.20$, adjusted $r^2 = 0.15$, $P = 0.049$). Parameter estimates indicate that the dose of morphine required decreases by 0.9 mg for every unit increase in electrical pain threshold.

Discussion

PCA has emerged as a practical modality for post-surgery pain, even though availability of PCA pumps may be limited in a hospital setting. PCA reduces the peaks and troughs in blood drug concentrations, lessens the work of floor personnel, is safe and convenient for the patient and results in higher satisfaction scores.[15]

Opioids target the somatic pain related to the wound itself. The anti-inflammatory and anti-pyretic properties of adjuvants have a complementing approach by easing the visceral pain originating from the uterus. The multimodal approach to post-operative pain relief has gained ample appreciation. Most methods rely on opioids supplemented by non-opioid analgesics, such as paracetamol and anti-inflammatory drugs.[16]

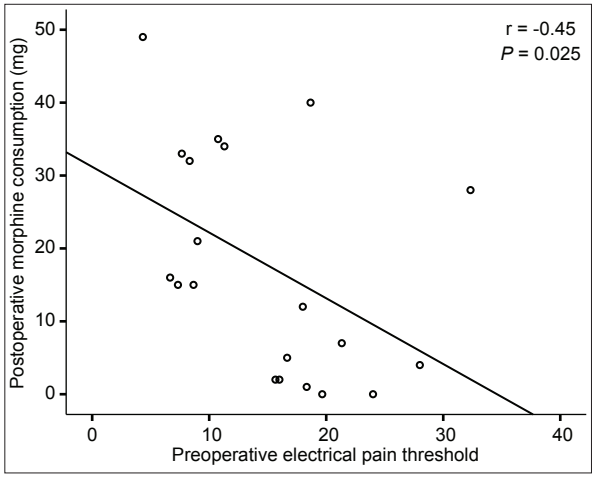

Figure 1: Correlation between pre-operative pain threshold, measured by PainMatcher® and morphine consumption in the first 48 h following surgery; $n = 20$

Often, in studies that have focused on the role of pre-operative pain sensitivity assessments in predicting the dose of opioids consumed by PCA,[7,9,17,18] supplementary analgesics were not given importance in the analyses. The present study, considered both morphine and paracetamol consumption as outcome variables, but there was no significant correlation between the two. This implies that a patient who self-administered high morphine doses did not necessarily consume more paracetamol (due to high pain sensitivity) or less paracetamol (due to adequate pain relief obtained by the opioid alone).

As opposed to the earlier patient population, in a study by Buhagiar *et al.*,[13] women no longer received predetermined doses of intramuscular pethidine, but had control over their intake of intravenous morphine through the PCA. Both populations reported somewhat similar pain scores post-cesarean section, with no statistically significant difference observed. Yet, the consumption of paracetamol was considerably higher in the present sample, yielding an important distinction between the two groups during ANOVA analysis ($F = 122.88$, $v_1 = 1$, $v_2 = 83$, $P < 0.0005$; Figure 2). Patients receiving morphine via PCA took significantly more time to open their bowels compared with the previous sample of patients, who received fixed pethidine doses intermittently ($F = 7.00$, $v_1 = 1$, $v_2 = 83$, $P = 0.010$).

While electrical pain threshold proved to be the best predictor of post-operative morphine requirement, its previously outlined predictive power with respect to paracetamol consumption[13] did not prove significant in this analysis. The different pattern in paracetamol consumption between the two groups is also considerable. In the present study, two analgesics were made available to the patient "on request" with less restrictions on dosing intervals. When given a relative choice to self-administer morphine and/or paracetamol, women (who were predominantly nursing mothers) may have opted for paracetamol trusting its safer profile. Yet, administering paracetamol every 4-6 h may result in a daily dose that is beyond the maximum recommended in guidelines. Nonetheless, research[19] shows that paracetamol clearance and distribution volume are higher in women undergoing cesarean delivery, resulting in lower peak and trough concentrations. Consequently, the use of shorter dosing intervals or greater maintenance doses of paracetamol in the peripartum period can counteract pregnancy related alterations in physiology that affect drug disposition and pharmacokinetics.[20]

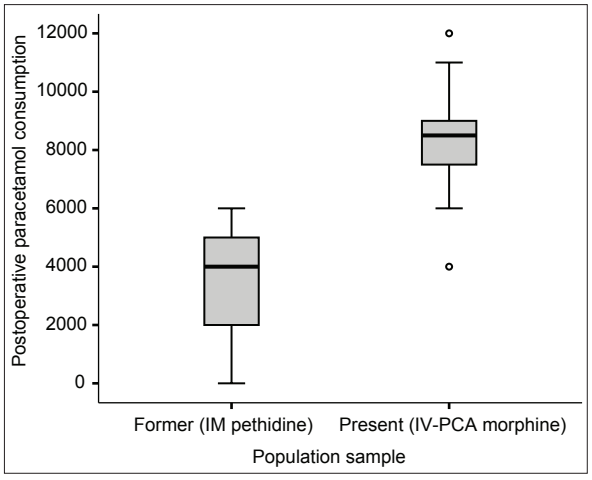

Figure 2: Box-plot showing difference in the dose of paracetamol (in mg) consumed by the 2nd post-operative day, among the two population samples; $n = 85$

Patients may have administered opioids via PCA, not with the aim of attaining complete pain relief, but rather to ease the pain intensity while limiting opioid side-effects, such as nausea and disorientation. Pre-operative education of patients receiving PCA is crucial. Wilder-Smith and Schuler[21] observed improvements in pain relief in patients who were aware of the aims and potential risks of pain therapy. Yet, knowledge of the complications of opioid drugs could make the patient reluctant to use PCA repeatedly.

Even though results obtained with the manual algometer may be less accurate than those of the digital algometer, both were included in the study for the sake of completeness. The manual device failed to provide significant correlating results. Notably, while pressure pain assessments were not predictive of paracetamol consumption in the previous study,[13] pain threshold and tolerance measured by PainTest™ FPX 25 were significantly correlated to morphine requirement in the present study. Opioid administration appears to be related more closely to pre-operative pain assessments than paracetamol.

Interestingly, there was no correlation between pain scores and analgesic consumption. A central difference in the present study was that patients had access to opioid administration throughout as opposed to the previous population sample who received static doses of intramuscular pethidine. Thus, the temporal relationship applied before (where the schedule of pain score reporting coincided with the time of opioid administration and women rated their pain just before the due dose of opioid) could not be sustained. The fact that post-operative NRS scores were not assessed in all patients at the same time interval from the last administration of analgesics could have affected the results.However the relationship between electrical pain threshold and pain scores 6 h post-surgery was sustained.

There are a number of limitations in this exploratory study other than the small sample size. Investigator characteristics and manual effort in conducting the pre-operative tests may not

be entirely reproducible. Placebo effects and acute tolerance issues could not be ruled out. The enrollment mechanism, being restricted to female patients scheduled for cesarean section, hinders observation of sex differences in response to pain and does not consider the possibly distinct outcomes that may present with emergency procedures. Pre-existing pain, pre-operative expectations and the information received by patients with respect to surgery and pain relief, were not taken into account. It was assumed that morphine was only being resorted to, for its analgesic properties. However, it is known that the anxiolytic and tranquilizing properties of opioids may influence the patient's desire to activate the PCA pump.[22] Recording patient anxiety scores would help determine whether the morphine consumption is more strongly related to the latter, rather than to actual pain intensity.

The fact that, at equianalgesic doses, morphine is more constipating than pethidine,[23] could explain the delay in passing stools observed in the PCA population sample. Comparison of opioid requirement and analgesic outcome between the two groups, particularly in view of opioid sensitivity issues,[24] was beyond the scope of this study. Whether PCA reduces the opioid consumption and side-effects remains questionable and different studies provide conflicting evidence.[25-27]

Several dimensions influence the pain experience. Herein, we report a median electrical pain threshold of 15.83, which contrasts with other studies using PainMatcher® in their evaluations. Lund *et al*.[28] included two subgroups: (1) young healthy volunteers, whose median electrical pain threshold was 15 and (2) pain patients, with a median threshold of 7. The median reported in this study is significantly higher than that of pain patients (sign test $P < 0.0005$), but not significantly different than that of the healthy group (sign test $P = 0.834$). Patients with pain disorders may exhibit lower pain thresholds than pain-free individuals due to central hypersensitivity causing a generalized decrease in nociceptive thresholds.[5] Furthermore, in test-retest situations, there is reduced variability in pain patient thresholds, compared to healthy groups, possibly due to patients' enhanced propensity in perceiving painful stimuli.

Käll *et al*.[29] recorded a significantly higher median pain threshold (19) for young male patients (1-tailed sign test $P = 0.021$). Women often demonstrate lower electrical pain thresholds than men, indicating gender-related differences in pain perception.[30,31] Consequently, in electrical stimulation studies in male groin hernia patients, no significant role for electrical pain thresholds was observed.[8] In general, pain threshold has been reported to increase with age, resulting in lower post-operative pain ratings and morphine requirements in the elderly.[32] One would expect the young women in our sample to have lower pain thresholds than the older male participants recruited by Aasvang *et al*.,[8] who noted a median of 8. Yet, the median we report is significantly higher (1-tailed sign test $P = 0.006$). Then again, pain threshold has been shown to increase in pregnancy due to the phenomenon of pregnancy-induced analgesia.[4,33] During gestation, pain pathways may be influenced by changes in nerve fiber conduction, decreased pain sensitivity and enhanced processes of pain modulation.[34,35] We found no significant difference between the median of our parturients and that of a very similar group enrolled by Nielsen *et al*.[3] who reported a median electrical pain threshold of 11 in women undergoing cesarean section (sign test $P = 0.503$).

The mode of painful stimulation and its location, frequency and duration,[30] as well as the motivation of the subject, may all impinge on the results of pain assessments. Hypervigilance,[17] depression, vulnerability and other psychologic factors can also influence pain response, although their inclusion in predictive models may provide merely modest improvements.[12] Response bias is influential too. There exists a possibility that some individuals consistently rate any given stimulus as high or low. Nonetheless, functional magnetic resonance imaging studies indicate that inter-individual differences in reports of pain intensity are directly related to the extent of activation in brain regions important in the processing of pain.[36] Of higher functional relevance is whether the correlation between experimental pain reports and the subsequent clinical pain experience translates to a similarly remarkable correlation with analgesic drug use, which is what this study attempted to establish.

Pre-operative pain assessment by a simple electric device is more feasible in clinical practice, compared to complex sensory tests and time-consuming psychometric questionnaires. Pain threshold is more reproducible than pain tolerance,[8] but can prove harder to assess, especially when compared to sensory thresholds (least detectable sensation).[28] Electrical pain threshold may not only predict acute post-operative pain, but also the risk of developing chronic pain.[5] Data reveals a superior correlation between electrical pain threshold and clinical pain, in women, compared to men.[12] This potentiates the prospect of having these tests as bedside screening tools on obstetric wards.

In conclusion, the predictive power of electrical pain threshold proved promising in another distinct, clinical scenario – particularly for predicting IV-PCA morphine requirements. A significant part of variability remains as yet unexplained and this warrants further research, particularly to determine whether the electrical pain model

can be generalized to all surgical patients. Combined with demographic, psychological and genetic factors,[37] experimental pain tests may assist in identifying patients at risk of developing severe pain post-cesarean section. In view of the extensive individual variability reported in PCA morphine doses,[32] individualization of the PCA protocol may avoid the risks of under or over-treatment, associated with standard pain management. Allocating resources to tailor-made treatment plans is the key to immediate, targeted, post-operative care.

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