Reports of Original Investigations

Locked out and still knocking: predictors of excessive demands for postoperative intravenous patient-controlled analgesia

[Quand il n'y en a plus mais qu'on en veut encore : les prédicteurs de besoins excessifs en analgésie postopératoire intraveineuse contrôlée par le patient]

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Background: Psychosocial factors governing the use of postoperative, intravenous patient-controlled analgesia (PCA) have received little attention in spite of the fact that PCA is the most common modality for managing pain after surgery. The motivation behind requests for analgesia during lockout periods is not known. Unrelieved pain and need for pain medication are obvious reasons but other factors may be involved. The aim of the present study was to predict PCA lockout interval demands based on preoperative psychosocial factors.

Methods: Approximately one week before major abdominal gynecologic surgery, 117 women completed the impact of events scale (IES) measuring intrusive thoughts and avoidant behaviours. Pain was measured by visual analogue scale at three, six, 12, 24 and 48 hr after surgery. Measures of anxiety and negative affect were obtained 24 and 48 hr after surgery. Cumulative morphine consumption and every PCA demand (drug delivered and not delivered) were downloaded from the PCA pump.

Results: Multiple regression analyses revealed that preoperative intrusive thoughts and avoidant behaviours about the upcoming surgery positively predicted PCA lockout interval demands after controlling for postoperative pain, morphine consumption, anxiety, and negative affect ($R^2 = 0.45$; $P < 0.0001$). Path analysis showed a direct pathway from preoperative IES scores to lockout interval demands ($\beta = 0.23$, $P = 0.002$) which was not associated with untreated pain, anxiety, or negative affect.

Conclusions: Excessive demands for postoperative intravenous-PCA morphine during lockout intervals appear to reflect, in part, poor preoperative adaptation to surgery involving intrusive thoughts and avoidant behaviours about the upcoming surgery.

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***Contexte** : Les facteurs psychosociaux régissant l'usage d'analgésie postopératoire intraveineuse contrôlée par le patient (ACP) n'ont reçu que peu d'attention, malgré le fait que l'ACP constitue le mode le plus fréquent de prise en charge de la douleur après une chirurgie. Les motivations derrière les demandes d'analgésie durant les intervalles d'interdiction ne sont pas connues. Bien qu'une douleur qui n'est pas soulagée et le besoin de médicaments anti-douleur constituent des raisons évidentes, d'autres facteurs pourraient jouer un rôle. L'objectif de cette étude était de prédire les demandes d'ACP pendant les intervalles d'interdiction sur la base de facteurs psychosociaux préopératoires.*

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Méthode *: Une semaine environ avant une chirurgie gynécologique abdominale importante, 117 femmes ont complété l'Échelle de répercussion des événements (IES – Impact of events scale) mesurant les pensées intrusives et les comportements d'évitement. La douleur a été mesurée à l'aide d'une échelle visuelle analogue à trois, six, 12, 24 et 48 h après la chirurgie. Les mesures de l'anxiété et de l'affect négatif ont été prises 24 et 48 h après la chirurgie. La consommation cumulative de morphine et chaque demande d'ACP (médicament fourni ou non) ont été enregistrées depuis la pompe d'ACP.*

Résultats *: L'analyse de régression multiple a révélé que les pensées intrusives avant l'opération et les comportements d'évitement au sujet de la chirurgie à venir constituaient des prédicteurs positifs de l'utilisation de l'ACP pendant les intervalles d'interdiction, et ce après avoir contrôlé pour la douleur postopératoire, la consommation de morphine, l'anxiété et l'affect négatif (R^2 = 0,45 ; P < 0,0001). L'analyse des pistes causales a montré une piste causale directe des scores IES préopératoires aux demandes d'ACP pendant les intervalles d'interdiction (β = 0,23, P = 0,002) qui n'étaient pas associées à une douleur non traitée, de l'anxiété, ou un affect négatif.*

Conclusion *: L'utilisation postopératoire excessive de morphine intraveineuse par ACP durant les intervalles d'interdiction semble refléter, en partie au moins, une mauvaise préparation préopératoire à la chirurgie impliquant des pensées intrusives et des comportements d'évitement quant à la chirurgie à venir.*

PATIENT controlled analgesia (PCA) is the gold standard for managing acute postoperative pain with systemic opioids.[1] Empirical research conducted over the past 20 years has demonstrated several advantages over conventional approaches to acute postoperative pain management. Patient-controlled analgesia is associated with a significant decrease in the incidence of moderate and severe pain after surgery compared with intramuscular opioids.[2] Patient satisfaction is higher with PCA than with nurse administered intramuscular injections.[3] In addition, caregivers are freed up to attend to other patient needs and patients value not having to request pain medication from caregivers.[4] Although the total dose of drug is greater when patients self administer the agent than when it is nurse administered,[4,5] with the exception of pruritus, PCA is not associated with a greater incidence of adverse effects.[3]

In spite of these advantages of PCA, we know very little about the factors that govern its effective use. Recent reviews and studies have focused on the role of various PCA parameters; including drugs,[6–8] routes,[9,10] doses and lockout intervals,[6,11,12] and background infusion rates,[13] but surprisingly little research has been conducted to understand the psychological and emotional factors that predict effective use of PCA. A better understanding of how specific psychosocial factors relate to postoperative PCA use may contribute to improved pain control and reduced adverse effects.

The few studies to examine psychological and emotional correlates of PCA have focused on predicting total drug consumption or total number of demands,[14–23] number of demands followed by drug delivery,[15,18] dose-demand ratio (i.e., proportion of total PCA demands that are followed by delivery of a bolus dose),[14,15,17–19] and/or number of lockout interval requests.[21,23] However, many of these studies suffer from methodological weaknesses that limit the interpretation of the results, including; small sample size,[21] use of non-validated questionnaires with unknown psychometric properties,[17,20] cross-sectional design,[16] and, importantly, failure to control for pain scores and/or total opioid consumption when predicting demands, dose-demand ratio, or lockout demands.[14–16,18–23] The last factor is especially important since one of the most obvious reasons for a low dose-demand ratio or a large number of lockout interval demands is unrelieved pain. Thus, preoperative or postoperative psychosocial factors that significantly predict a low dose-demand ratio or a large number of lockout interval demands may no longer do so once pain has been controlled.

Notwithstanding the methodological weaknesses noted above, total PCA consumption, low dose-demand ratios, or number of lockout interval demands appear to be associated with increased state and/or trait anxiety[16,17,19–21] (but see[6,14] for two exceptions) and other anxiety-related constructs.[17,18,23] For example, Jamison *et al.*[17] showed that greater anticipated pain and postoperative anxiety were significantly related to a lower dose-demand ratio. Similarly, Logan and Rose[18] found that higher preoperative trait anxiety and anticipated discomfort predicted a lower dose-demand ratio. Yang *et al.*[23] reported that preoperative physical avoidance and negative affect (NA) predicted the total number of lockout interval demands after hemicolectomy. Taken together, the results of these studies suggest that perioperative anxiety, worry and avoidance are related to excessive PCA demands or inefficient use of the modality.

In the present study, we sought to determine the factors that predict PCA lockout interval demands. We selected this outcome measure because, in the context of adequate pain control and after controlling for cumulative PCA dose, it 1) suggests that demands are being made for reasons other than pain; 2) is not confounded by other PCA parameters (e.g., total

number of demands, cumulative dose, and successful demands); and 3) raises the possibility that frequent lockout demands also may be associated with excessive opioid consumption (i.e., a proportion of the total opioid delivered may be unnecessary). Given the possibility noted above that patients who are anxious, worried and avoidant, make excessive demands or inefficient use of PCA, we hypothesized that preoperative levels of intrusive thoughts and avoidant behaviours regarding the upcoming surgery [as measured by the impact of events scale (IES)] would predict PCA lockout interval demands after controlling for relevant covariates such as total PCA consumption, pain, and other postoperative NA states.

Materials and methods

Participants

Data from 117 women were used in the present analyses. The data were part of a larger trial examining the benefits of perioperative epidural anesthesia for women undergoing major gynecological surgical procedures by laparotomy.[24] Inclusion criteria were ASA physical status I–II, age between 19 and 75 yr, weight between 45 and 90 kg, height between 150 and 175 cm, body mass index less than or equal to 30, and ability to speak and read English. Exclusion criteria were contraindications to PCA morphine or regional anesthesia; history of a major psychiatric disorder; history of a substance use disorder; and current opioid use.

The same general anesthesia protocol was used in all patients, who had been randomly assigned to either receive 1) preincisional epidural lidocaine with epinephrine and fentanyl, with epidural saline given 35–40 min after incision; 2) preincisional epidural injections of normal saline, with epidural lidocaine with epinephrine and fentanyl given 35–40 min after the incision; or 3) sham epidural catheter and administration of saline before and after surgery. Importantly, when asked to guess the group to which they had been assigned patients performed at a chance level. The study was approved by the Toronto General Hospital Research Ethics Board.

Procedure

PREOPERATIVE ASSESSMENTS

A member of the research team approached prospective patients at their pre-admission appointment approximately seven to ten days before surgery. Following informed written consent, patients completed the pre-assessment battery of questionnaires, which included measures of coping and distress (general mental health, intrusive and avoidant thoughts about surgery, and state-based NA).

POSTOPERATIVE ASSESSMENTS

After surgery, a visual analogue pain scale at rest (VAS-R), anxiety, and NA were assessed by administering self-report measures 24 and 48 hr after surgery. Morphine consumption by PCA was assessed up to 48 hr after surgery.

Measures

PRESURGICAL PSYCHOSOCIAL MEASURES

The mental health inventory (MHI)[25] is an 18-item scale that measures symptoms of psychological distress and well-being along five dimensions – anxiety, depression, loss of behavioural/emotional control, positive affect, and interpersonal ties – and also yields a total score.[26] Subjects rated how often in the past 24 hr they had experienced each symptom. For the present analyses, we used the anxiety subscale score measured at 24 and 48 hr after surgery which showed very good internal consistency (Cronbach's alpha = 0.87–0.89). The anxiety subscale score ranges from 5–30, with higher scores indicative of less anxiety.

The IES[27] is a 15-item, self-report scale that assesses two categories of cognitive responses to stressful events: intrusion (intrusively experienced ideas, images, feelings, or bad dreams) and avoidance (consciously recognized avoidance of certain ideas, feelings, or situations). The correlation between the intrusion and avoidance subscales was 0.71 ($P < 0.0001$), so the IES total score, which is the sum of the two subscale scores, was used for the analyses. Impact events scale total scores range from 0–60 with higher scores indicating worse functioning. Patients rated the frequency of intrusive thoughts and avoidance behaviours in relation to their upcoming surgery at the preadmission visit. Internal consistency of the IES was good (Cronbach's alpha = 0.86).

Negative affect was assessed using a 26-item stress scale that has been shown to be a reliable measure of acute distress.[28,29] Each item was rated on a five-point scale ranging from "not at all" to "extremely." Subjects rated the level of stress-related feelings they were currently feeling along affective (feeling worried, feeling nervous, feeling at ease, spells of terror or panic, etc.) and somatic dimensions (hot or cold spells, trembling, feeling low in energy or slowed down, heart pounding or racing, etc.). We chose to use this measure instead of other measures of distress, anxiety or NA/mood, as it was brief, included both affective and somatic aspects of stress, and was validated in acute stress situations.[28,29] Negative affect scores range from 0-104 with higher scores indicative of increased NA. For the present analyses, we used NA scores assessed 24 hr and 48 hr after surgery (Cronbach's alpha = 0.81).

Pain measure

Pain at rest was measured using a 10-cm VAS-R at three, six, 12, 24 and 48 hr after surgery. For the present analyses we used the mean of the five pain scores. We chose to average the VAS-R pain scores for three reasons: 1) we wanted a measure that reflected pain across the 48 hr study period; 2) and was weighted more to the earlier hours after surgery as were morphine consumption and lockout interval demands; and 3) given our sample size, we were limited in the number of variables we could enter into the regression and path analyses.

Morphine consumption

Patients were assessed immediately upon arrival in the postanesthesia care unit and were connected to a PCA pump system (Abbott Life Care Infuser, Chicago, IL, USA) containing morphine syringes. The PCA pump was set to deliver a 1.0 to 1.5 mg *iv* bolus dose of morphine with a lockout time of five minutes, a maximum dose of 40 mg in any four-hour period, and no continuous background infusion. This regimen was overseen by the Acute Pain Service and was continued on the ward for 48 hr, during which no other analgesics were administered. For the present analyses, we used cumulative morphine consumption at 48 hr after surgery.

Demands for morphine during lockout intervals

The PCA pump records each demand (button press) for morphine and stores these according to time of request and whether or not a bolus dose was delivered. Demands made during lockout periods were calculated from hard copy records (Abbott TRW Printer, Model TP 40, Abbott Laboratories, Chicago, IL, USA) of the 48 hr study period. For the present analyses, we used the 48 hr cumulative number of lockout interval demands as the primary outcome measure.

Data analyses

Data were analyzed using Statistical Package for the Social Sciences (SPSS version 15.0.1. for Windows, SPSS Inc., Chicago, IL, USA) and Statistical Analysis System (SAS version 9.1, SAS Institute Inc., Cary, NC, USA). Missing data points, which were an extremely rare occurrence, were replaced using the sample mean. Pearson correlation coefficients were calculated to examine bivariate relationships among variables. Two types of analyses were conducted to evaluate the extent to which preoperative IES scores predicted PCA lockout intervals demands. First, we conducted a three-step multiple regression analysis. In step 1, we entered mean VAS-R pain scores and 48 hr cumulative PCA morphine consumption. In step 2, we entered mean MHI-anxiety scores and mean NA scores. In the final step, we entered the preoperative IES total score. Thus, we were interested in determining the proportion of variance in PCA lockout interval demands explained by preoperative IES scores after controlling for postoperative pain, morphine consumption, anxiety and NA. We selected a three-step model in order to separately evaluate the effects of 1) pain-related variables (i.e., pain scores and morphine consumption); 2) emotional variables (i.e., NA and anxiety); and 3) IES total scores on total lockout intervals demands.

We also used path analysis. A path analytic model is similar to a multiple regression model, but may contain multiple predictor and outcome variables, and any given variable may serve both as predictor and outcome. In the path model, antecedent variables precede and predict consequent variables. The flow of influence among the variables in the model may be direct, or a mediator variable may convey this effect so that the flow of influence also may be indirect. In this study, the influence among variables is recursive, meaning that effects are unidirectional (from antecedent to consequent variables, but not the reverse). Since there are no antecedent variables preceding IES scores, it is said to be exogenous, with only unmeasured exterior variables exerting their influence upon it. In this study, IES is temporally and theoretically antecedent to all other measured variables which are therefore considered endogenous to the model. An endogenous variable is one that is influenced by one or more variables

TABLE I Demographic, clinical, and psychosocial variables

Variable	*Mean*	*SD*	*Median*	*Range*
Demographic and clinical variables				
Age (yr)	46.0	9.7	45	50
Weight (kg)	70.1	12.1	68.2	58.3
Duration of surgery (min)	90.4	33.4	80.0	159
48 hr cumulative PCA lockout demands (*n*)	49.1	59.5	27.0	353.0
48 hr cumulative morphine (mg)	93.5	50.6	86.0	273.2
Psychosocial variables				
Preoperative IES total score	21.9	14.5	20.0	70.0
Mean VAS-R pain scores	3.6	1.6	3.7	8.8
Mean 24 and 48 hr NA score	27.0	7.0	26.0	45.0
Mean 24 and 48 hr MHI-Anxiety score	22.8	4.1	23.8	21.0

PCA = patient-controlled analgesia; IES = impact events scale; VAS-R = visual analogue pain scale at rest; NA = negative affect; MHI = mental health inventory.

TABLE II Pearson correlation coefficients among variables in the regression and path models. Also shown are significance levels (*P*)

Measure	*48 hr PCA lockout demands*	*48 hr cumulative morphine*	*Mean VAS-R pain score*	*Mean NA score*	*Mean MHI - anxiety*	*IES total score*
48 hr cumulative PCA lockout demands (*n*)	1.0					
48h cumulative morphine (mg)	0.63 *P* < 0.0001	1.0				
Mean VAS-R pain score	0.25 *P* = 0.007	0.34 *P* = 0.0002	1.0			
Mean NA score	0.23 *P* = 0.011	0.14 *P* = 0.12	0.05 *P* = 0.62	1.0		
§Mean MHI-anxiety	-0.31 *P* =.0007	-0.24 *P* = 0.008	-0.28 *P* = 0.002	-0.39 *P* < 0.0001	1.0	
IES total score	0.38 *P* < 0.0001	0.27 *P* = 0.003	0.26 *P* = 0.004	0.29 *P* = 0.002	-0.57 *P* < 0.0001	1.0

§Lower MHI-anxiety scores are indicative of higher anxiety levels. PCA = patient-controlled analgesia; VAS-R = visual analogue scale pain scores at rest; NA = negative affect; MHI = mental health inventory; IES = impact events scale; Mean VAS-R pain score = mean of VAS-R pain ratings at three, six, 12, 24 and 48 hr after surgery; mean NA and MHI-anxiety scores are calculated from the 24 hr and 48 hr assessments.

from within the model. Standardized path coefficients describe the directional relationship between antecedent and consequent variables with the effects of the remaining variables in the model held constant; these are equivalent to standardized partial regression coefficients and are referred to and symbolized as beta (β). We show standardized path coefficients in the Figure to facilitate direct comparison between various paths and to ease interpretation since they are all expressed in the same standard deviation unit of measurement (however, unstandardized coefficients and their 95% confidence intervals are also shown separately).

Results

Descriptive statistics and correlation coefficients

Table I shows descriptive statistics for relevant demographic, clinical, and psychological variables. The correlation matrix of the model variables in Table II shows that every variable is significantly related to PCA lockout requests and, with the exception of NA, each variable shows at least a minimally significant association with every other variable. Table III shows the means and standard deviations for the VAS-R pain scores taken across the 48-hr study period. The following regression and path analyses used the mean of these five pain scores as the measure of pain.

Multiple regression analyses

Using the forced-entry method, the overall regression model predicting the cumulative number of PCA lockout interval demands was significant [$F(5, 111) = 18.057$, $P < 0.0001$] with a total R^2 of 0.45. Tables IV and V show the total variance accounted at each step, the level of significance, and the beta coefficients for each variable in the total model. Not surprisingly, cumulative morphine consumption and VAS-R pain ratings across the 48-hr study period were highly significant predictors of requests during lockout intervals. In addition, mean postoperative MHI-anxiety scores and NA scores averaged across the 48 hr significantly predicted lockout requests. Table V shows that, in the final model, the two variables that made a significant contribution to explaining PCA lockout interval demands were morphine consumption and preoperative IES total score. The final model indicates that preoperative intrusive thoughts and avoidant behaviours about surgery are independent predictors of the total number of PCA lockout interval demands, although its contribution to the explained variance of the model is quite small (2.2%).

Path analysis

Path analysis was used to test the model shown in the Figure using a maximum likelihood procedure for parameter estimation, and employing the variance-

TABLE III Means and standard deviations (SDs) for postoperative visual analogue scale pain scores at rest (VAS-R)

Hours after surgery	*VAS-R Mean*	*VAS-R SD*
3	4.9	2.5
6	4.9	2.4
12	3.6	2.1
24	2.7	2.1
48	1.7	1.7

TABLE IV Summary of three-step regression model predicting 48 hr cumulative number of PCA demands made during lockout periods showing the total R^2, R^2 change and the *P* value associated with the change in variance explained at each step

*Step**	*Total R^2*	*R^2 change*	*P change*
1	0.39	0.39	0.0001
2	0.43	0.034	0.041
3	0.45	0.022	0.038

*Mean VAS-R pain scores and cumulative PCA morphine consumption at 48 hr were entered in Step 1; Mean 24 and 48 hr MHI anxiety and negative affect scores were entered in Step 2; and preoperative IES scores were entered in Step 3. PCA = patient-controlled analgesia; VAS-R = visual analogue scale pain scores at rest; MHI = mental health inventory; IES = impact events scale.

covariance matrix derived from the study data. The SAS (version 9.1, SAS Institute Inc., Cary, NC, USA) system's CALIS procedure[A] was used for all analyses. Normalized residuals were small in magnitude (range: -1.04 to 1.58) and symmetrically distributed. The Chi-squared statistic was appropriately non-significant, χ^2 (5, n = 72) = 2.94, P = 0.71. Other goodness of fit indices provided strong indications of a good overall fit between the initial model and the data: the non-normed fit index[30] = 1.04; the comparative fit index[B] = 1.00; and the normed fit index[30] = 0.98. Parameter estimates and associated tests of statistical significance are described below. Each significance test was associated with a standard error of sufficient magnitude to demonstrate linear independence between parameters. Satisfying this assumption supports unique causal inferences between antecedent and consequent variables in this model. An examination of the Lagrange multiplier and Wald test failed to identify any useful model modification. A Chi-squared difference test, used to examine potential model improvement by eliminating NA from the model, also failed to demonstrate any benefit from model modification. Therefore the path model was retained in its initial form without modification.

The path model depicted in the Figure shows the direct and indirect effects of preoperative IES total scores on total 48 hr lockout interval demands. Preoperative intrusive thoughts and avoidant behaviours exert their effects indirectly through two main paths. The first involves the effect of IES on postoperative anxiety (β = 0.57, $P < 0.001$) leading to heightened pain (β = 0.22, P = 0.041) and from pain to cumulative PCA morphine consumption (β = 0.29, P = 0.001) which, not surprisingly, is a potent and relatively straightforward predictor of lockout interval demands (β = 0.56, $P < 0.001$). The second indirect path from IES total scores to total lockout interval demands is also mediated through total cumulative morphine consumption (β = 0.20, P = 0.027) but this effect is independent of the previous indirect path involving pain intensity. Importantly, this path indicates that higher IES scores are associated with greater morphine consumption independent of pain. Finally, the direct path from IES total to 48 hr lockout interval demands (β = 0.23, P = 0.002) indicates that preoperative intrusive thoughts and avoidant behaviours are directly related to excessive PCA demands. The standardized path coefficient can be interpreted as follows: there is an increase of 0.23 standard deviation units in number of lockout demands for every unit increase in preoperative IES. The equivalent unstandardized path coefficient for this particular path is equal to 0.93, indicating approximately one extra lockout demand for every unit increase in preoperative IES. Table VI shows the unstandardized path coefficients and their 95% confidence intervals.

Discussion

The results of the present study indicate that preoperative intrusive thoughts and avoidant behaviours about the upcoming surgery predict a higher intravenous PCA lockout interval demand rate during the first two days after abdominal gynecological laparotomy even after controlling for postoperative anxiety, NA, and pain scores. The magnitude of the unique predictive effect of preoperative IES scores, however, is very small, accounting for approximately 2% of the total variance in lockout interval demands. The path analytic model (Figure) revealed a direct pathway, and two indirect pathways, from preoperative IES scores to the total number of PCA lockout interval demands. Previous studies have provided evidence for several of the bivariate relationships shown in the Figure, but

A *Hatcher L.* A Step-By-Step Approach to Using the SAS System for Factor Analysis and Structural Equation Modeling. Cary, NC: SAS Institute; 1994.

B *Bentler PM.* EQS: structural equations program manual, program version 3.0. Los Angeles, CA: BMDP Statistical Software Inc; 1989.

TABLE V Standardized and unstandardized regression coefficients, standard errors, and *P* values for the final regression model predicting 48 hr cumulative number of PCA demands made during lockout periods. Standardized regression coefficients, which have a mean of zero and standard deviation of 1, can be compared among variables and represent the change in 48 hr cumulative number of PCA lockout demands that result from a change of one standard deviation in a predictor variable.

Predictor variable	*Unstandardized coefficient B*	*Unstandardized coefficient standard error*	*Standardized coefficient Beta*	*P*
Mean VAS-R pain	-0.22	2.99	-0.006	0.94
48 hr cumulative PCA morphine	0.65	0.091	0.55	0.0001
Mean 24-48 hr negative affect	0.72	0.66	0.085	0.28
Mean 24-48 hr MHI anxiety	-0.58	1.32	-0.040	0.66
Preoperative IES-intrusive thoughts/avoidant behaviours	0.75	0.36	0.18	0.040

PCA = patient-controlled analgesia; VAS-R = visual analogue scale pain scores at rest; MHI = mental health inventory; IES = impact events scale.

TABLE VI Unstandardized path coefficients and 95% confidence intervals for the path model shown in the Figure

Path between variables	*Unstandardized path coefficient*	*95% confidence interval*	
		lower	*upper*
IES → negative affect	0.051	-0.047	0.15
IES → MHI anxiety	-0.16	-0.21	-0.12
IES → VAS-R pain	0.017	-0.0054	0.040
IES → 48h cumulative PCA morphine	0.68	0.08	1.29
IES → 48h cumulative PCA lockout demands	0.93	0.34	1.51
MHI anxiety → negative affect	-0.56	-0.90	-0.21
MHI anxiety → VAS-R pain	-0.086	-0.17	-0.0032
Negative affect → VAS-R pain	-0.019	-0.061	0.022
VAS-R pain → 48 hr cum PCA morphine	9.40	3.71	15.084
48 hr cum PCA morphine → 48 hr cum PCA lockout demands	0.66	0.49	0.83

PCA = patient-controlled analgesia; VAS-R = visual analogue scale pain scores at rest; MHI = mental health inventory; IES = impact events scale.

this is the first study to test these variables in combination using multiple regression and path analysis.

One indirect pathway (Figure) involves the effect of preoperative intrusive thoughts and avoidant behaviours on postoperative anxiety, which, through pain intensity, increases cumulative PCA morphine consumption, and, consequently, the number of lockout interval demands. These relationships are consistent with previous studies showing that high levels of perioperative anxiety are associated with heightened postoperative pain, greater PCA morphine consumption as well as a low dose-demand ratio.[16,17,19–21] The present results are also consistent with three previous studies[17,18,23] that measured psychological and emotional constructs similar to the IES. In those studies, preoperative anxiety, anticipation of pain[17,18] and physical avoidance[23] predicted a low dose-demand ratio or a relatively large number of lockout interval demands.

The results of the multiple regression analysis and the direct pathway in the path analysis indicate that preoperative intrusive thoughts and avoidant behaviours predict total number of lockout demands after controlling for the other effects in the models. Taken together with the indirect pathway from IES to total lockout interval demands with morphine consumption as the mediator, these data suggest that PCA demands are being made for reasons other than pain. Similar to the present results, Gil *et al.*[16] found that patients with higher pain intensity make more frequent demands during the lockout interval. They suggest that the unavailability of drug during the lockout interval increases anxiety which could then serve as the trigger for additional demands. It is also possible that patients use the PCA device to terminate other aversive states such as NA, to obtain reassurance, and to help them sleep.[31] We did not test these non-recursive paths in our model, but the direct pathway from IES to lockout interval demands, which bypasses anxiety and NA, indicates that some other mediator is involved.

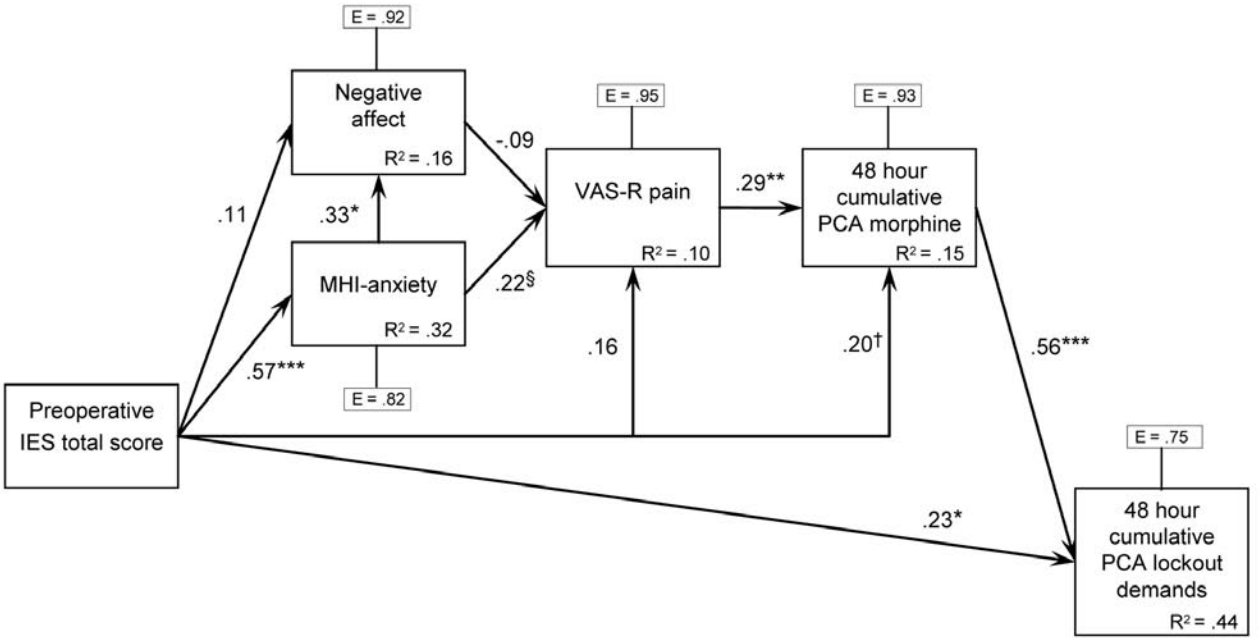

FIGURE Path model showing standardized path coefficients (β) between variables. R^2 shown reflects the percentage of variance in an endogenous variable that is predictable by its direct antecedents. E, the residual path coefficient, represents the proportion of an endogenous variable's standard deviation that is caused by all (unmeasured) variables outside the set of variables under consideration in the path model. ***$P < 0.001$; **$P = 0.001$; *$P = 0.002$; †$P = 0.027$; §$P = 0.041$.

Consistent with other research,[17,18] we suggest that this mediator might be the anticipation or fear of pain. From an operant conditioning perspective, the process involved in self-administering morphine from a PCA pump can be seen as a form of escape or avoidance learning. Whether the button press represents an escape or avoidance response depends on whether the patient is responding to current pain intensity (escape) or to the anticipation of future pain (avoidance). Often patients are discouraged from waiting until the pain is intense before pressing the PCA button and are encouraged to press the button in anticipation of pain before physiotherapy, dressing changes or getting out of bed[32] (i.e., to avoid future pain). In either case, the operant response (button press) is negatively reinforced and therefore more likely to occur in the future, since the subsequent delivery of morphine terminates (or avoids) the (anticipated) aversive pain state. As time from surgery increases, pain intensity decreases, and so PCA button presses are more likely to be made in response to anticipated pain than actual pain.

The direct pathway from preoperative IES scores to lockout interval demands, and the indirect pathway with morphine consumption as the mediator (Figure), can be explained by the maintenance of escape and/or avoidance responding in at-risk individuals characterized by high preoperative IES scores. That is, patients who, preoperatively, endorse high levels of intrusive thoughts and avoidant behaviours about their upcoming surgery would be more likely than those who are low in IES scores to engage in ongoing avoidance behaviours after surgery, such as a high number of PCA demands. Given that these anticipatory button presses are avoidance responses, patients may be self-administering bolus doses of morphine when not in pain. Furthermore, this pattern of behaviour, and the tendency to avoid in general, does not encourage "reality testing", in that patients' expectation that pain will ensue if they do not press the button is never put to the test. These results are consistent with recent fear-avoidance models of pain[33,34] and suggest future research might focus on the relationships among PCA demands, fear of pain, fear of movement, and pain avoidance.

Avoidance behaviour is usually motivated by fear. Many patients with pain are afraid that movement will cause re-injury and pain.[33,35,36] For example, in the days and weeks after surgery, it is common for pain

to be exacerbated by movement. Depending on the location of the incision, deep breathing, coughing, laughing, getting in and out of bed all may substantially increase pain. It is reasonable that many patients fear, and therefore avoid, moving about.

Understanding the personal meaning of the fear is important. Patients may fear that in sitting up or walking after surgery, their stitches will break and the wound will split open. Or they may fear these activities will cause internal damage. Other patients simply fear the increase in pain associated with activity; they may feel helpless in the presence of intense pain or they may feel dependent on the nursing staff for pain relief. These fears may be associated with catastrophic thinking and heightened postoperative pain.[37,38] Apprehension about moving about after surgery is based on authentic feedback which has taught the patient that activity causes increased pain. However, the misinterpretation of activity and pain as harmful engenders avoidance behaviours that may set the stage for decreased activity and increased pain and disability.

Avoidant coping strategies are usually adaptive shortly after an injury because they minimize ongoing pain, reduce the risk of exacerbation through further injury, and thus promote healing. However, avoidance of activities after surgery may be maladaptive even in the short term since early mobilization after surgery is important for recovery. The long-term consequence of ongoing avoidance behaviours is reinforcement of the belief that avoidance prevents further pain, thus promoting continued isolation, inactivity, and faulty reality testing.[33,39]

Self-management programs focused on behavioural exposure and non-avoidance in chronic low back pain patients lead to improved self-efficacy and a reduction in pre-occupation with pain because patients acquire increasingly realistic appraisals of the relationship between pain and behaviour.[39] Recent controlled case reports[40,41] and clinical trials[42] show that in patients with chronic low back pain, pain-related fear can be effectively treated by *in vivo* exposure in which patients are exposed to fear-eliciting and hierarchically ordered physical movements. Results showed concomitant reductions in catastrophic thinking, pain intensity and pain disability.[40,41] To our knowledge studies have not examined fear-avoidance beliefs about postoperative pain in patients scheduled for major surgery.

The direct pathway from preoperative IES scores to lockout interval demands, and the indirect pathway with morphine consumption as the mediator raise another interesting hypothesis. It is possible that with time, the PCA button itself, or the tone that signals delivery of a bolus dose, becomes a safety signal or cue, since both are reliably associated with termination of the anticipated or actual aversive state. A safety cue is a discrete feedback signal that has been paired with periods during which the aversive event does not occur[43] and reliably predicts its absence. Thus, over time, the PCA pump button or the auditory signal (on some pumps) accompanying delivery of a bolus dose may become a safety signal that predicts a period of reduced pain or no pain.

Evidence from animal studies supports the existence of an antianalgesia system that is signaled by environmental cues for safety and that facilitates nociception.[44,45] The antianalgesia system is thought to operate in a manner opposite to the better known endogenous analgesia system which is activated during times of danger and stress. Activation of the antianalgesia system by safety signals following injury is adaptive since it would promote recuperation by permitting the organism to begin to experience pain and tend to its wounds. Wiertelak and colleagues demonstrated that safety signals reverse conditioned analgesia[44,45] and even inhibit morphine-induced analgesia[44] through a cholecystokinin (CCK)-mediated antianalgesia system in the spinal cord. Rat tail flick latencies to radiant heat were measured in an experimental context in which electric foot shock was delivered in an unpredictable fashion. In this context, rats typically develop conditioned analgesia, demonstrated by significantly increased tail flick latencies. As part of the conditioning paradigm, each shock was followed by a safe interval, signaled by a light source, during which shock was never delivered. Thus, the light became a safety cue that reliably signaled the absence of shock. The investigators then demonstrated not only that conditioned analgesia was abolished in the presence of the safety signal, but so too were the analgesic effects of intrathecal morphine. Furthermore, intrathecal administration of the CCK-B antagonist, L-365,260 restored morphine-induced analgesia in the presence of the safety signal (i.e., it prevented the light from abolishing morphine-induced analgesia).[44]

The results of the study by Wiertelak[44] suggest that the safety signal triggers CCK release in the spinal cord which then contributes to a state of relative hyperalgesia to subsequent noxious input. The possibility of a similar antianalgesia system in humans may offer an additional explanation for the excessive PCA demands for morphine, both when the patient is eligible for a dose and during lockout intervals. If the PCA button, tone, or other environmental cue comes to signal safety after surgery, one might expect a pattern of increasing demands for morphine, since pain relief and safety may be followed by activation of the CCK-

induced antianalgesia system thereby increasing pain (i.e., the PCA morphine and CCK release operate at cross purposes). Cholecystokinin is also implicated in anxiety[46] and it underlies anxiety mediated hyperalgesia.[47,48] Administration of proglumide, a mixed CCK-A and B receptor antagonist reduces anxiety-induced facilitation of pain (i.e., nocebo hyperalgesia).[47,49]

These data suggest two alternative possibilities. It is possible, as described above, that with time after surgery, the PCA button or tone becomes a safety signal that is associated with a CCK-mediated increase in pain and lockout interval demands. On the other hand, the absence of such an antianalgesia system in humans, or its non-activation in the postoperative PCA context described above, would predict conditioned placebo analgesia not nocebo hyperalgesia. That is, the PCA button or tone (or some other environmental cue) might acquire secondary reinforcing properties, and after several pairings with drug delivery, would mimic (facilitate) the effects of morphine and result in pain relief, even in the absence of a bolus dose. Further research is required to empirically evaluate these competing hypotheses.

Notwithstanding the prospective design of the present study, we have not shown that heightened preoperative intrusive thoughts and avoidant behaviours are causally related to more frequent PCA pump demands. There are several other possibilities. It may be that the preoperative state characterized by intrusive thoughts and avoidant behaviours persists after surgery and it is these concurrent thoughts and actions that cause the patient to make excessive PCA pump demands. Alternatively, it is possible that the relationship between IES scores and PCA pump demands is not causal and that a third, heretofore unidentified, factor is responsible for both heightened IES scores and frequent PCA demands. Further research is required to determine the nature of the associations among the variables examined in the present study and their relationship to pain related measures of fear and anxiety.

In conclusion, excessive demands for postoperative intravenous PCA morphine during lockout periods appear to reflect, in part, poor preoperative adaptation to surgery involving intrusive thoughts and avoidant behaviours. The direct pathway from preoperative IES scores to PCA lockout interval demands suggests a proportion of the total morphine patients self-administer is unnecessary since it is unrelated to ongoing pain. Further research is necessary to identify the mediator(s) of this relationship, but candidates include anticipation of pain, fear of pain, and fear of movement evoked pain.

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