Regional Anesthesia and Pain

Gender and pain upon movement are associated with the requirements for postoperative patient-controlled *iv* analgesia: a prospective survey of 2,298 Chinese patients

[Les besoins d'analgésie iv auto-contrôlée sont liés au sexe du sujet et à la douleur au mouvement : une enquête auprès de 2 298 Chinois]

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Purpose: To investigate prospectively the influence of patient characteristics upon, and the association of postoperative measurements with, the requirements for postoperative morphine and the assessment of resting pain and pain upon movement in Chinese patients.

Methods: From January 1998 to December1999, patients receiving patient-controlled *iv* morphine subsequent to general anesthesia and surgery at our institute (Kaohsiung Veterans General Hospital), were enrolled in the study. Demographic data (such as gender, age, weight, height and education level) and postoperative measurements, including pain scores at rest or during movement, sedation scores and morphine consumption, were recorded.

Results: In total 2,298 patients were recruited. Females consumed significantly less morphine via patient-controlled analgesia (PCA) in the first three postoperative days than was the case for males ($P < 0.05$). Gender was the strongest predictor for postoperative morphine requirements. Postoperative pain upon movement was another effective predictor for morphine requirement ($P < 0.05$). Age, body height, body weight, education and operation sites were not associated with morphine consumption.

Conclusion: Gender and postoperative pain upon movement are the major factors influencing morphine requirement for patient-controlled *iv* morphine analgesia during the first three postoperative days in Chinese patients.

Objectif : *Examiner prospectivement si les caractéristiques du patient, et l'association des mesures postopératoires des douleurs, influencent les besoins de morphine postopératoire et l'évaluation de la douleur au repos et lors de mouvement chez des malades chinois.*

Méthode : *De janvier 1998 à décembre 1999, les patients qui ont reçu de la morphine iv auto-contrôlée, à la suite d'une opération sous anesthésie générale au Kaohsiung Veterans General Hospital, ont participé à l'étude. Les données démographiques (sexe, âge, poids, taille et niveau d'instruction) et les mesures postopératoires, incluant les scores de douleur au repos et pendant le mouvement, les scores de sédation et la consommation de morphine, ont été enregistrées.*

Résultats : *Nous avons recruté 2 298 patients. Pendant les trois premiers jours postopératoires, les femmes ont utilisé significativement moins de morphine que les hommes ($P < 0,05$) au moyen de l'analgésie auto-contrôlée (AAC). La variable prédictive la plus significative de la consommation de morphine postopératoire a été le sexe du patient. La douleur postopératoire pendant le mouvement a été un autre prédicteur efficace ($P < 0,05$). L'âge, la taille, le poids, l'instruction et le type d'opération n'ont pas été significatifs pour la consommation de morphine.*

Conclusion : *Le sexe et la douleur postopératoire pendant le mouvement sont les principaux facteurs d'influence des besoins de morphine pour l'analgésie iv auto-contrôlée pendant les trois premiers jours postopératoires chez des sujets chinois.*

THE management of acute pain has improved over the last few years since the introduction and increasingly widespread use of patient-controlled analgesia (PCA) devices. The technique itself generally seems to be accepted well by both patients and staff. However, clinically, we have found ourselves unable to predict individual analgesic requirements because a wide inter-patient variation in dose requirements appears to exist. The reasons may be attributable to a poor setting for PCA, unfounded concerns regarding the risk of opioid-related side effects or addiction, poor education of medical and nursing staff leading to an inadequate knowledge for PCA prescription, or discrepancy of patient characteristics and/or follow-up. Previous studies have examined factors that might influence patient opioid consumption and found that the opioid doses did not correlate with patient weight, body height, and surface area.[1] Such conclusions, however, were mostly drawn from data deriving from retrospective reviews. Most of the studies were conducted amongst Western patients, and data pertaining to the Chinese population appear to be rare. One retrospective study conducted upon predominantly Chinese patients investigated the relationship between morphine dose and patients' weight. Unfortunately, the study relied upon statistical analyses exhibiting an increased probability of ß error.[2] Therefore, we conducted a prospective study in order to determine which factors influence postoperative opioid requirements and pain intensities amongst Chinese patients.

Methods
Subjects
This prospective study was performed at Kaohsiung Veterans General Hospital, a teaching medical center in South Taiwan. The study was restricted to conscious hospitalized patients, aged from 20–70 yr, over a two-year period from January 1998 to December 1999 inclusively. All patients referred from the outpatient department to receive elective surgery under general anesthesia were enrolled in this study, although any patients with impaired cardiac, renal, or hepatic function were excluded. Patients were also excluded from analysis if previous chronic opioid use was suspected. The patients who met our inclusion criteria were referred to the acute pain service (Kaohsiung Veterans General Hospital) for management of postoperative pain using PCA morphine.

Procedure
All patients involved underwent general anesthesia. General anesthesia was induced with *iv* thiopental 5 mg·kg^{-1} and fentanyl 2–3 µg·kg^{-1}. Tracheal intubation was facilitated by the administration of *iv* succinylcholine 1.5–2 mg·kg^{-1}. Halothane/isoflurane 1–2 MAC in oxygen was given to maintain anesthesia depth, and atracurium 0.4–0.5 mg·kg^{-1} or pancuronium 0.1–0.15 mg·kg^{-1} was administered to maintain muscle relaxation. Ventilation was controlled mechanically and adjusted to keep an end-tidal CO_2 concentration between 30 and 40 mmHg. Supplementary analgesia was provided with boluses of *iv* fentanyl (50 µg) in order to keep the blood pressure and heart rate within baseline ± 20%. At the completion of the operation, *iv* glycopyrrolate 0.01 mg·kg^{-1}, and neostigmine 0.05 mg·kg^{-1} were administered for reversal of the residual paralysis. Patients were not discharged from the recovery room until vital signs were stable. All patients were instructed on how to use the PCA device (Abbott Pain Management Provider- Abbott Laboratories, Chicago, IL, USA) at the time of the preoperative visit. Instructions were reviewed again before initiating PCA therapy. Patients were encouraged to use the PCA to maintain a satisfactory level of pain relief. Patients receiving postoperative sedation or analgesia other than morphine were not included in the study. The authors' Institutional Human Investigation Committee approved the study program.

Assessments
Demographic details including age, gender, weight, height, operation site, and education level were recorded for all study participants. Maximum education level was recorded as: 1) not educated; 2) elementary school; 3) junior high school; 4) senior high school; and 5) further education beyond senior high school. Operation sites were grouped as: 1) surgical wound on thorax; 2) surgical wound on abdomen; 3) surgical wound extending from thorax to abdomen; 4) surgery on the limbs; and 5) other types of surgery (e.g., spine). A visual analogue pain score, a scale of 0 to 10, with 0 representing no pain and 10, the most severe pain imaginable, was used to assess the pain intensity of participating patients (subjects mark the position on a 10 cm line, which denotes the severity of their pain). Patients provided a subjective pain intensity rating, at rest (visual analogue scale at rest, VASR) and during an incident, such as moving or coughing (visual analogue scale on movement, VASM). Pain at rest was defined as that experienced while lying motionless in bed, pain on movement as that experienced ambulating or with movement (e.g., turning in bed, transferring from bed to chair, breathing deeply or coughing).

Postoperative management

The PCA pump was programmed to deliver a loading dose of 2 mg morphine and a bolus dose of 1 mg morphine with a lockout time of five minutes and a one-hour limit of 10 mg morphine. To avoid diurnal variations in pain threshold, a trained nurse anesthetist from our acute pain service team visited all patients between 8 and 10 a.m. daily for the first three postoperative days in order to evaluate the patients' condition in regard to pain intensity, respiratory rate, etc. A VASR score 3 was considered satisfactory with regard to the effectiveness of pain relief. A respiratory rate of <8 breaths·min^{-1} was considered to constitute respiratory depression. If patients experienced emesis more than three times per day postoperatively, antiemetic treatment was prescribed (metoclopramide 10 mg *im* per six hours as required).

Staff anesthesiologists collected the preoperative data, and research nurses collected the postoperative outcome data. Those data were entered into a computer database separately (Microsoft Access 7.0, Microsoft Corp, Roselle, IL, USA), and the authors merged the two data sets at the completion of the study period.

Statistical analysis

All patients underwent general anesthesia, so anesthetic factors were not taken into consideration for the analysis, except for the *iv* loading doses of morphine administered to all patients in the recovery room, these data being included in the morphine requirements summary. The association between gender, age, weight, height, education level, operation site, VASR, VASM, and morphine consumption were analyzed. A recent observation suggested that parametric statistical tests assuming the visual analogue scale (VAS) to be normally distributed reflect similar power and false-positive rates as non-parametric tests,[3] especially when the sample is large. Thus, Philip *et al.* suggested parametric statistics might be used to analyze VAS data.[4]

Stepwise linear multivariate regression was used to analyze the main factors influencing either the morphine dose used in PCA or the pain scores. The criterion for inclusion and elimination of variables was that a variable would be included if its partial regression coefficient was significant at the 0.05 level and eliminated if its regression coefficient failed to be significant at the 0.1 level. A Student's t test was performed in order to compare the differences between binominal variables if any significant correlation was found to exist. The ANOVA test was used to compare the morphine consumption differences between different education-level and surgical-site groups. If a significant

TABLE I The demographic data, education level, and surgical sites of total 2,298 participants

	Female	Male	Total
n (%)	1,444 (63%)	854 (37%)	2,298
Age	53.3 ± 11.1	61.9 ± 10.2	56.5 ± 12.6
Body height (cm)	155.4 ± 8.2	165.8 ± 6.6*	160.2 ± 11.7
Body weight (kg)	58.0 ± 9.8	68.4 ± 9.6*	63.5 ± 10.2
Education level			
Not educated	315 (66%)	163 (34%)	478
Elementary	453 (67%)	225 (33%)	678
Junior high	144 (55%)	117 (45%)	261
Senior high	310 (63%)	183 (37%)	493
Above senior	222 (57%)	166 (43%)	388
Surgical sites			
Abdomen	910 (69%)	400 (31%)	1,310
Thorax	43 (47%)	49 (53%)	92
	31 (50%)	31 (50%)	62
Thorax-abdomen			
Limb	228 (54%)	191 (46%)	424
Other	232 (57%)	178 (43%)	410

Data were presented with number (%). * *P* <0.05 compared with female group.

difference was noted (*P* <0.05), the post-hoc Tukey's test was performed.

All statistical analyses were performed using the statistical package for the social science 10.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 2,430 patients receiving patient-controlled *iv* analgesia with morphine in our hospital were assessed. Of these patients, 132 did not meet the inclusion criteria and were excluded from the analysis. These included 40 patients with cardiovascular disease, 31 patients with renal impairment, 26 patients with hepatic impairment, and 35 patients receiving postoperative sedation therapy or other analgesics. The demographic data of excluded patients did not differ from that of included patients. Hence, a total number of 2,298 patients were included in our study, the demographic data for whom is presented in Table I. Of this study group, 334 did not complete the third postoperative measurement series because of discharge from the hospital. The missing data pertaining to the third postoperative day were not included in the analysis, but the data corresponding to the other two days were included.

Predictors of PCA morphine consumption

All the potential factors, such as age, weight, height, pain score, educational level, operation area, and gender, were entered into the stepwise linear regression

TABLE II Summarized results of the stepwise regression analyses associated with postoperative morphine consumption

	Beta	R^2	B	SE	P
		Morphine consumption			
Day one (n=2,298)					
Gender	-0.186	0.059	-17.056	5.268	<0.01
VASM	0.181	0.034	5.156	1.461	<0.01
Day two (n=2,298)					
Gender	-0.289	0.151	-45.057	9.536	<0.01
VASM	0.269	0.089	14.014	2.843	<0.01
Day three (n=1,964)					
Gender	-0.277	0.102	-51.128	12.995	<0.01
VASM	0.148	0.099	9.977	4.737	0.02

VASM=visual analogue scores during coughing or on movement; Beta=standardized coefficients; R^2=adjusted R square; B=unstandardized coefficients; SE=standard errors of B. *P*=P values.

TABLE III Postoperative measurements for female and male patients

	Female	Male	Total
n (Day one)	1,444	854	2,298
VASM	4.9 ± 1.6	5.2 ± 1.3	5.2 ± 1.7
VASR	2.3 ± 1.3	2.3 ± 1.4	2.3 ± 1.5
Dose (mg)	15.3 ± 8.8	18.9 ± 8.9*	16.6 ± 9.0
n (Day two)	1,444	854	2,298
VASM	3.9 ± 1.4	4.7 ± 1.3*	4.3 ± 2.0
VASR	1.2 ± 1.1	1.6 ± 1.2	1.5 ± 1.3
Dose (mg)	23.2 ± 15.0	31.9 ± 12.4*	26.3 ± 13.6
n (Day three)	1,246	718	1,964
VASM	3.4 ± 1.1	4.3 ± 1.0	3.7 ± 1.6
VASR	0.9 ± 0.9	1.1 ± 1.1	0.9 ± 0.8
Dose (mg)	28.9 ± 17.3	41.4 ± 15.3†	32 ± 16.7

Data were presented with mean ± SD or number; *n*=case number; *P <0.05 compared with female group; †P <0.01 compared with female group.

analysis. We examined the major factors influencing the morphine dose throughout day one, day two and day three postoperatively. We noted a significant association between gender and PCA morphine consumption such that gender was the variable first included in the model, suggesting it made the most contribution for postoperative PCA morphine requirement (Table II; *P* <0.01 for three days). As indicated by the above results, the postoperative measurements were further separated by gender (female and male) and compared using Student t test (Table III). The VASM and VASR did not differ according to gender, apart from the VASM at postoperative day two. Male patients rated a 21% higher pain level on movement than did females

(*P* <0.05). Furthermore, male patients consumed 24 to 43% more PCA morphine than did female for each of the three days postoperatively.

VASM was included into the stepwise regression model, but VASR was not, suggesting pain at rest may be less predictive of morphine requirements. Weight, height, education level, and surgical site did not influence postoperative PCA morphine consumption.

Predictors of postoperative pain intensity
Table IV indicates the predicators of the daily VASR (or VASM) scores, and a range of potentially associated factors including age, weight, height, gender, site of operation, and level of education in the stepwise regression model. A negative correlation between gender and VASM score was present on postoperative day two (Beta coefficient= -0.169, adjusted R square=0.036, *P* <0.05) but not on days one or three. In addition, the surgical site was significantly associated with pain scores (VASR at day one, VASM at day three, and VASR at day three). A post-hoc Tukey's test indicated that thoracic and/or abdominal surgery was associated with higher pain-intensity ratings than other surgical procedures (*P* <0.05).

Discussion
Predictors for PCA morphine consumption
In our study, female patients used significantly less PCA morphine than males during each of the first three days postoperatively. The magnitude of the regression coefficients indicates the relative importance of the variable in determining the dose requirement or pain scores. It can be seen that, for the variables recorded in this study, gender difference is the major predictor of PCA morphine consumption, with male patients requiring 23 to 43% more morphine than female patients.

Previous animal studies have indicated the existence of important gender-related differences in opioid-mediated analgesia, where male rats and mice almost uniformly display greater opioid analgesia across several nociceptive assays.[5] Prospective human studies on the interaction of gender and the analgesic effects of opioids appear to be scarce. Gear *et al.* have reported that postdental surgery pain relief by opioids acting at the -receptor was greater amongst females than amongst males.[6] Miaskowsi and Levine recently reviewed studies for the period from 1966 to 1998 in which a PCA was used to administer opioids for postoperative pain, and found that a slight majority of studies noted larger PCA opioid consumption amongst males as compared to females[1,7-9] in line with our results. The reasons for this gender related difference remain unclear and several mechanisms may be invoked.

TABLE IV Summarized results of the stepwise regression analyses associated with postoperative pain

	VASM				VASR			
	R^2	Beta	B	SE	R^2	Beta	B	SE
Day one								
Surgical site					0.002*	0.105*	0.188	0.105
Day two								
Age					0.008*	-0.106*	0.339	0.188
Gender	0.036*	-0.169†	-0.599	0.232				
Day three								
Surgical site	0.027*	0.163*	0.275	0.118	0.022*	0.200†	0.240	0.085

VASR=visual analogue scale at rest; VASM=visual analogue scale during coughing or moving; $\tilde{R}$=adjusted R square; Beta=standardized coefficients; B=unstandardized coefficients; SE=standard errors of B; *P <0.05; †P <0.01.

TABLE V Comparison of pain intensities on different surgical areas

	Abdomen	Thorax	Thorax-abdomen	Limbs	Others
Age (yr-old)	50.1 ± 13.7	47.7 ± 12.5	59.7 ± 14.5	55.6 ± 15.3	52.2 ± 14.1
Weight (kg)	60.4 ± 10.6	64.3 ± 12.9	64.8 ± 11.3	65.2 ± 9.3	59.1 ± 9.3
Height (cm)	160.8 ± 6.9	161.4 ± 10.1	159.2 ± 7.4	160.7 ± 6.9	160.0 ± 5.9
Day 1 (*n*)	1,310 (57%)	92 (4%)	62 (3%)	424 (18%)	410 (18%)
VASM	5.0 ± 1.6	5.1 ± 1.5	5.5 ± 1.3*	4.2 ± 1.0	4.9 ± 1.6
VASR	2.3 ± 1.4	2.9 ± 1.1†	2.5 ± 1.5	2.3 ± 1.2	1.7 ± 1.0
Morphine (mg)	16.0 ± 10.1	16.5 ± 7.4	15.5 ± 8.9	15.6 ± 7.8	16.8 ± 8.6
Day 2 (*n*)	1,310 (57%)	92 (4%)	62 (3%)	424 (18%)	410 (18%)
VASM	3.8 ± 1.4	4.1 ± 1.1	4.2 ± 1.5	3.3 ± 1.0	3.6 ± 1.3
VASR	1.5 ± 1.2	2.1 ± 1.3	1.5 ± 1.3	1.3 ± 1.0	1.4 ± 0.7
Morphine (mg)	30.7 ± 14.7	28.5 ± 13.8	27.2 ± 14.9	28.1 ± 16.0	25.3 ± 17.2
Day 3 (*n*)	1,082 (55%)	92 (5%)	62 (3%)	360 (18%)	368 (19%)
VASM	3.7 ± 1.1*	3.3 ± 1.2	3.3 ± 1.5	2.7 ± 0.9	3.0 ± 1.0
VASR	1.0 ± 0.9	1.3 ± 1.1†	1.0 ± 0.9	0.9 ± 0.8	0.5 ± 0.4
Morphine (mg)	34.7 ± 16.9	31.1 ± 14.2	30.8 ± 14.1	31.6 ± 15.7	30.8 ± 16.5

n=case number (%); VASR=visual analogue scale at rest; VASM=visual analogue scale on movement; morphine=cumulative morphine requirement (mg); *P <0.05 when compared with "Limbs" group; †P <0.05 when compared with the "Others" group.

For example, previous investigations have found better pain relief with kappa opioids (nalbuphine and butorphanol) after wisdom-tooth extraction in female patients than in male patients,[10] more rapid recovery from anesthesia in females than in males,[11] significant differences between males and females with regard to morphine-induced ventilation depression,[12] and male/female pharmacokinetic variations for some drugs.[13] This suggests that both gender-related pharmacokinetic and/or pharmacodynamic factors may contribute, at least in part, to these sex-based differences, and/or that many gender-specific and gender-dependent factors, such as the mediation of endogenous opiates, neurotransmitters or hormones, may influence patient perception of pain.[13] A controlled study further suggested that the gender-based differences in morphine-mediated analgesia are more likely to arise from a pharmacodynamic origin than from a pharmacokinetic origin.[14] Most studies have evaluated the relationship between opioid consumption and pain intensity over a period of less than 24 hr, whereas our study extended the evaluation period to three days. In our study, gender correlated consistently with morphine consumption on each of the three postoperative days, supporting the existence of gender-differences in post-surgery morphine consumption.

Our results failed to indicate that age was a predictor for PCA-morphine consumption, in keeping with the findings of Tamsen *et al.*[15] By contrast, Burns *et al.*[1] and Macintyre *et al.*[7] reported an inverse association between patient age and morphine consumption. Possible explanations for these apparently conflicting results may be related to postoperative confusion, or a

lack of understanding of PCA by older patients, hence affecting the appropriate use and efficacy of PCA. Both studies of Burns et al.,[1] and Macintyre et al.,[7] were conducted amongst Western people, and the impact of different socio-cultural origins on reported pain ratings and opioid usage should be considered. An acknowledged potential limitation of our study is that we restricted the age range from 20–70 yr and thus may have influenced the results somewhat.

A number of related studies have reported failure to demonstrate any correlation between opioid consumption and the weight, height, or body mass of study patients,[10,16] apart from one retrospective analysis which reported that patient weight was a weak predictor and demonstrated less influence upon clinical morphine consumption,[7] our study concurring with their conclusions.

VASM scores were the other variable included into the model, meaning it was significantly associated with PCA morphine requirement. Macintyre et al. noted that pain intensities both at rest and during movement postsurgery bore significant correlation with postoperative morphine usage.[7] Our results indicated that pain intensity during movement was a better predictor than was pain intensity at rest. Postoperative pain incorporating a motion component such as turning or coughing has not received much attention in pain management. A recent review addressed the clinical importance of pain upon movement when managing patients postoperatively, and demonstrated a more than twofold difference between the mean incident and resting visual analogue pain scores during the first day post-surgery (5.9 and 2.8 respectively).[8] Our results were similar (Table III). Although the mean pain score at rest was 3 or below, pain upon movement was not relieved effectively via PCA morphine. Such results suggest a need for more attentive and aggressive pain control during mobilization.

The possibility of inadequate pain relief being available to patients involved in our study would appear remote since the PCA pump was programmed to allow delivery of up to 1 mg of morphine every five minutes, with a one-hour limit of 10 mg, according to the acute pain service algorithm for increasing morphine dose.[17]

Predictors for postoperative pain intensities
We observed no correlation between pain intensity scores and gender, either at rest or on movement[18] except during the second day postoperatively when male patients rated their pain intensity upon movement significantly higher than did female patients.

Abdominal and thoracic surgical procedures are traditionally considered more painful and require more postoperative analgesia than is the case for surgery conducted at other sites.[8,19] Our results certainly concur with this view, these specific surgical sites demonstrating a significant association with postoperative pain intensity, but not with increased morphine consumption.

It was assumed that education level would be associated with different pain perception and related behaviour. Weisenberg et al. have shown previously that female patients with lower education levels returned higher ratings for birth pain and exhibited more pain-related behaviour than better educated patients.[20] Our study, however, did not show any difference in postoperative pain intensities in relation to level of education.

Many previous studies have noted ethnic or cultural differences in response to various forms of experimental pain, Walsh et al. reporting a greater tolerance to pain for whites than African Americans.[21] Faucett et al. demonstrated that patients of European descent rated postoperative dental pain less severely than patients of African and Latin descent.[22] Differing from previous studies conducted in this area, our study was conducted in Taiwan with a Chinese population of Eastern socio-cultural background as the study group. The distinct racial and cultural differences between various studies may have some bearing upon pain perception and expression,[23,24] with concomitant variation with respect to some results. A retrospective survey conducted in Hong Kong compared morphine consumption between 1,004 Chinese and 67 Caucasian patients, and found no difference in either group or subgroups, although the authors did report a high probability of Type II error.[2]

For this study, we excluded intraoperative factors from the analysis. One potential confounding factor for our study could be the (variable) dose of opioids given during surgery. Another weakness of the study is the use of stepwise regression analysis. When predictor variables are highly correlated to each other, once one such variable has been included into the model, the other will not be included, even though it may be related to the outcomes.

In conclusion, our results suggest that, in the population studied, gender is a significant predictor of the requirement for postoperative morphine. Pain intensity during movement is the other important predictor, during the first three days postoperatively. These results should have important clinical implications for the postoperative management of pain amongst Chinese patients.

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