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CLINICAL INVESTIGATIONS

Predictive factors of early morphine requirements in the post-anaesthesia care unit (PACU)

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Use of morphine by titration in the post-anaesthesia care unit (PACU) is often the first step in postoperative pain management. This approach provides rapid analgesia but shows a wide inter-individual variability in morphine requirements and may prolong patient stay in the PACU. The aim of this study was to identify the patient characteristics, surgical, anaesthetic, and post-operative factors predictive of early morphine requirements. The study included 149 patients undergoing various non-cardiac surgical procedures under general anaesthesia. In the multiple regression analysis of nine variables, only ethnicity (Caucasian), emergency surgery, major surgery, surgery exceeding 100 min, and pain score on arrival in PACU were predictive factors of morphine requirements. This observational study identifies for the first time independent predictive factors of morphine requirements in the early postoperative period. Future studies are warranted to evaluate the impact of intervention on these factors and any resulting improvement in postoperative pain treatment.

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The management of acute pain has undoubtedly improved over the last few years. There is now increased interest in it, and effective pain relief after surgery is an essential element of good postoperative management.

In the post-anaesthesia care unit (PACU), the use of titrated doses of morphine is often the first step in postoperative pain treatment. Morphine by titration requires initial assessment of the pain but provides rapid analgesia and the ability to adapt the dose to individual requirements.[1 2] Although in common use, there are several limitations of this approach. Intravenous (i.v.) administration of boluses of morphine needs regular pain and sedation assessment. Such management is time consuming for nurses, prolongs patient stay,[3] and contributes to the increased cost of PACU admission. There is also wide inter-individual variability in opioid requirements.[4 5] Contrary to the later postoperative period (24 h plus) where correlation between physical characteristics, psychological factors, and opioid requirements has been reported,[6–8] there has been little evaluation of the factors that contribute to variations in morphine requirement in the early postoperative period.

The aim of this study was to identify the patient characteristics, surgical, anaesthetic, and postoperative factors that contribute to variability in early postoperative morphine requirements.

Methods

Study site

This prospective study was carried out during a 2-week period in a university hospital. This hospital has 402 surgical beds and admits on average 12 600 surgical patients each year. All surgical procedures except cardiac surgery (i.e. orthopaedic, general, urological, gynaecological, and ear, nose and throat) were included in the study.

Patients

All in-patients (including for emergency procedures) undergoing surgery under general anaesthesia, were included in the study. Patients underwent routine pre-operative assessment and were informed about postoperative pain manage-

Table 1 Types of operation classified as major, intermediate, and minor procedures according to the expected level of postoperative pain[9 10]

Major	Intermediate	Minor
Gastrectomy	Appendicectomy	Minor urological procedures (transurethral prostatectomy, testicular surgery)
Splenectomy	Laparoscopic procedures	Circumcision
Liver/pancreatic surgery	Mastectomy	Superficial surgery
Oesophageal surgery	Inguinal hernia	Examination under anaesthesia/anal fissure repair/anal stetch
Laparotomy/bowel resection	Vaginal/hysterectomy	Varicose veins
Laparotomy/cholecystectomy	Thyroidectomy	
Laparotomy/hysterectomy	Ear, nose and throat surgery	
Haemorrhoidectomy	(other than adenoidectomy)	
Thoracic surgery	Total hip replacement	
Spinal fusion		
Renal surgery		
Total knee replacement or arthrolysis		
Adenoidectomy		

ment. Patients having any one of the following criteria were excluded: regional block, epidural or spinal anaesthesia or analgesia, inability to read or speak French, the likelihood of delayed postoperative tracheal extubation in the PACU, ASA physical status over 3, or incomplete records.

Study design

We performed an observational study and patients were included consecutively as they presented. During the study period, the anaesthetic and postoperative pain management did not vary from routine practice; hence, ethics committee approval and informed consent were not needed. We prospectively collected the physical characteristics, surgical, anaesthetic, and postoperative data of each patient. A data sheet was kept postoperatively (from day 1) for each patient by the PACU resident. Operations were grouped as major, intermediate, or minor procedures according to the expected level of postoperative pain as proposed by Gould and the French Society of Anaesthesiology (Table 1).[9 10]

In the PACU after surgery, patients complaining of pain were given i.v. bolus doses of morphine that were repeated until the patient felt comfortable. Pain intensity level was assessed using a verbal score (VS) (Fig. 1). Morphine boluses were given by the nurse using the standardized procedure currently used in our hospital (Fig. 1). The procedure sets no limit to the total dose that can be given in the absence of excessive sedation or hypotension.

For patients who did not require morphine titration because of low pain intensity (VS $\leqslant$1), postoperative analgesia was achieved with i.v. propacetamol. Patients were not discharged from the recovery room until they were comfortable with a VS $\leqslant$1.

Statistical analysis

Data were categorized as shown in Table 2. In the analysis, all factors have been considered as binary variables: age ($\leqslant$65 yr=1, >65 yr=2); sex (female=1, male=2); ethnicity (African and Asian people=1, Caucasian=2); type of surgery (major=1, intermediate and minor=2); context of surgery (scheduled=1, emergency=2); duration of surgery ($\leqslant$100 min=1, >100 min =2); surgeon grade (senior=1, junior=2); type of intra-operative opioid (none or alfentanil=1, fentanyl or sufentanil=2); total dose of intra-operative opioid (low=1, high=2); intra-operative administration of non-opioid analgesic (none=1, propacetamol, nefopam or ketoprofen=2); time between last injection of opioid and arrival in the PACU (low=1, high=2); sedation score on arrival in the PACU (0 or 1=1, 2 or 3=2); and pain score on arrival in the PACU (0 or 1=1, 2 or 3=2). For each variable, the total corresponding morphine dose (mg) is

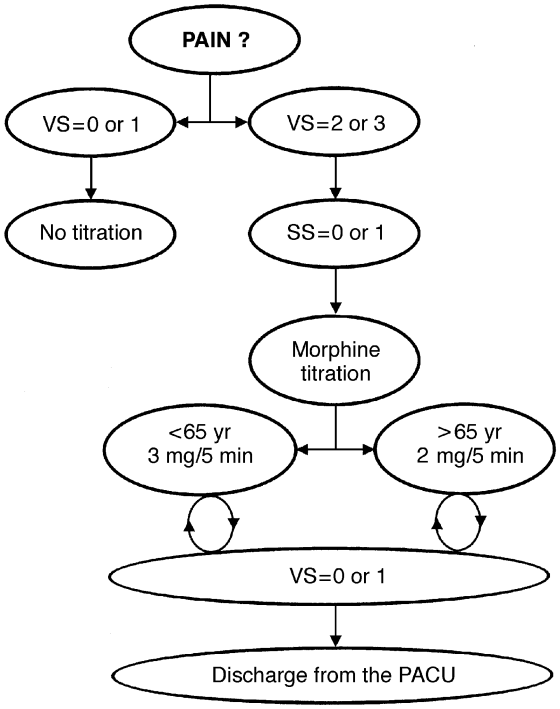

Fig 1 Standard procedure for morphine titration in PACU. Pain assessment with the verbal score (VS): ask the patient 'Which of the following words best describes the pain you are experiencing at the moment': none=0, mild pain=1, moderate pain=2, severe pain=3. Sedation score (SS): look at the patient and decide which of the following apply: awake=0, dozing intermittently=1, mostly sleeping=2, only awakens when aroused=3.

Table 2 Data categorization used for statistical analysis. *For the duration of surgery and the dose of intra-operative opioid, the categorization is determined by the mean value of each variable. Patients received any one of the three opioids. §For the time between last injection of opioid and arrival in PACU, the categorization into low or high is based on the duration of analgesic effect of each opioid

Variable	Low	High
Duration of surgery* (min)	⩽100	>100
Dose of intra-operative opioid*	Fentanyl ⩽250 μg Sufentanil ⩽30 μg Alfentanil ⩽1000 μg	Fentanyl >250 μg Sufentanil >30 μg Alfentanil >1000 μg
Time between last injection of opioid and arrival in PACU§ (min)	Fentanyl ⩽60 Sufentanil ⩽45 Alfentanil ⩽30	Fentanyl >60 Sufentanil >45 Alfentanil >30

expressed as mean (SD) with 95% confidence intervals. For all variables, an appropriate test has been performed to ensure the data is normally distributed. For small subgroups (below 30 patients each) we used a graphical technique. The total dose of morphine required for pain relief was compared between groups using analysis of variance (ANOVA).

To identify predictive factors of morphine consumption, variables that were found significant using ANOVA were included in a stepwise, backward, multivariate analysis model. The multiple regression analysis (MRA) model used was: $Y=B+B_1X_1+B_2X_2+B_3X_3+ \ldots B_nX_n$, where Y is the dependent variable (total morphine dose titrated) and $X_{1,2,3}...$ the independent variables.

A P value of <0.05 was considered statistically significant. All statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 9.0 for Windows 95/98.

Results

Patient characteristics

During the study period, 205 patients underwent a surgical procedure under general anaesthesia and 149 patients fulfilled the criteria for inclusion in the analysis. Fifty-six patients were subsequently excluded from the study because of: delayed extubation (13 patients); ASA physical status over 3 (eight patients); inability to read or speak French (15 patients); and incomplete data records (20 patients). The characteristics of the study population are shown in Table 3.

Univariate analysis

Factors for which a significant difference in the total dose of morphine was found were: sex, ethnicity, type, context and duration of surgery, type and amount of intra-operative opioids, time between last injection of opioid and arrival in the PACU, and finally, postoperative pain on arrival in the PACU. In contrast, there was no significant difference for age, surgeon grade, intra-operative administration of non-opioid analgesics such as propacetamol, nefopam or ketoprofen, and sedation score at the arrival in the PACU (Table 3).

Table 3 Morphine requirements for pain relief in the PACU

	n	Morphine (mg) (mean (SD))	95% confidence interval of mean (mg)	*P* value
Age				
⩽65 yr	114	3 (5)	2–4	NS
>65 yr	35	3 (5)	2–5	
Sex				
Male	93	2 (4)	3–5	<0.001
Female	56	3 (3)	1–5	
Ethnic group				
Caucasian	93	5 (6)	3–5	<0.001
Others (African, Asian)	56	1 (3)	1–2	
Type of surgery				
Major	49	4 (5)	3–5	<0.001
Intermediate/minor	100	1 (3)	0–2	
Scheduled	127	3 (4)	2–4	<0.05
Emergency	22	5 (6)	2–8	
Duration of surgery				
⩽100 min	91	2 (4)	1–3	<0.001
>100 min	58	5 (5)	4–7	
Surgeon grade				
Senior	89	3 (5)	2–3	NS
Assistant	60	3 (4)	3–6	
Type of opioid used				
None/alfentanil	63	4 (5)	3–6	0.001
Fentanyl/sufentanil	86	1 (4)	0–2	
Intra-operative opioid dose				
Low	85	4 (6)	3–6	0.01
High	64	2 (4)	1–3	
Non-opioid analgesic				
None	85	3 (5)	2–4	NS
Propacetamol/ nefopam/ketoprofen	64	4 (5)	2–5	
Time between last injection of opioid and arrival in PACU				
Low	70	2 (4)	1–3	<0.05
High	79	6 (6)	3–6	
Sedation score				
0 or 1	117	3 (5)	2–4	NS
2 or 3	32	3 (4)	1–4	
Pain score (verbal score)				
0 or 1	102	1 (3)	1–2	<0.001
2 or 3	47	6 (6)	5–8	

Multiple regression

Independent predictive factors of morphine requirements were: context of surgery (emergency), duration (>100 min), pain score on arrival in the PACU (2 or 3), ethnicity (Caucasian), and type of surgery (major) with a R^2=0.38. The equation for the regression model was: Y=2.3 (emergency surgery)+1.9 (duration of surgery >100 min)+1.6 (pain score on arrival in PACU at 2 or 3)+1.6 (Caucasian ethnicity)+0.9 (major surgery)–1.36. Sex, type, and amount of intra-operative opioid, and time between last injection of opioid and arrival in PACU were not found to be independent predictive factors of morphine requirements (Table 4).

Discussion

This prospective, observational study suggests that ethnicity, type, context and duration of surgery, and initial

Table 4 Independent predictive factors of morphine requirements in the PACU from the multiple regression analysis

Variable	Odds ratio	95% Confidence interval	*P* value
Context of surgery (emergency)	9.5	1.3–67	0.02
Duration of surgery (>100 min)	7	1.5–33	0.01
Pain score on arrival in PACU (2 or 3)	5	2.6–10	0.0001
Ethnicity (Caucasian)	5	1.1–22.7	0.03
Type of surgery (major)	2.4	1.1–5.8	0.04

postoperative pain score are predictive factors of morphine requirements in the PACU after general anaesthesia.

However, some methodological limitations have to be considered. First, this study included only a restricted sample of 149 patients. This may have decreased the power of the study, particularly for the negative findings, which were significant in the univariate analysis but not in the multiple regression analysis. Second, there is a possibility of confounders among the factors identified as significant in the univariate analysis. However, multiple regression analysis looks at the independency of these factors thereby ruling out those considered as possible confounders. Third, the value of R^2 in the multiple regression was 0.38. This means that 38% of the variability in the morphine requirements was explained by variability in the factors analysed. That leaves 62% of the variability that is not explained by any of the measured variables. Factors not considered in this study have to be taken into account. For example, psychological factors may be responsible for some of the inter-patient variability.[11–13] In our study, an increased anxiety level could probably explain the finding that emergency surgery is a predictive factor of morphine requirements. Patients operated on as an emergency are more anxious because they receive less information and do not benefit from any anxiolytic pre-medication. Because of these methodological considerations, this study can only be considered as preliminary work.

The positive findings in this study are not exactly the same as those reported for the later postoperative period (24 h plus). Ethnicity appears as a predictive factor of morphine consumption. Caucasian people required more morphine than Africans and Asians. It could be argued that this result is related to a higher incidence of Caucasian people in our study. However, the expression of pain and analgesic requirements has been shown to differ in various ethnic groups.[14–17] In addition, Uhl and colleagues[18] have demonstrated that a major source of variability in pain sensation and response to opioids is genetic. Alternatively, our finding could be explained by a higher socioeconomic status and level of formal education in Caucasian people in our institution.[19] It cannot be excluded that the predictive value of ethnicity could be related to other variables such as alcohol intake with hepatic enzyme induction, as increased requirements for intra-operative opioid have been reported in chronic alcoholics.[20]

As with previous observations,[21 22] we found a significant influence of surgical factors on morphine requirements. An original finding was that surgery exceeding 100 min duration was associated with increased morphine requirements. Pain score on arrival in PACU (moderate or severe) was also a predictive factor of morphine requirements. This is in agreement with previous work that reported an increase in postoperative opioid requirements with increased postoperative pain levels.[23] It could be argued that this result was to be expected as the procedure for morphine titration was based on pain scores. Nevertheless, the sedation score also used in the procedure did not appear as a predictive factor of morphine requirements.

In contrast, some variables previously reported to predict postoperative opioid requirements had no significant influence on morphine consumption in the PACU in our study. Increasing age has been found to decrease opioid requirements in numerous studies.[6–8 24] However, we failed to show a significant influence of age on early morphine requirements. This result could be related to the procedure used because it took into account the age of the patients (boluses of 3 mg under 65 yr and 2 mg over 65 yr, Fig. 1). Nor was our procedure weight related because it has been demonstrated that morphine requirements are better correlated to the age than the weight of the patient.[7] Procedures of morphine titration only based on age are used in other institutions.[25] Sex also did not appear as a predictive factor of morphine consumption in the PACU. This result is consistent with a clinical study in volunteers that has failed to find an effect of sex on morphine-induced behavioural and physiological responses.[26]

For the later postoperative period, previous results are conflicting. Macintyre and Jarvis[7] noted that male gender was a predictive factor of postoperative PCA morphine requirements although in their study, age was the best predictive factor. In contrast, other authors have reported a greater need for pain relief in women.[27]

Surprisingly, the type of anaesthetic, the amount of opioid used intra-operatively, and the time of the last injection of opioid, although significantly related to morphine consumption in the univariate analysis, were not independent predictive factors in the multiple regression analysis. This discrepancy could be related to the fact that these variables are probably dependent on the type of surgery performed and could be considered as confounding factors. An

important finding of this study is the lack of significant association between intra-operative administration of propacetamol, ketoprofen or nefopam, and morphine requirements. These analgesics were usually administered between 30 and 60 min before the end of surgery in anticipation of postoperative pain. Although these results do not support the use of non-opioid analgesics, further work is required because of the lack of power of our study.

How can the identification of these predictive factors improve postoperative pain management? Few of these variables are accessible to medical intervention. However, reduction of pain intensity on arrival in the PACU can be considered a reasonable goal. This can be achieved by the use of regional analgesia when possible.[28–30] The concept of pre-emptive analgesia has been also suggested.[31] Although pre-emptive analgesia is an attractive working hypothesis, the results appear conflicting in the literature.[32–34] Other approaches such as intra-operative titration of morphine could be investigated further. This technique decreases postoperative pain scores, morphine requirements, and patient length of stay in the PACU.[25]

In conclusion, this study opens up areas for further investigation of pain management in the early postoperative period. It is of importance because this period has clinical and economic implications.

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