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Postoperative Titration of Intravenous Morphine in the Elderly Patient

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Background: **Intravenous morphine titration is used to obtain rapid and complete postoperative pain relief. Whether this titration can be safely administered in the elderly patients remains a matter for debate.**

Methods: **Intravenous morphine titration was administered as a bolus of 2 (body weight ≤ 60 kg) or 3 (body weight > 60 kg) mg. The interval between each bolus was 5 min. There was no limitation in the number of boluses given until pain relief or severe adverse effect occurred. The visual analog scale threshold required to administer morphine was 30 mm, and pain relief was defined as a visual analog scale score of 30 mm or less. Patients were divided into two groups: young and elderly (age ≥ 70 yr) patients. Data were expressed as mean ± SD.**

Results: **Eight hundred seventy-five patients (83%) were young and 175 patients (17%) were elderly. At the end of morphine titration, the visual analog scale score and the number of patients with pain relief were not significantly different between groups. The total dose of morphine per kilograms of body weight administered was not significantly different between groups (0.15 ± 0.10 *vs.* 0.14 ± 0.09 mg/kg, not significant). No significant differences were observed in the incidence of morphine-related adverse effects (13 *vs.* 14%, not significant), the number of sedated patients (60 *vs.* 60%, not significant), and the number of patients whose titration had to be stopped (2 *vs.* 2%, not significant).**

Conclusion: **Intravenous morphine titration can be safely administered to elderly patients. Because titration is adapted to individual pain, the same protocol can be applied to young and elderly patients.**

ELDERLY patients undergo surgery with increased frequency. This trend will be enhanced in the near future as a result of demography and an increase in life expectancy in developed countries.[1] Aging is associated with a variety of changes, such as diminished functional status and chronic diseases.[2] Postoperative analgesia is associated with potential adverse effects or complications that might be more pronounced or more frequent in the elderly patients.[3] On the other hand, inadequate analgesia has been reported to be more frequent in the elderly patients.[4–6]

The most outstanding feature of the clinical use of opioids is the extraordinary variation in dose requirements for pain management.[7,8] Intravenous administration of morphine is usually recommended for acute pain relief in the immediate postoperative period.[9] Indeed, the use of small intravenous boluses of morphine in the postanesthesia care unit (PACU) allows a rapid titration of the dose needed for adequate pain relief.[8–10] Few studies have assessed morphine titration in the PACU period.[11,12] In a previous study, we demonstrated that intravenous morphine titration every 5 min with an unlimited number of 2- or 3-mg boluses provided the best and most rapid analgesic regimen, without significant increase in opioid-related adverse effects.[12]

In elderly patients, a decrease in the dose of opioids is usually recommended because of changes in pharmacodynamics and pharmacokinetics.[2,13–15] However, because of the extraordinary variation in dose requirements for pain management in the PACU and because titration strictly adapts the dose to the pain, there is no evidence that a titration protocol should also take into account the age of the patients. Moreover, titration is performed over a short period in which age-related changes in pharmacodynamics and pharmacokinetics might be less important. Thus, in a prospective study, we compared intravenous morphine titration in the postoperative period in young and elderly patients. We hypothesized that the same protocol of intravenous morphine titration could be used in young and elderly patients in the PACU without significant increase in morphine-related adverse effects.

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Materials and Methods

The current study was approved by the hospital's ethical committee. Because data were recorded without any intervention and according to a protocol already used routinely in our PACU,[12] authorization was given to waive informed consent.

Nurse Training

All nurses in the PACU have been trained to assess pain using unidimensional scales and to perform morphine titration. They used the visual analog scale (VAS; 0–100 mm, handheld slide-rule type).[16] When patients had difficulties in manipulating the VAS, nurses were allowed to

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use a numeric rating scale (0–100 mm)[17] because these two methods are equivalent.[18]

Regimen of Intravenous Morphine Titration

A strict protocol had been implemented in the PACU after a preliminary study had determined the optimal regimen of morphine titration.[12] This protocol defined the dose of intravenous boluses of morphine, the interval between boluses, the absence of limitation on the total dose, the VAS threshold required to administer morphine, and the criteria to stop titration. Immediately after the patients had tracheal extubation and were awake, they were questioned about the presence of pain in the PACU (at least every 15 min before the onset of morphine titration) and asked to rate pain intensity on a scale (VAS). When the pain increased to more than 30 mm, intravenous morphine was titrated every 5 min by 3-mg increments (2 mg in patients weighing 60 kg or less) and pain was assessed every 5 min until pain relief, defined as a VAS score of 30 mm or less. When the patient was asleep, no attempt was made to wake the patient and he or she was considered as having pain relief. When pain was too severe to obtain a VAS (patient refusal), it was scored as 100. The delay to morphine titration was defined as time elapsed between the arrival in the PACU and onset of intravenous morphine titration. Clinical monitoring included respiratory rate (RR) measurements, oxygen saturation measured by pulse oximetry, sedation according to the Ramsay score,[19] and arterial blood pressure and heart rate measurements. All patients were given oxygen supplementation. Morphine titration was stopped if the patient had an RR of less than 12 breaths/min, an oxygen saturation measured by pulse oximetry of less than 95%, or a serious adverse event related to morphine administration (allergy, vomiting, severe pruritus). In case of severe ventilatory depression (RR $<$ 10 breaths/min) an intravenous bolus of 0.04 mg naloxone was administered until RR was greater than 12 breaths/min, and this was defined as a severe morphine-related adverse effect. During the data collection period, 1,050 consecutive patients who fulfilled the following criteria were included: (1) VAS score greater than 30 mm and (2) understanding of the unidimensional methods. Thus, patients with minor pain (defined as a VAS score of 30 mm or less), patients with delirium or dementia, or patients who were non–French speaking were not included in the study.

In the current study, nurses could not be blinded for the patient's age; thus, a possible bias could have occurred. Therefore, all data sheets were retrospectively assessed for potential protocol deviation. These deviations were classified as follows: error in the dose of each bolus (2 *vs.* 3 mg) according to the weight of the patient, error in one dose during titration (usually because a vial of morphine does not always contain a finite number of boluses), and inappropriate total dose according to pain relief. For each of these three items, the dose could be either underestimated or overestimated. Two analysis were performed: intention to treat (all patients) and protocol compliance (excluding patients with protocol violation).

End Points

Patients were divided into two groups according to age: young and elderly (age $\geq$ 70 yr). The primary end point was the percentage of patients with morphine-related adverse effects. The secondary end points were the VAS score and the percentage of patients with pain relief (VAS score of 30 mm or less). The following adverse effects were noted during the PACU period: ventilatory depression defined as RR below 10 min^{-1} or need for naloxone administration, nausea and vomiting, pruritus, retention of urine requiring drainage in the PACU, bradycardia, bronchospasm, and cutaneous rash or other allergic events. Sedation was defined as a Ramsay score[19] above 2 but was not considered as an adverse effect. However, the percentage of sedated patients was also recorded.

The anesthesiologists made the decision to move the patient from the PACU after the nurse had verified that the patient fulfilled the Aldrete criteria[20] and did not have emesis, severe pain, or major postoperative bleeding. Like the nurses, the anesthesiologists were not aware of the data collecting period.

Statistical Analysis

Data are expressed as mean $\pm$ SD or median values and their 95% confidence interval in nongaussian variables (time delay and duration). Student *t* test and repeated-measures analysis of variance were used for continuous Gaussian variables. The Mann-Whitney U test was used to compare two medians. The chi square test or Fisher exact method was used for categorical variables. When percentage was equal to 0, the 95% confidence interval was calculated as previously reported.[21] Correlation between two variables was performed using the least-squares method. For multivariate analysis, a logistic regression was used. All comparisons were two-tailed, and a *P* value of less than 0.05 was required to rule out the null hypothesis. Statistical analysis was performed using a computer and NCSS version 6.0 software (Statistical Solutions Ltd., Cork, Ireland).

Results

One thousand fifty patients were included in the study over an 18-month period. Mean patient age was 50 $\pm$ 18 yr; 576 (55%) patients were men and 474 (45%) were women. They were admitted in the PACU after orthopedic surgery in 778 (74%) patients, urologic surgery in 159 (15%) patients, abdominal or gynecologic surgery in

Table 1. Main Characteristics of Young and Elderly Patients

	Young Patients (n = 875)	Elderly Patients (n = 175)	*P* Value
Age (yr)	45 ± 15	76 ± 6	—
Male sex	508 (58)	68 (39)	< 0.001
Weight (kg)	70 ± 14	68 ± 14	0.05
Type of surgery			
Orthopedic	650 (74)	124 (71)	
Urologic	131 (15)	28 (16)	NS
Abdominal	51 (6)	9 (5)	
Others	43 (5)	14 (8)	
Delay to titration (min)	60 [50–65]	105 [80–130]	< 0.001
Duration of PACU stay (min)	255 [240–270]	370 [340–400]	< 0.001
Initial VAS (mm)	76 ± 20	74 ± 21	NS

Data are mean ± SD, median [95% confidence interval], or n (%). No significant differences exist between groups. Because of rounding, adding percentages may not provide a sum of 100%.

NS = not significant; VAS = visual analog scale; PACU = postanesthesia care unit.

56 (5%) patients, vascular surgery in 46 (4%) patients, and thoracic or maxillofacial surgery in 11 (1%) patients. Eight hundred seventy-five patients (83%) were young, and 175 patients (17%) were 70 yr of age or older (table 1). The distribution of these two populations according to age is shown in figure 1.

The VAS score was not significantly different in the two groups during and at the end of morphine titration (fig. 2A). In the same manner, the number of patients with pain relief was not significantly different (fig. 2B). The total dose of morphine administered during titration was lower in elderly patients, but the body weight was also significantly lower in elderly patients (table 2). When the dose was normalized for body weight, no significant difference was observed between groups (table 2). No significant differences in morphine-related adverse effects were observed between the two groups (table 2). No patient required naloxone administration. The incidence of severe morphine-related adverse effects was 0 in elderly patients (95% confidence interval, 0%–1.7%). The number of sedated patients and the number of patients requiring termination of morphine titration were not significantly different between groups. Elderly patients exhibited significantly longer delay in morphine titration and duration of stay in the PACU compared with young patients (table 1).

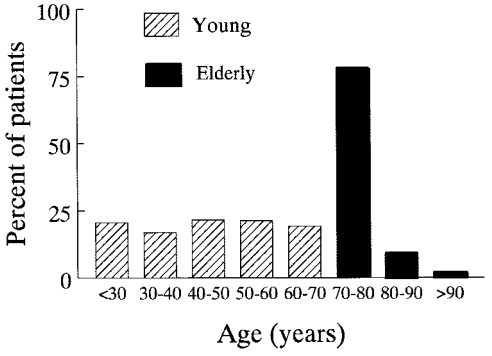

Fig. 1. Distribution of age in young (n = 875) and elderly (n = 175) patients.

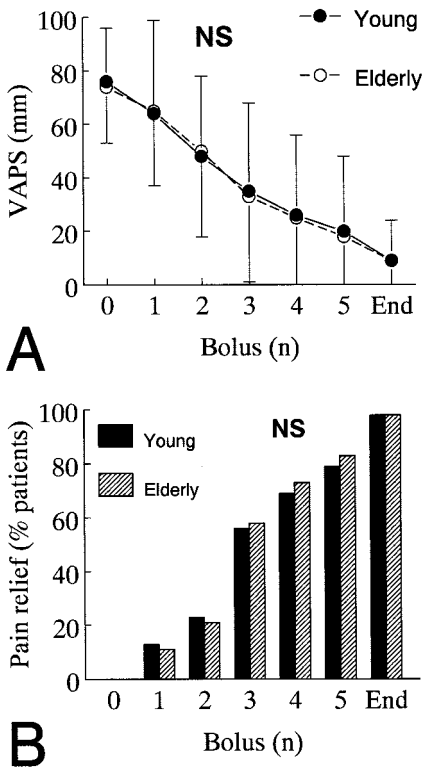

Fig. 2. Comparison of (*A*) the score on the visual analog pain scale (VAPS; mean ± SD) and (*B*) the percentage of patients with pain relief in young (n = 875) and elderly (n = 175) patients. Pain relief is defined as a score on the VAPS of less than 30 mm. NS = not significant. The result of the initial five boluses and the result at the end of morphine titration (end) are shown, but the number of boluses was not limited.

Table 2. Comparison of Intravenous Morphine Dose and Adverse Effects

	Young Patients (n = 875)	Elderly Patients (n = 175)	*P* Value
Dose of intravenous morphine (mg)	10.5 ± 6.2	9.5 ± 3.9	0.05
Dose of intravenous morphine (mg/kg)	0.15 ± 0.10	0.14 ± 0.09	NS
Number of morphine boluses	3 [3–4]	3 [3–3]	NS
Adverse effects			
Nausea or vomiting	86 (10)	23 (13)	
Ventilatory depression	3 (0.3)	1 (0.5)	
Pruritus	3 (0.3)	0	
Urinary retention	23 (3)	4 (2)	
Allergy	3 (0.3)	1 (0.5)	
Total*	115 (13)	26 (15)	NS
Titration stopped	21 (2)	4 (2)	NS
Sedated patients	524 (60)	104 (60)	NS

Data are mean ± SD, median [95% confidence interval], or n (%).

* The total is the number of patients with at least one side effect. One patient may have had several different side effects.

NS = not significant.

Table 3. Comparison of Protocol Violations

	Young Patients (n = 875)	Elderly Patients (n = 175)	*P* Value
Overestimation	4 (0.5)	2 (1)	NS
One bolus	4	2	
Each bolus	0	1	
Total dose	0	0	
Underestimation	25 (3)	6 (3)	NS
One bolus	17	2	
Each bolus	4	3	
Total dose	4	1	
Total	29 (3)	9 (5)	NS

Data are n (%). See text for explanation of overestimation and underestimation.

NS = not significant.

The number of protocol violations was not significantly different in young and elderly patients (3 *vs.* 5%, not significant [NS]; table 3). Most of these protocol violations (67%) were related to the fact that morphine vial does not contain a finite number of boluses (*i.e.*, error in only one bolus). However, when considering only patients who had full compliance to the protocol (845 young and 166 elderly patients), there were no significant differences in the dose of morphine (10.3 ± 6.0 *vs.* 9.6 ± 5.5 mg [NS]), the dose of morphine per body weight (0.15 ± 0.09 *vs.* 0.14 ± 0.09 mg [NS]), the number of morphine-related adverse effects (13 *vs.* 14% [NS]), the number of sedated patients (61 *vs.* 60% [NS]), and the number of patients requiring termination of morphine titration (2 *vs.* 2% [NS]).

The delay to morphine titration was significantly greater in elderly patients. However, when considering only patients who were given morphine titration within 120 min (621 young and 94 elderly patients; mean delay to morphine titration of 35 [95% confidence interval, 30–40] *vs.* 45 [95% confidence interval, 35–55] min [NS]), there was a significant difference in the dose of morphine (10.8 ± 6.3 *vs.* 9.4 ± 5.3 mg, $P < 0.05$), but not in the dose of morphine per kilogram of body weight (0.16 ± 0.09 *vs.* 0.15 ± 0.09 mg [NS]), the number of morphine-related adverse effects (14 *vs.* 13% [NS], the number of sedated patients (61 *vs.* 64% [NS]), and the number of patients requiring termination of morphine titration (2 *vs.* 3% [NS]).

A significant but weak correlation was observed between the initial VAS score and the dose of morphine required during titration ($R = 0.37$, $P < 0.001$). The dose of morphine titration was also weakly correlated to the body weight ($R = 0.12$, $P < 0.001$) but not to age ($R = 0.01$ [NS]). Using a logistic regression, we observed that a high dose of morphine during titration (> 10 mg) was significantly associated with initial VAS score (odds ratio per 10-mm increase: 1.45 [95% confidence interval, 1.36–1.56], $P < 0.001$), but not with age (odds ratio per 10-yr increase: 0.95 [95% confidence interval, 0.88–1.01] [NS]).

Discussion

The main finding of the current study is that intravenous morphine titration in the PACU can be safely administered to elderly patients using the same protocol that is used in young patients. Surprisingly, the morphine requirements were not significantly different between these two groups during morphine titration.

Elderly patients have been noted to be more susceptible to the effects of opioid analgesic than young patients.[2,22,23] Some phases of pharmacokinetics are affected in aging, including distribution,[24] metabolism,[25,26] and elimination.[25,27] For any given weight-adjusted dose of an opioid, elderly patients have been shown to have higher blood levels and more pronounced pharmacologic effects than young patients.[6,14] In elderly patients, morphine volume of distribution is approximately half that of young patients. The smaller central compartment distribution is thought to be attributable, at least in part, to decreased cardiac output.[28] Plasma clearance of morphine is also lower in elderly patients.[29] Moreover, renal failure is more frequent in elderly patients and can induce an accumulation of morphine metabolites (morphine-3-glucuronide and morphine-6-glucuronide), explaining the prolonged effect of opioids in the elderly patients.[25]

Previous studies assessing factors that might influence the dose of opioid that patients require in the postoperative period have found that there was no significant correlation to the patient's weight but a significant correlation to patient age.[30–32] Nevertheless, these studies assessed the variables influencing morphine requirements over a larger time period (the initial 24 h), using patient-controlled analgesia (PCA). No previous study has examined the immediate and short-term postoperative period of intravenous morphine titration. Egbert *et al.*[32] performed a randomized trial of postoperative PCA *versus* intramuscular opioids in frail elderly men. A standard intravenous loading dose of morphine was administered to both groups, but no results were provided concerning this titration. Mann *et al.*[33] compared the effectiveness on postoperative pain and safety of patient-controlled epidural analgesia and PCA after major abdominal surgery in the elderly patient (> 70 yr of age). In the PCA group, analgesia was begun after an initial loading dose of up to 5 mg of intravenous morphine. It was administered as a single shot, PCA was immediately connected to the patient, and no assessment of the efficacy was performed. No serious side effects were reported in that group, but no comparison was performed with young patients.[33] More recently, Gagliese *et al.*[34] assessed PCA and observed that elderly patients attained comparable levels of analgesia but using less opioid than young patients. However, although patients were given intravenous morphine just before PCA, this

initial dose was not compared between young and elderly patients.[34]

There is an important discrepancy between our current study (morphine requirements during intravenous titration were not significantly different in young and elderly patients) and the well-accepted concept that opioids are more potent in elderly patients. We offer the following comments: (1) No previous study has compared dose requirements during intravenous morphine titration for acute postoperative pain, and the results obtained in other clinical conditions, mainly intraoperative[35,36] or prolonged postoperative periods,[34] may not be relevant because the influence of pharmacokinetic variables may not be identical. (2) Most previous studies in the intraoperative period did not directly assess pain in conscious patients but rather measured hemodynamic or electroencephalographic variables and could not avoid the interference with anesthesia.[35,36] (3) This is not a simple two-variable (age, dose of morphine) model; indeed, there is at least one other important variable (pain intensity), and we cannot rule out the hypothesis that differences in pain intensity (or pain sensitivity to morphine) occur between young and elderly patients (*vide infra*). (4) Our study may lack sufficient power to detect a significant difference between groups; however, the small difference observed (−10% of morphine dose expressed as milligrams, −7% of morphine expressed as mg/kg; table 2) is far below the 50% decrease in opioid requirements reported during the intraoperative period[35,36] or the 41% decrease reported over the period of first postoperative day.[34]

Prevalence of painful conditions in elderly patients is greater than in the young.[37] Some studies have shown that pain tolerance is slightly increased in elderly patients.[38] In contrast, other studies did not find any significant differences between young and elderly patients.[39] Pain complaint have been listed as being less frequent in elderly patients.[2] In our study, the dose of morphine per kilogram of body weight, the initial VAS score, and the percentage of patients with pain relief were similar in the two groups. Nevertheless, it is not possible to conclude definitely that morphine requirements are the same in young and elderly patients during morphine titration. Obviously, these two populations might differ from many points of view (*e.g.*, type of surgery undertaken, duration of anesthesia and surgery, American Society of Anesthesiologists status, associated diseases) that are potential bias for this comparison. The longer delay to morphine titration related to prolonged awakening or postoperative mechanical ventilation in elderly patients, as well as the longer stay in the PACU (table 1) reflect these differences and thus suggest potential bias in the analysis of morphine requirements. It should be emphasized that even when we excluded patients with a long delay to morphine titration, no significant differences were noted. Further studies (same surgery in patients without associated diseases) are required to answer to this question. However, this was not the primary end point of the present study.

Inadequate postoperative analgesia is an important problem in the elderly. Analgesic use declines with advancing age.[4] In older patients, fewer opioids are prescribed and consumed.[4,5] Nociception in the elderly population can induce postoperative pulmonary complications, postoperative coronary insufficiency, ileus, nausea, vomiting, constipation, urinary retention, and anxiety.[6] In the same way, conditions exacerbated by pain, such as dementia, are more frequent in frail elderly patients.[40] Most of the time, lack of information about pain in elderly patients, lack of pain assessment in the postoperative period in the oldest population, and fear of increased risks of adverse effects lead to undertreatment of pain in elderly patients, although it has been shown that respiratory depression after a single intravenous bolus of morphine is comparable in young and elderly patients.[41] In our study, pain relief was similar in the two groups because of the strict protocol implemented in our PACU; all patients were assessed with the same tools, and consciousness supervision and rigorous clinical monitoring including hemodynamic and respiratory variables were implemented by a skilled medical staff. However, there was a possibility for bias because the nurses were not blinded to patient age and thus might have behaved differently in the two groups. The audit of our study shows that protocol violations occurred rarely, were minor in most of the cases, and did not occur more frequently in elderly patients (table 3). In addition, exclusion of patients with protocol violation did not modify the results of our study. Therefore, although the nurses were not blinded to age, we can conclude that our two groups were managed in the same way, whatever the age, and that comparable pain relief was obtained in the two groups.

In our study, morphine titration was applied with a strict protocol with two degrees of freedom, one of them major, the intensity of pain assessed by VAS, and one minor, the weight of the patient, which determined the dose of each bolus. The question raised by our study was the following: Is a third degree of freedom, namely, age, required? Therefore, we made the hypothesis that, if the incidence of morphine-related adverse effects differs between young and elderly patients, morphine titration should also be adjusted according to the patient's age. Incidence of adverse effects was similar in the two groups (table 2). We did not observe any significant differences between elderly and young patients for sedation and ventilatory depression. Some authors have examined factors inducing hypoxemia in the recovery room and demonstrated that age was not significantly associated with hypoxemia.[41] In the same way, Moller *et al.*[42] studied hypoxemia in the PACU in 200 patients and showed that there were no significant differences be-

tween the age groups of 40—60 yr and greater than 60 yr. Nevertheless, Arunasalam *et al.*[43] described more apneic periods, periodic breathing, and paradoxical breathing in the elderly patients after intravenous morphine, in contrast to the study of Daykin *et al.*[41] It should be pointed out that we decided to stop morphine titration as soon as the patient was asleep to avoid ventilatory depression. However, our study indicates that the same protocol of morphine titration can be safely applied to all patients, whatever their age.

Remarks must be included to assess the limitations of our study. First, the results apply only to the immediate and short-term postoperative period of intravenous morphine titration in the PACU, where differences in pharmacokinetics are likely to play a less important role than during a longer period. We did not evaluate pain management and morphine administration on the ward. Using PCA over a period of several days, Gagliese *et al.*[34] observed that morphine requirements were decreased in elderly patients. Therefore, the dose and the rate of morphine administration after titration should probably be adjusted according to age, as demonstrated by numerous studies.[29,30,34] Second, polypharmacy occurs often in the elderly population. Further studies are required to assess, in addition to age-related changes in the pharmacokinetics and the pharmacodynamics of the opioids, interactions, accumulation, and toxicity risks between analgesics and other drugs that are used before prescription of the pain treatment. Third, the reliability of the pain measurement tools might be affected by age.[44,45] We limited this problem by excluding severely cognitively impaired patients,[46] but we cannot rule out the hypothesis that a subtle difference occurs. Fourth, further studies are required to compare morphine titration in the elderly (70–90 yr of age) and the very elderly (> 90 yr of age) populations. Patients older than 90 yr of age represented only 2% of the elderly population in the current study (fig. 1). Fifth, we did not observe any severe adverse effects in elderly patients, but the power of our study is limited by the relatively small sample size (n = 175 elderly patients). Larger studies are required to obtain a smaller confidence interval of the incidence of severe morphine-related adverse effects than that recorded in the population in the current study.

In conclusion, intravenous morphine titration can be safely administered to elderly patients using the same protocol that is used in young patients. Nevertheless, these results apply only to short-term control of pain in the PACU and not to long-term administration of morphine.

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