Anesthesiology
1998; 89:1377–88
© 1998 American Society of Anesthesiologists, Inc.
Lippincott Williams & Wilkins

Efficacy and Costs of Patient-controlled Analgesia versus Regularly Administered Intramuscular Opioid Therapy

Manon Choinière, Ph.D., Brian E. Rittenhouse, Ph.D.,† Sylvie Perreault, Ph.D.,‡ Daniel Chartrand, M.D., Ph.D.,§ Pierre Rousseau, M.D.,‖ Bruce Smith, M.D.,# Carolyn Pepler, R.N., Ph.D.***

Background: **Many studies have shown the efficacy of patient-controlled analgesia (PCA). However, it is not clear whether PCA has clinical or economic benefits in addition to efficient analgesia. The current study was designed to evaluate these issues by comparing PCA with regularly administered intramuscular injections of opioids after hysterectomy.**

Methods: **This prospective study included 126 patients who underwent abdominal hysterectomy and were randomly assigned to receive PCA or regularly timed intramuscular injections of morphine during a period of 48 h. Doses were adjusted to provide satisfactory analgesia in both treatment groups. Pain at rest and with movement, functional recovery, drug side effects, and patient satisfaction were measured using rating scales and questionnaires. The costs of PCA and intramuscular therapy were calculated based on personnel time and drug and material requirements.**

Results: **Comparable analgesia was observed with the two treatment methods, with no significant differences in the incidence of side effects or patient satisfaction. The medication dosage had to be adjusted significantly more frequently in the intramuscular group than in the PCA patients. The PCA did not favor a faster recuperation time compared with intramuscular therapy in terms of times to ambulation, resumption of liquid and solid diet, passage of bowel gas, or hospital discharge. The results of the economic evaluation, which used a cost-minimization model and sensitivity analyses, showed that PCA was more costly than regular intramuscular injections despite the fact that no costs for the pump were included in the analyses. Cost differences in nursing time favoring PCA were offset by drug and material costs associated with this type of treatment.**

Conclusions: **Compared with regularly scheduled intramuscular dosing, PCA is more costly and does not have clinical advantages for pain management after hysterectomy. Because of the comparable outcomes, the general use of PCA in similar patients should be questioned. (Key words: Analgesics; expenses; gynecology.)**

* Research Associate Professor, Department of Anesthesia, Faculty of Medicine, University of Montreal.

† Associate Professor, Rhone-Poulenc Chair of Pharmacoeconomics, Department of Pharmacology, Faculty of Medicine, University of Montreal. Current position: Director, ICOM Health Economics, Johnson and Johnson, Raritan, New Jersey; and Clinical Associate Professor, Department of Medicine, Robert Wood Johnson School of Medicine, University of Medicine and Dentistry of New Jersey, Newark, New Jersey.

‡ Postdoctoral Fellow, Department of Clinical Epidemiology, Faculty of Medicine, McGill University.

§ Assistant Professor, Department of Anesthesia, Faculty of Medicine, McGill University.

‖ Clinical Assistant Professor, Department of Anesthesia, Faculty of Medicine, University of Montreal.

Associate Professor, Department of Anesthesia, Faculty of Medicine, McGill University.

** Associate Professor, School of Nursing, McGill University.

Received from Centre Hospitalier de l'Université de Montréal, Campus Hôtel-Dieu, the Royal Victoria Hospital, and McGill University, Montréal, Québec, Canada. Submitted for publication December 15, 1997. Accepted for publication July 24, 1998. Supported by grants 931267 and 952254 from the Fonds de la Recherche en Santé du Québec (FRSQ). Drs. Choinière and Chartrand were supported as FRSQ research scholars when the study was conducted. Presented in part at the annual meeting of the Canadian Pain Society, May 22–24, 1997, Niagara-on-the-Lake, Ontario, Canada, and at the 13th Annual Meeting of the International Society of Technology Assessment in Health Care, May 25–28, 1997, Barcelona, Spain.

Address reprint requests to Dr. Choinière: Centre Hospitalier de l'Université de Montréal, Campus Hôtel-Dieu, Département d'anesthésie, 3840 St-Urbain, Montréal, (Québec), Canada H2W 1T8. Address electronic mail to: choiniem@ere.umontreal.ca

THE efficacy and safety of patient-controlled analgesia (PCA) have been shown in many clinical trials and in several patient populations.[1–3] In addition to being an efficacious analgesia, several advantages have been ascribed to PCA, including high patient acceptability,[4–6] faster postoperative recovery,[7–10] earlier hospital discharge,[7,11–12] and reduced nursing time.[6] In a recent meta-analysis, Ballantyne *et al.*[13] noted, however, that the magnitude of the observed differences between PCA and conventional intramuscular analgesia often is modest in view of the immense popularity of PCA. In terms of analgesic efficacy for example, they estimated that the mean additional benefit of PCA was only of 5.6 units on a 0–100 pain scale.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/89/6/1377/396173/0000542-199812000-00015.pdf by guest on 20 April 2024

Because many of these comparative studies were based on small samples, one explanation for the frequent observation of little or no difference in efficacy between PCA and conventional therapy is simply the lack of sufficient statistical power to detect a difference. However, it is possible that the advantages of PCA in terms of analgesic efficacy are indeed of a small magnitude, particularly if one makes the comparison with regular dosing of intramuscular opioids. Most frequently, PCA has been compared with on-demand intramuscular dosing despite the long-recognized inadequacies of this mode of administration.[14,15]

In the *Canadian Journal of Anaesthesia*, Ready[16] and Moote[17] debated whether regular intramuscular dosing and rescue analgesia can provide pain relief equal to PCA. Other authors[14,18] argue that PCA is not necessary or realistic for most patients and that prophylactic intramuscular dosing coupled with regular pain measurement and dose adjustments according to individual needs can provide equally effective analgesia. The current study was designed to test this hypothesis and to determine whether PCA has clinical or economic benefits in addition to efficient analgesia.

Previous economic studies have compared PCA with different alternatives, most often to on-demand intramuscular injections. These studies used various methods and often overlooked particular costs. Sometimes, only primary drug and some share of equipment costs were totaled.[19] Frequently, methods were described only superficially.[20,21] Estimates of nursing time (when included) were made in various ways (*e.g.*, continuous timing of activities,[22] time-in-motion studies,[23,24] staff questioning[20,25,26]). Some study objectives were limited ("What is the cost benefit to nursing?"[27]), whereas others suggested nonresearch agendas, explicitly setting out to "prove" that PCA is cost-effective. The qualities and results of these studies are mixed, although there is general, if not universal, agreement that PCA is less nurse intensive than are intramuscular injections.

The current study departs from the usual line of research to PCA in two important aspects: (1) PCA was compared with regular rather than on-demand intramuscular dosing of opioids and (2) the comparison was made with the goal of achieving optimal analgesia with both treatment methods and then evaluating the additional clinical and economic benefits of each therapy.

Materials and Methods

The ethics committees of the Centre Hospitalier de l'Université de Montréal, Hôtel-Dieu Campus (HD), and the Royal Victoria Hospital (RV) in Montreal approved the study. One hundred twenty-six adult women, who were classified as American Society of Anesthesiologists physical status I to III and scheduled to undergo abdominal hysterectomy were included in the study. Exclusion criteria were age younger than 18 yr or older than 65 yr, body mass index (measured in kilograms per square meter) more than 30 units, malignant disease, insufficient comprehension of French or English, and history of drug abuse or severe psychologic disorders.

The day before surgery, the research nurse responsible for data collection in each hospital met with the eligible patients and obtained written informed consent. The patients were then allocated to one of the two treatment groups (PCA or intramuscular) using a table of random numbers. The randomization protocol was stratified according to study site, and a sealed envelope system was established in each hospital. The analgesic regimen to which they were assigned was then carefully explained to each patient and they were familiarized with the visual analog scale (VAS) for pain assessment.[28] After operation, patients in the PCA group were instructed again before the analgesic therapy was begun.

Surgery was performed during general anesthesia using a standardized protocol in which thiopental was used for induction, isoflurane and nitrous oxide in oxygen were used for maintenance, and vecuronium was used for muscle relaxation. Intraoperative analgesia was provided by intravenous fentanyl or alfentanil, with the dose determined by the attending anesthetists.

Postoperative Management

After surgery, patients were transferred to the postanesthesia care unit and were asked every 10 min whether they needed pain relief. If so, the nursing staff administered boluses of 3 mg intravenous morphine until either the patient appeared to be resting comfortably or a maximum of 15 mg had been administered. The study protocol was then started (time 0) and lasted for 48 h. Patients allocated to the PCA group were provided with a Graseby 3300 PCA Pump (Minogue Medical, Montreal, Quebec, Canada) programmed to deliver 1 mg intravenous morphine with a lockout interval of 6 min. Patients assigned to the intramuscular group received the first intramuscular injection of morphine (0.15 mg/kg) 4 h after the study started (time 0) or earlier if they reported inadequate pain relief (pain score $\geq$ 4). Injections were administered regularly every 4 h. No analgesic other than morphine was used during the study, and sedative drugs were not allowed.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/89/6/1377/396173/0000542-199812000-00015.pdf by guest on 20 April 2024

A protocol for dose adjustments was used and was part of a standardized prescription order included in the patient's medical file. If a patient in the PCA group reported pain (VAS $\geq$ 4) and was using the pump appropriately, the PCA bolus of morphine was increased by 0.5 mg. If a patient in the intramuscular group reported inadequate pain relief within 3 h after injection (VAS $\geq$ 4), she was administered a rescue injection that corresponded to 50% of the initial dose of morphine, and the next injection was increased by 50%. If the patient reported inadequate pain relief during the fourth hour after injection, no rescue dose was administered, but the next injection was increased by 50% of the initial dose. If pain control was still unsatisfactory in either group (PCA or intramuscular), the anesthetist on call was contacted, and further dose increases were made as appropriate. In the presence of severe sedation or a respiratory rate less than 11 breaths/min, the nurse was instructed to stimulate the patient to breathe and to decrease the next dose of morphine by 50% of the initial dose if the patient was in the intramuscular group. In the PCA group, the pump control was removed from the patient until she was breathing normally (respiratory rate > 10 breaths/min). Naloxone was administered if the respiratory rate was less than 8 breaths/min, the anesthetist was called, and the next intramuscular injection (or the PCA bolus) was reduced by 50% of the initial dose. Nausea and vomiting were treated as needed with 50 mg intravenous dimenhydrinate. Intravenous diphenhydramine or an oral dose (25 mg) was prescribed for pruritus. In the event of unsatisfactory resolution of side effects, inadequate analgesia, or both after adjustments were made, the PCA or intramuscular treatment was discontinued and the choice of analgesic treatment was left to the surgeon.

Evaluation of Efficacy

Measures. Patients' pain was assessed using two set of measures. The first series was collected at 1, 3, and 5 h after the start of the study (time 0) and every 4 h thereafter. On each occasion, the ward nurse asked the patient to rate the intensity of her present pain (pain at rest) using a 10-cm VAS type of scale with the end points labeled "no pain" and "unbearable pain."[28] At 24 and 48 h after the start of the study, a second set of pain measures was collected by the research nurse in charge of the study. She used the VAS to assess pain relief and pain intensity with movement, that is, when the patient was changing position and walking. The McGill Pain Questionnaire[29] was also administered to assess overall pain during the previous 24 h. This questionnaire consists of 20 sets of adjectives from which the patient selects those that best describe her pain. The adjectives are scaled according to relative intensity within each set. Minimum and maximum scores on this questionnaire are 0 and 78, respectively.

When the study was complete at 48 h, the research nurse assessed patient satisfaction with analgesic treatment using two measures. One was a VAS rating of the overall treatment efficacy ("not at all" to "extremely effective"), whereas treatment acceptability was measured using a category scale that assessed the probability that the patient would choose the same analgesic treatment (PCA or intramuscular) if she had to undergo another operation.

Respiratory rate was monitored 1 h after the start of the study, every 2 h for 4 h, and every 4 h thereafter. On the same occasion, the ward nurse rated the patient's degree of sedation using a four-point scale in which 0 (none) = wide awake and alert, 1 (mild) = drowsy on occasion but easily aroused, 2 (moderate) = somnolent but easily aroused, and 3 (severe) = somnolent but difficult to arouse. Any other side effects of the analgesic medication also were noted. This information was recorded on a special data form left in the patient's room on which the nurse also noted the first time (in hours) the patient (1) sat in a chair with assistance and without assistance, (2) walked in the corridor, (3) took liquid and solid diets, and (4) had a bowel sound.

Statistical Analysis. Before the start of the study, a power-based sample size estimation was performed using postoperative pain and recovery rate as primary outcomes. We estimated the sample size necessary (1) to test the hypothesis that postoperative pain control would be equivalent in the PCA and intramuscular groups (mean intergroup differences $\geq$ 1 cm on the VAS pain at rest and during movement; group equivalence testing[30]) and (2) to detect clinically significant group differences on the rate of recovery (mean intergroup differences of at least 1 day for the duration of hospital stay, and half a day (12 h) for the other recovery variables; group difference testing[31]). Based on previous work at the HD campus in the same surgical population using a similar set of outcome measures, we estimated that a sample size of 70 patients per group was necessary to give the study a power of 0.80 with a type 1 error rate of 0.05. However, we did not have this many patients because of time limitations and financial constraints. Statistical power was, therefore, reassessed after the study was completed for each VAS measure and recov-

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/89/6/1377/396173/0000542-199812000-00015.pdf by guest on 20 April 2024

ery parameter. Secondary outcome measures were patient satisfaction, medication data, and side effects.

Data obtained from all the patients enrolled in the study, including those whose treatment was discontinued prematurely, were entered in intent-to-treat statistical analyses, and these results were used to confirm those obtained with the group of patients who completed the entire study period. This was true for all outcome measures except those that were collected every 4 h (*e.g.*, pain at rest), at 24 and 48 h (*e.g.*, pain during movement), and when the study was complete (*e.g.*, satisfaction measures). If treatment was discontinued in the last 4 h preceding the end of the study, all data normally obtained at 48 h at study completion were collected at that time.

Data obtained for continuous variables are presented as mean values ± SD and were evaluated with analyses of variance using treatment group and study site as factors. For those variables that were measured once a day, a time factor (first and second 24 h of treatment) was added in the analyses of variance. The same type of analysis was used for medication data, which were cumulated over 24-h periods and for the data collected every 4 h. Missing scores on the 4-h measures (< 5% of the total data) were replaced by the mean of the preceding and following measures, and the data were averaged over 24-h periods. Incidence data and categoric measures are summarized as frequencies and percentages and were analyzed using chi-squared analysis or Fisher's exact test, with study sites as strata. Statistical significance was fixed at $P < 0.05$, and Bonferroni's corrections were applied within each of the following groups of variables: (1) pain measures, (2) recovery parameters, (3) satisfaction measures, (4) medication data, and (5) side effects.

Evaluation of Costs

The costs for PCA and intramuscular therapy were calculated based on estimates of personnel time and drug and material requirements.

Labor Costs. Costs were assessed for the pharmacy, orderly, and nursing time. Only the pain management activities that differed for PCA and intramuscular treatment were considered. In other words, events unrelated to pain management (*e.g.*, bathing) and related events that were identical in the treatment arms (*e.g.*, pain measurement every 4 h) were ignored. Pharmacy (technician) times were assessed only for activities related to the different morphine preparations. An orderly cleaned each PCA pump after treatment and returned it to the postanesthesia care unit. Nurses had to instruct the PCA patients to use the pump (plus instruct them again in the postanesthesia care unit), record morphine use, set up and dismantle the PCA pump, replace cartridges as needed, administer regular intramuscular injections and rescue doses if necessary and verify their effect, and manage adverse events. Narcotic-control regulations require that a second nurse witness disposal of any morphine not used in a cartridge or in a morphine vial. The second nurse's time was included for these events. We added the time to find a second nurse (assumed to be at the nursing station) whenever there was a cartridge change or PCA pump program change and whenever a vial was not entirely used in the intramuscular group.

To assess nursing time, we did not time individual patient-specific events. Rather, the per-patient incidence of treatment-related events (*e.g.*, nausea) was noted and the activities associated with these events were timed and averaged. These times were then allocated to the event frequencies observed with the study patients. For example, any PCA patient who needed a second morphine cartridge was assigned an identical time for that event, and consequently any difference between patients in time associated with changing PCA cartridges was determined solely by the difference in frequency of that event for the patients in the study.

To determine times associated with treatment-related events, a comprehensive time-motion study was performed.[32,33] The activities related to PCA and intramuscular treatment were separated into their constituent tasks, which were then timed by the two research nurses after satisfactory interrater reliability was established. The timings were accomplished with ward nurses performing the activities at "normal" speeds††,[32,33] and the obtained values were averaged. These values were multiplied by the frequencies per patient to estimate the total time for each patient. In some cases, times related to rare events (*e.g.*, respiratory depression) had to be estimated or simulated by a sample of nurses with varying work experience on the unit.

Wages for the staff were estimated as the midpoint in the range of the pay scales in the Montreal area for 1996.

††Although nurses do not always perform their tasks at "normal" speeds, that is what is of interest for these purposes to prevent random effects between treatments from influencing results. Furthermore, under the opportunity cost theory in economics, if nurses are rushed, it is presumably because their time is at that moment more valuable than when they are not rushed. It reflects a higher productivity at that moment. Counting the time actually spent would undercount the cost of the time and bias the analysis.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/89/6/1377/396173/0000542-199812000-00015.pdf by guest on 20 April 2024

Because of the presumed importance of nurse timing, the wage varied from its midpoint ($25 Canadian) to the lower ($18 Canadian) and upper ($32 Canadian) values in the range.

Nonlabor Costs. The purchase ("sunk") costs of the PCA pumps were ignored, as were those relating to training and pump maintenance. Nonlabor costs were estimated by hospital acquisition costs. For PCA, these include the tubing ($9.70 Canadian) and morphine cartridge costs, which were assumed to be those in effect at the conclusion of a pump contract without purchase ($8.75 Canadian per cartridge). This was the lowest cost in the available range ($8.75 to $19.35 Canadian). For intramuscular injections, the nonlabor costs were the regular and rescue dose injections (each at $0.27 [drug + material]).

Sensitivity Analysis. Because most of the economic data were not sampled data but rather assigned data (as described), the economic evaluation was "deterministic" rather than "stochastic."[34] Consequently, it was not possible to submit cost estimates to meaningful statistical treatment (probability values and confidence intervals). To account for uncertainty, the economic evaluation included sensitivity analyses to determine whether changes in key assumptions affected the basic results.

Results

A total of 126 patients (63 PCA, 63 intramuscular) were enrolled in the study. One patient was excluded because of a severe allergic reaction to morphine that occurred in the postanesthesia care unit before the assigned PCA therapy was begun. Two other PCA patients were excluded after study completion: one had a painful pneumothorax that was diagnosed only on the third day after surgery; the other had a defective PCA pump.

Table 1. Patients' Demographic and Clinical Characteristics

	PCA Group (N = 60)	IM Group (N = 63)	*P*
Age (yr)	43 ± 5	43 ± 6	0.70
Body mass index (kg/m^2)	24.3 ± 3.5	25.1 ± 3.5	0.22
ASA physical status I/II/III	54/5/1	59/4/0	0.53
Duration of surgery (min)	95 ± 29	91 ± 29	0.36
Intraoperative opioid (mg)*	26 ± 8	25 ± 9	0.79
PACU time (min)	170 ± 52	168 ± 44	0.73
PACU morphine (mg)	14 ± 3	14 ± 2	0.16

Values are mean ± SD.

PACU = postanesthesia care unit; PCA = patient-controlled analgesia; IM = intramuscular.

* Morphine equivalents (mg).

Table 2. Reasons for Premature Treatment Discontinuation

	PCA Group (N = 60) (n)	IM Group (N = 63) (n)
Total number of patients	13	15
Reasons*		
Intractable side effects	10	7
Inadequate pain relief	1	4
Anxiety	0	2
Pump defect (memory)	2	NA
Protocol errors	1	2
iv line interstitial	1†	NA
Refusal of injection (no more pain)	NA	3

PCA = patient-controlled analgesia; IM = intramuscular; NA = not applicable.

* Some patients counted twice if treatment was interrupted for more than one reason.

† This patient had an infiltrated iv line 4 h before the end of the study, which was not replaced.

Table 1 summarizes demographic and clinical characteristics of the 123 other patients. No significant differences were found between the two treatment groups for any of these variables. Twenty-eight patients did not complete the 48-h study period (PCA, 13 of 60 *versus* intramuscular, 15 of 63 patients; $P = 0.77$). Reasons are outlined in table 2.

Efficacy

Pain levels at rest were low and comparable in the two treatment groups (fig. 1). The same was true for pain when patients changed position and walked. Comparable scores also were observed on the pain relief scale and the McGill Pain Questionnaire (table 3). Results of the power analysis[30] indicated that the lack of a significant difference on the VAS measures could not be attributed to insufficient sample size. As shown in table 3, the 1-β values exceeded 0.80 for all VAS measures except one.

Analysis of the postoperative recovery parameters revealed no significant differences between the PCA and intramuscular groups (table 4). The only exception was the time to sit in a chair without assistance, which was significantly longer in the PCA patients than in the intramuscular patients. Statistical power[31] was adequate for most of the recovery measures (see 1-β values in table 4).

Substantial interhospital differences were observed for some of the recuperation variables. Time to resumption of a solid diet differed by more than 30 h in the two hospitals (HD: 49 ± 13, n = 70; RV: 83 ± 28, n = 35; $P < 0.0001$). Interhospital differences were also noted in times to return of bowel function after surgery (HD:

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/89/6/1377/396173/0000542-199812000-00015.pdf by guest on 20 April 2024

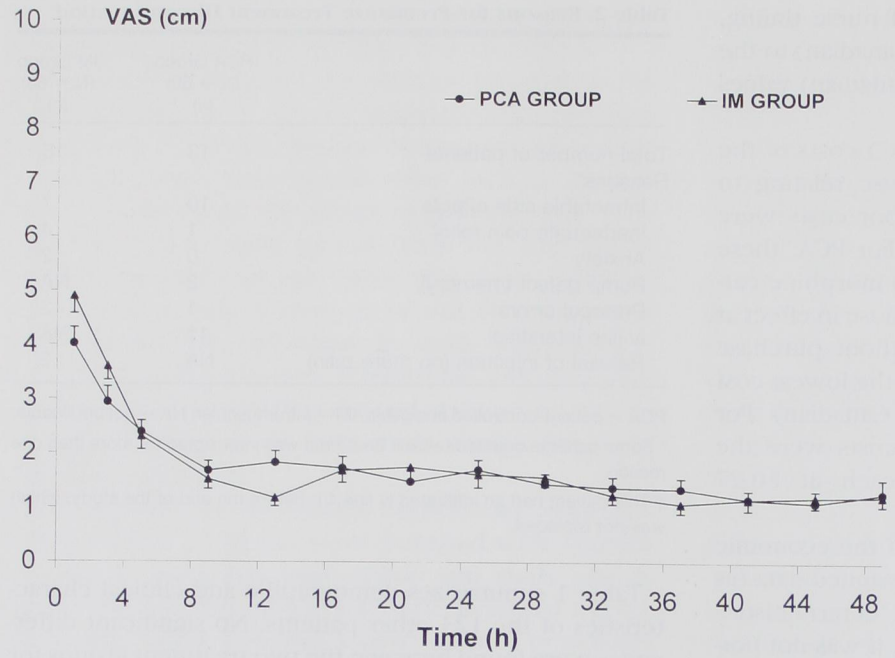

Fig. 1. Pain scores at rest in the patient-controlled analgesia and intramuscular groups during the study. Values are the mean ± SEM.

77 ± 30; RV: 57 ± 16 h; $P < 0.004$) and hospital discharge (HD: 7 ± 1; RV: 5 ± 1 days; $P < 0.0001$).

In terms of patient satisfaction, there was no difference between the PCA and intramuscular groups. Mean VAS ratings for the overall efficacy of the analgesic treatment were 8.7 ± 1.5 and 8.8 ± 1.5, respectively ($P = 0.79$). Ninety-four percent of the patients in the PCA group reported that they would certainly or probably choose the same analgesic method for hypothetical future surgery, compared with 83% in the intramuscular group ($P = 0.34$).

Patients in the intramuscular group (n = 48) received more morphine than did the patients in the PCA group (n = 47) during the 48-h study period (132 ± 37 *vs.* 93 ± 50 mg; $P < 0.0001$). None of the PCA patients required rescue medication, compared with 30% in the intramuscular group (14 of 47). Dose adjustments were necessary more frequently in the intramuscular group (63%) than in the PCA group (15%) ($P < 0.0001$).

Analgesic treatment for more than 10% of the study participants was discontinued because of intractable side effects (table 2). The distribution was similar in the PCA (10 of 60; 17%) and intramuscular groups (7 of 64; 11%) ($P = 0.37$). Table 5 shows the occurrence of side effects in all patients enrolled in the study (n = 123) and who needed medical treatment for adverse side effects. No difference was found between the two treatment groups, and median sedation levels also were comparable during the 48 h of the study (PCA: 0.8; range, 0–3; Intramuscular: 0.7; range, 0–3; $P = 0.51$).

Table 3. Mean Ratings Obtained on the Various Pain Measures in the PCA and IM Groups

	PCA Group (N = 51)	IM Group (N = 54)	*P*	95% CI of the Mean Difference	1-β
VAS pain scales					
At rest	1.8 ± 1.0	1.7 ± 1.1	0.73	(−0.4, 0.4)	0.94
When changing position	4.1 ± 2.4	3.7 ± 1.9	0.34	(−0.5, 1.2)	0.84
When walking	4.0 ± 2.5	2.9 ± 1.9	0.03 (NS)*	(−0.3, 2.1)	0.03
VAS pain relief scale	7.9 ± 1.4	8.3 ± 1.5	0.28	(−1.0, 0.1)	0.91
McGill Pain Questionnaire	21 ± 12	21 ± 13	0.89	(−4.7, 5.4)	—

PCA = patient-controlled analgesia; IM = intramuscular; CI = confidence interval.

* Bonferroni's corrected α level: 0.05/5 tests → *P* value = 0.01.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/89/6/1377/396173/0000542-199812000-00015.pdf by guest on 20 April 2024

Table 4. Postoperative Recovery Times in the PCA and IM Groups

	PCA Group (N = 51)	IM Group (N = 54)	*P*	95% CI of the Mean Difference	1-β
Sit with assistance (h)	20 ± 4	20 ± 3	.58	(−0.9, 2.0)	1.00
Sit without assistance (h)	43 ± 16	35 ± 11	.003	(3.7, 15.8)	0.99
Walk out the room (h)	53 ± 14	48 ± 15	.10	(−1.4, 10.7)	0.98
Oral fluids (h)	26 ± 8	23 ± 7	.06	(−0.4, 5.8)	1.00
Solid diet (h)	60 ± 20	61 ± 29	.69	(−11.5, 10.3)	0.68
Bowel gas (h)	70 ± 28	65 ± 25	.31	(−6.9, 15.9)	0.62
Hospital discharge (days)	6 ± 1	6 ± 1	.19	(−0.9, 0.1)	0.97

PCA = patient-controlled analgesia; IM = intramuscular; CI = confidence interval.

* Bonferroni's corrected α level: 0.05/5 tests → *P* value = 0.007.

Costs

Because comparable efficacy outcomes were observed with both treatments, the economic evaluation took the form of a cost-minimization analysis,[35] in which the analysis is solely of costs. A primary issue in any economic evaluation is what costs are to be counted. Because the hospital is the decision maker in the current case, its costs are of primary importance, and the cost-minimization analysis therefore was calculated from the perspective of the hospital.[36,37] The results of the analysis are presented in tables 6 and 7. All the calculations were made for 48 h of PCA or regular intramuscular therapy and included the patients in whom treatment was discontinued prematurely.

Table 6 indicates the mean-labor-time implications of each treatment. There are categories associated with normal nursing activities and those occurring on a patient-specific basis (*e.g.*, cartridge changes, adverse events treatment, dose changes). Such events are combinations of the time necessary to treat the event and the mean frequency of the event in each treatment group. Regular intramuscular dosing required more nursing time than did PCA.

Table 7 indicates the labor and nonlabor cost implications. Labor costs for nurses (and the total cost results) are reported for three different assumptions about nurse wages. In all cases, the intramuscular method was found to be a cost-saving treatment. Even if PCA treatment was limited to 24 h (because it could be argued that 48 h is not necessarily appropriate for all patients), this would still favor regularly scheduled intramuscular dosing because of the higher fixed costs of PCA.

Table 5. Patients in the PCA and IM Groups Who Required Medical Treatment for Adverse Side Effects

	PCA Group (N = 60) [n (%)]	IM Group (N = 63) [n (%)]	*P*
Nausea/vomiting	45 (75)	40 (64)	0.17
Pruritus	25 (42)	21 (33)	0.34
Urinary retention	8 (13)	14 (22)	0.20
Respiratory depression	4 (7)	1 (2)	0.15

PCA = patient-controlled analgesia; IM = intramuscular.

Dosage changes were the only variable in the study with a significant difference between PCA and intramuscular treatment. The cost implications of such changes were asymmetric. Although dose changes were more frequent in the intramuscular group, the time associated with those changes was minimal (table 6). For PCA, the implications for nursing time were more significant, because the pump program needed to be changed and confirmed, which required an extra nurse for confirmation, finding the extra nurse, and so forth. As a result, the mean time associated with dose changes for PCA and intramuscular treatments were similar, despite the different frequencies of dose changes between treatment groups. The total expected time associated with rescue doses and dose changes in the intramuscular group was 259 s, whereas in the PCA group it was 75 s (a difference of approximately 3 min). Thus, the only significant difference in frequency of events has a minimal influence on any cost differential.

Because nursing time was an important parameter, it was subjected to sensitivity analysis.[34] Additional time to find the narcotics key and to gather materials for injections was allowed. This was done by varying the walking-time assumption to and from patient rooms so it affected the times for all activities that required extra nurse visits to patients. Only by increasing the time to more than 300% of baseline did PCA total costs equal total costs with intramuscular injections, and this was achieved only with the accompanying extreme assump-

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/89/6/1377/396173/0000542-199812000-00015.pdf by guest on 20 April 2024

Table 6. Personnel Times for 48 h of PCA and Regular IM Treatment

Personnel Time Category	PCA Time (s)	Reg IM Time (s)
Nurse time category		
1. Instruct patient	544	360
2. Reinstruct (postop)	48	0
3. Get pump	30	0
4. Record, etc.	715	0
5. Set up pump	384	0
6. Dismantle pump	424	0
7. Extra cartridge	300	0
8. Regular IM injections	0	4,029
9. Verify IM efficacy	0	112
10. Pick up narcotics	28	18
11. Respiratory problems	372	366
12. Nausea	607	587
13. 2nd iv	63	0
14. Occlusion	225	0
15. iv infiltration	21	0
16. Reinstruct (pain ≥ 4)	30	0
17. Pruritis	269	225
18. Recatheterization	190	278
19. Dose increases	57	64
20. Dose decreases	18	45
21. Rescue doses	0	150
22. Treatment discontinued*	440	388
Total nursing time	4,765 (79.4 min)	6,622 (110.4 min)
Pharmacy technician time	149 (2.5 min)	107 (1.8 min)
Orderly time	780 (13 min)	0 (0 min)

IM = intramuscular.

* This category corresponds to the mean time associated with patients who had their PCA or IM treatment discontinued prematurely.

tion that only nurses commanding the highest wage were used.

Several other sensitivity analyses were performed by changing assumptions that would intentionally bias the analysis against intramuscular therapy in an extreme manner. This was done by reducing to minimum values (and to 0 when applicable) all the cost categories that were unique to PCA (*e.g.*, pump set up, intravenous infiltration; see table 6). These results again favored intramuscular therapy for all assumptions except in the extreme, artificial situation in which all the nurses on the ward would be paid at the highest wage rate. In such a case, the cost difference shifted to favor PCA therapy by $1.92 (Canadian). In the more realistic situation in which there would be a mix of nurse wages in the ward, the results of this exercise stacked against intramuscular injection still favored this mode of treatment.

Discussion

The current study is the first to show that regularly administered intramuscular injections of morphine coupled with frequent pain evaluation and adequate dose adjustments can provide analgesia comparable to PCA after hysterectomy. The lack of difference between the two treatments groups was not caused by insufficient statistical power, and, contrary to most previous trials, the current study measured pain at rest and with movement.

When we consider the multiplicity of studies that established the analgesic superiority of PCA, the results of the current trial may appear surprising. However, most

Table 7. Costs ($ Canadian) Associated with 48 h of PCA and Regular IM Treatment

	PCA	Reg IM
Labor costs		
Nurse		
$25/h	$33.09	$45.99
$32/h	$42.36	$58.86
$18/h	$23.83	$33.11
Pharmacy technician $14.99/h	$0.62	$0.45
Orderly $14.77/h	$3.20	0
Total labor		
$25/h	$36.91	$46.43
$32/h	$46.18	$59.31
$18/h	$27.65	$33.56
Nonlabor costs		
Number of cartridge	1.468	0
Number of (material + vials)	0	11.6
Drug	$22.55	$3.13
Respiratory problems	$0.82	$0.11
Nausea	$4.89	$4.79
Occlusion	$0.08	0
Intravenous infiltration	$0.12	0
Pruritis	$1.32	$1.17
Recatheterization	$1.68	$2.46
Rescue doses	0	$0.11
Treatment discontinued*	$1.09	$0.73
Total nonlabor	$32.54	$12.50
Total costs		
$25/h	$69.46	$58.93†
$32/h	$78.72	$71.81†
$18/h	$60.19	$46.06†

PCA = patient-controlled analgesia; IM = intramuscular.

* This category corresponds to the mean time associated with patients who had their PCA or IM treatment discontinued prematurely.

† Less expensive alternative.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/89/6/1377/396173/0000542-199812000-00015.pdf by guest on 20 April 2024

of these studies compared PCA with on-demand intramuscular dosing,[7,11,38,39] whereas a regularly scheduled mode of administration was used in the current study. Furthermore, the doses of the intramuscular injections were adjusted to meet the patients' specific needs, an extremely important factor in the success of any analgesic therapy.[1,14,18] As a result, dose changes were more frequent in the intramuscular group than in the PCA group.

In terms of medication intake, the PCA patients received less morphine than did the patients in the intramuscular injection groups. Several research and clinical reports[1,5,40–42] indicate that patients using PCA rarely medicate themselves to complete relief. Less-than-optimal analgesia can be observed with PCA simply because patients prefer pain rather than drug side effects. Adequate patient instruction obviously is not the only solution to this problem. More aggressive strategies to treat and even prevent opioid side effects (*e.g.*, prophylactic antiemetic therapy) must also be implemented; this is true regardless of the type of opioid regimen used.

We did not find that PCA improves postoperative recovery or that it reduces the duration of hospital stay. If faster recuperation is indeed related to superior analgesia, the current results are not surprising because both treatment methods were equally effective for controlling pain. However, it is also possible that treatment group differences were obscured by important variations in surgical practice patterns, as suggested by the significant interhospital differences on several recovery parameters. As noted by several authors,[17,23,43] measures such as times to resumption to solid diet, first ambulation, and hospital discharge may depend not only on the patient's rate of recovery, but also on factors such as surgeon practices, hospital discharge policies, social conditions, and geographic realities.

Criteria other than efficient pain relief must be considered when judging an analgesic method, and patient satisfaction is certainly important.[4,44] In the current study, patient satisfaction with PCA or intramuscular therapy was comparable. As noted by Brown,[45] the evidence to support better patient satisfaction with PCA is not strong in the literature. We cannot deny that patient acceptability is high for PCA. However, patients can be as satisfied with the pain relief provided by regular intramuscular administration of opioids. It is tempting to speculate that patient satisfaction could even be enhanced if the intramuscular injections were replaced by subcutaneous injections administered through a winged infusion set, thereby preventing the pain associated with subsequent intramuscular injections.

It is often argued that intramuscular dosing cannot provide adequate analgesia for the pain associated with activities (incident pain) without imposing excessive doses of medication and the resulting side effects during periods of rest.[16] In the current study, the incidence of side effects was comparable in the PCA and intramuscular groups, and the two treatment methods were equally effective for controlling the incident pain.

In summary, regular administration of opioids coupled with frequent pain evaluation and dosing flexibility can provide as good an analgesia as PCA after hysterectomy. Although the results need to be replicated with other types of surgery, PCA does not appear to have clinical advantages in terms of patient satisfaction, the side-effect profile, or the rate of postoperative recovery after hysterectomy. The intramuscular therapy necessitates more dose adjustments than PCA, and this may be viewed as a drawback. However, by making dose changes part of a standardized prescription of the intramuscular therapy, the procedure can be made considerably easier.

Our study suggests that relative cost is another important argument in favor of regular intramuscular therapy after hysterectomy. Fixed intramuscular dosing required more nursing time than PCA, but overall costs were lower. Cost differences in nursing time favoring PCA were offset by drug and material costs associated with this type of treatment, even though the costs of the pumps themselves were counted as zero. Because the analysis was predicated on the pumps already owned by hospitals, ignoring purchase price (a nonrecoverable, "sunk" cost) was appropriate.[36,37] For a similar model, in which the purchase of such pumps is being considered for this indication, the results would be even more favorable for intramuscular injection, because the purchase (and training) costs would need to be added to the other costs of using PCA. Even if these pumps were already owned by the hospitals, it does not appear as if they should be used in this indication area unless institutional environments are significantly different (favoring intramuscular) or unless the very mild preference exhibited by patients for PCA as a hypothetical retreatment option (93% compared with 83% for the intramuscular group) can be translated into a definitive magnitude that overwhelms the cost advantage of intramuscular injection. Based on previous observations,[20,45,46] this is doubtful, but further research may be useful.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/89/6/1377/396173/0000542-199812000-00015.pdf by guest on 20 April 2024

The economic analysis emphasized nursing time costs. Smythe *et al.*[24] found increased nursing time for PCA, but they concluded, mistakenly, that because nursing time differences would not affect staffing, their costs could be ignored. We do not assume that time savings implies fewer personnel and therefore cost savings. If so, saving less than a person-shift would appear as no savings. However, the notion that "unless we . . . discharge the nurse with the patient, savings may be impossible to achieve"[17] is false. We appeal to the standard notion in economic theory of "opportunity cost," in which it is assumed that personnel have alternative uses for their time at any moment and that saving time in performing one task frees time for others. This savings is not "theoretical"; rather it is productivity enhancement and should be valued at the cost of labor.

For regularly administered intramuscular therapy, nursing time obviously was expected to be an important contributor to total costs. It was also important in PCA, although, for all assumptions, intramuscular required more nursing time. In all cases in which events were common to both PCA and regular intramuscular injections (as opposed to events that were unique to either treatment, such as setting up the PCA pump or giving rescue doses in the intramuscular group), mean differences in nursing time between treatment groups were minimal (< 60 s for all event categories except one; see table 6). Consequently, any errors in timing estimates in such categories would have little effect on cost differences because the errors would appear in both treatment arms and readjustment to more precise numbers would still net out to a small difference. Further tests of the sensitivity of the results to errors in timing estimates were made by decreasing several PCA-related events to minimum values. In no case, even with these extremely PCA-favorable assumptions, did PCA have any important economic advantage.

Although the observed cost differences between the two treatments were not large, it would be a mistake to ignore them, because in fact "small-ticket" items frequently have large financial implications precisely because they are easily ignored.[47] More importantly, if PCA is no more effective than regular intramuscular injections, the incremental cost-effectiveness ratio for PCA is infinite,[48] and therefore, according to all economic methodologic arguments, it is a clearly undesirable alternative—one is paying extra for something that is no better. In this cost-conscious environment, there are interventions that provide a positive benefit that are not used because the added benefits do not justify the added costs. It is therefore particularly difficult to justify an intervention that is more costly and only equally effective.

Perhaps many positive opinions about PCA costs are based on overly simplistic notions of what is necessary with PCA treatment. For example, Jones and Brooks[49] stated that, "all the nurses needed to do for the PCA patients was attach the filled device, check the approximate morphine usage every shift, and then discontinue it after three days." As Ready[50] suggested, however, "There is a widespread misconception that pain relief with PCA is completely automatic. In fact, PCA can only be used optimally when it is accompanied by regular, expert nursing and medical supervision." The current study indicates that PCA treatment costs are more complex than commonly thought.

The economic or clinical results do not exclude that PCA may be a superior alternative in other types of patients (*e.g.*, where longer-duration treatment is necessary so high PCA fixed costs are diluted by time). As noted before, the conclusions are limited to patients undergoing hysterectomy. However, issues having a broader reach are raised. Economic evaluations rarely show that a reasonably effective intervention is never or always cost-effective. Rather, for particular types of patients (risk groups), many efficacious interventions also may be cost-effective. For other patients it may never be so. Perhaps PCA should be targeted specifically to patients expected to do poorly with regularly administered intramuscular injections, as its originators intended it to be used.[17] In such patients, it may be both less costly and more effective. To say that fixed intramuscular dosing of opioids is an efficacious analgesic regimen at low costs does not mean that it is a panacea. As is the case for any other analgesic regimen, some techniques (or route of administration) are better suited to certain patients than others. A fruitful area of research would be to identify patient characteristics that best match a particular analgesic method.

The authors thank Hélène Lanctôt, B.Sc, R.N., and Lucie Beauregard, B.Sc, R.N., for assistance during this study; the nursing staff, the gynecologists, and the anesthetists of the Hôtel-Dieu and Royal Victoria Hospital for their collaboration; M. Marc Dumont, who conducted the statistical analyses; Jocelyne Fortin for secretarial work; and Minogue Medical Inc. (Montreal, Quebec, Canada) and David Bull Laboratories (Montreal, Quebec, Canada), which provided the PCA pumps and the prefilled cartridges for the study.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/89/6/1377/396173/0000542-199812000-00015.pdf by guest on 20 April 2024

References

1. Lehmann KA: New developments in patient-controlled postoperative analgesia. Ann Med 1995; 27:271–82

2. Owen H, Mather LE, Rowley K: The development and clinical use of patient-controlled analgesia. Anaesth Intens Care 1988; 16:437–47

3. Smythe M: Patient-controlled analgesia: A review. Pharmacotherapy 1992; 12:132–43

4. Egen KJ, Ready LB: Patient satisfaction with intravenous PCA or epidural morphine. Can J Anaesth 1994; 41:6–11

5. Jamison RN, Taft K, O'Hara JP, Ferrante FM: Psychosocial and pharmacologic predictors of satisfaction with intravenous patient-controlled analgesia. Anesth Analg 1993; 77:121–5

6. Ready LB: Acute and postoperative pain services. Pain Digest 1991; 1:17–21

7. Wasylak TJ, Abbott FV, English MJM, Jeans M-E: Reduction of post-operative morbidity following patient-controlled morphine. Can J Anaesth 1990; 37:726–31

8. Bennett RL, Batenhorst RL, Foster TS, Griffen WO, Wright BD: Postoperative pulmonary function with patient-controlled analgesia. Anesth Analg 1982; 61:171

9. Bollish SJ, Collins CL, Kirking DM, Bartlett RH: Efficacy of patient-controlled versus conventional analgesia for postoperative pain. Clin Pharm 1985; 4:48–52

10. Lange MP, Dahn MS, Jacobs LA: Patient-controlled analgesia versus intermittent analgesia dosing. Heart Lung 1988; 17:495–8

11. Thomas V, Heath M, Rose D, Flory P: Psychological characteristics and the effectiveness of patient-controlled analgesia. Br J Anaesth 1995; 74:271–6

12. Boulanger A, Choinière M, Roy D, Bouré B, Chartrand D, Choquette R, Rousseau P: Comparison between patient-controlled analgesia and intra-muscular meperidine after thoracotomy. Can J Anaesth 1993; 40:1–7

13. Ballantyne JC, Carr DB, Chalmers TC, Dear KBG, Angelillo IF, Mosteller F: Postoperative patient-controlled analgesia: Meta-analyses of initial randomized control trials. J Clin Anesth 1993; 5:182–93

14. Mitchell RWD, Smith G: The control of acute postoperative pain. Br J Anaesth 1989; 63:147–58

15. Oden RV: Acute postoperative pain: Incidence, severity, and the etiology of inadequate treatment. Anesthesiol Clin North Am 1989; 7:1–17

16. Ready LB: Postoperative pain management-beyond basics (letter). Can J Anaesth 1996; 43:193–4

17. Moote CA: Postoperative pain management—back to basics (editorial). Can J Anaesth 1995; 42:453–7

18. Rawal N, Berggren L: Organization of acute pain services: A low-cost model. Pain 1994; 57:117–23

19. Albert JM, Talbott TM: Patient-controlled analgesia vs. conventional intramuscular analgesia following colon surgery. Dis Colon Rectum 1988; 31:83–6

20. Cohen SE, Subak LL, Brose WG, Halpern J: Analgesia after cesarean delivery: Patient evaluations and costs of five opioid techniques. Reg Anesth 1991; 16:141–9

21. Rayburn WF, Geranis BJ, Ramedei CA, Woods R, Patil KD: Patient-controlled analgesia for post-cesarean section pain. Obstet Gynecol 1988; 72:136–40

22. Chan VWS, Chung F, McQuestion M, Gomez M: Impact of patient-controlled analgesia on required nursing time and duration of postoperative recovery. Reg Anesth 1995; 20:506–14

23. Colwell CW Jr, Morris BA: Patient-controlled analgesia compared with intramuscular injection of analgesics for the management of pain after an orthopaedic procedure. J Bone Joint Surg Am 1995; 77:726–33

24. Smythe M, Loughlin K, Schad RF, Lucarotti RL: Patient-controlled analgesia versus intramuscular analgesic therapy. Am J Hosp Pharm 1994; 51:1433–40

25. Ready LB, Oden R, Chadwick HS, Benedetti C, Rooke GA, Caplan R, Wild LM: Development of an anesthesiology-based postoperative pain management service. ANESTHESIOLOGY 1988; 68:100–6

26. Rosaeg OP, Lindsay MP: Epidural opioid analgesia after Caesarean section: A comparison of patient-controlled analgesia with meperidine and single bolus injection of morphine. Can J Anaesth 1994; 41:1063–8

27. DeFede JP, Dhanens BE, Keltner NL: Cost benefits of patient-controlled analgesia. Nursing Management 1989; 20:34–5

28. Choinière M, Amsel R: A visual analogue thermometer for measuring pain intensity. J Pain Symptom Manage 1996; 11:299–311

29. Melzack R: The McGill pain questionnaire: Major properties and scoring methods. Pain 1975; 1:277–99

30. Kirshner B: Methodological standards for assessing therapeutic equivalence. J Clin Epidemiol 1991; 8:839–49

31. Cohen J: The concept of power analysis, Statistical Power Analysis for the Behavioral Sciences. Edited by Cohen J. New York, Academy Press, 1988, pp 1–17

32. Lindler CA: Work measurement and nursing time standards. Nurs Manage 1989; 20:44–9

33. Wirth P, Kahn L, Perroff GT: Comparability of two methods of time and motion study used in a clinical setting: Work sampling and continuous observation. Med Care 1977; 15:953–60

34. O'Brien BJ, Drummond MF, Labelle RJ, Willan A: In search of power and significance: Issues in the design and analysis of stochastic cost-effectiveness studies in health care. Med Care 1994; 32:150–63

35. Drummond MF, Stoddart GL, Torrance GW: Basic types of economic evaluation, Methods for the Economic Evaluation of Health Care Programmes. Edited by Drummond MF, Stoddart GL, Torrance GW. Oxford, Oxford University Press, 1987, pp 5–17

36. Dranove D: Measuring costs, Valuing Health Care. Edited by Sloan FA. Cambridge, Cambridge University Press, 1995, pp 61–75

37. Finkler SA: Costing for nonroutine decisions, Cost Accounting for Health Care Organizations. Concepts and Applications. Edited by Finkler SA. Gaithersburg, Aspen Publishers, 1994, 229–39

38. Hecker BR, Albert L: Patient-controlled analgesia: A randomized, prospective comparison between two commercially available PCA pumps and conventional analgesic therapy for postoperative pain. Pain 1988; 35:115–20

39. Passchier J, Rupreht J, Koenders MEF, Olree M, Luitwieler RL, Bonke B: Patient-controlled analgesia (PCA) leads to more postoperative pain relief, but also to more fatigue and less vigour. Acta Anaesthesiol Scand 1993; 37:659–63

40. Eisenach JC, Grice SC, Dewan DM: Patient-controlled analgesia following cesarean section: a comparison with epidural and intramuscular narcotics. ANESTHESIOLOGY 1988; 68:444–8

41. Harrison DM, Sinatra R, Morgese L, Chung JH: Epidural narcotic and patient-controlled for post-cesarean section pain relief. ANESTHESIOLOGY 1988; 68:454–7

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/89/6/1377/396173/0000542-199812000-00015.pdf by guest on 20 April 2024

42. Vickers MD: Clinical trials of analgesic drugs, Patient-Controlled Analgesia. Edited by Harmer M, Rosen M, Vickers MD. London, Blackwell Scientific, 1985, pp 42–50

43. Liu SS, Carpenter RL, Mackey DC, Thirlby RC, Rupp SM, Shine TSJ, Feinglass NG, Metzger PP, Fulmer JT, Smith SL: Effects of perioperative analgesic technique on rate of recovery after colon surgery. ANESTHESIOLOGY 1995; 83:757–65

44. Sandler AN, Katz J: Postoperative analgesia and patient satisfaction (editorial). Can J Anaesth 1994; 41:1–5

45. Brown BW Jr: Meta-analysis and patient-controlled analgesia (editorial). J Clin Anesth 1993; 5:179–81

46. Smith CV, Rayburn WF, Karaiskakis PT, Morton RD, Norvell MJ: Comparison of patient-controlled analgesia and epidural morphine for postcesarean pain and recovery. J Reprod Med 1991; 36:430–4

47. Neuhauser D, Lewicki AM: What do we gain from the sixth stool guaiac? N Engl J Med 1975; 293:226–8

48. Rittenhouse BE: Designing and conducting cost-minimization and cost-effectiveness analyses, Quality of Life and Pharmacoeconomics in Clinical Trials. 2nd ed. Edited by Spilker B. Philadelphia, Lippincott-Raven Publishers, 1996, pp 1093–103

49. Jones L, Brooks J: The ABCs of PCA. RN 1990; May:54–64

50. Ready LB: Patient-controlled analgesia—does it provide more than comfort (editorial)? Can J Anaesth 1990; 37:719–21

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/89/6/1377/396173/0000542-199812000-00015.pdf by guest on 20 April 2024