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Anesthesiology
69:428-432, 1988

Patient-controlled Analgesia: A Comparison of Intravenous Versus Subcutaneous Hydromorphone

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Patient controlled analgesia (PCA) allows patients to self-administer small doses of analgesic medications as necessary to control postoperative pain. This technique has the advantage of allowing for interpatient variability in analgesic requirements, while minimizing the delay between the perception of pain and its relief.¹ In addition, anxiety may be decreased by providing patients with immediate access to pain-relieving medication and a measure of control over their medical care.² The efficacy of the technique has been well-established for the commonly used opioid analgesics, morphine, and meperidine.³⁻¹³ Hydromorphone hydrochloride (Dilaudid®) is a narcotic analgesic that is approximately six to seven times more potent than morphine.¹⁴ It has a pharmacokinetic (*e.g.*, elimination half-life of 2-4 h) and pharmacodynamic profile (*e.g.*, duration of analgesia of 3-6 h), which would suggest that it could be a useful alternative to morphine and meperidine by the PCA route of administration.¹⁴⁻¹⁷

A potential disadvantage of conventional PCA therapy is the requirement for intravenous (iv) access, thus limiting its use in patients with difficult iv access, as well as for patients undergoing operations on an ambulatory (outpatient) basis. The subcutaneous (SQ) administra-

tion of narcotic analgesics, either by bolus injection or continuous infusion, can produce effective pain relief after surgery.¹⁵⁻¹⁸ If safe and effective, SQ-PCA may offer the advantages of PCA therapy to a wider spectrum of patients. The objective of this study was to compare the efficacy of SQ-PCA to conventional iv-PCA for providing postoperative pain relief.

MATERIALS AND METHODS

Thirty ASA physical status I-III patients, who were scheduled for elective abdominal or extremity surgery, participated in the study after giving their informed consent. The study protocol was approved by the Committee for the Protection of Human Subjects at Stanford University. Patients were randomly assigned to receive either iv or SQ-PCA, and were instructed in the use of the Abbott Lifecare® PCA infuser prior to their surgical procedure. All patients received general anesthesia; however, the anesthetic and analgesic drugs administered were at the discretion of the attending anesthesiologists.

When the patient began to complain of pain in the Post-Anesthesia Care Unit (PACU), hydromorphone, 0.2 mg iv, was administered every 5 min by the PACU nurse until the patient was no longer experiencing dis-

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Received from the Department of Anesthesia, Stanford University, Stanford, California. Accepted for publication April 20, 1988. Presented at the American Society of Anesthesiologists Annual Meeting, Atlanta, Georgia, October, 1987.

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Key words: Analgesic, narcotic: hydromorphone. Analgesic techniques: patient-controlled analgesia (PCA). Pain: postoperative.

TABLE 1. Demographic Data for the Two Study Groups

	iv	SQ
Number (N)	15	15
Age (years)*	52 ± 15	44 ± 15
Weight (kg)*	73 ± 14	73 ± 18
Gender (F/M)	9/6	9/6
Hydromorphone loading dose (mg)*	0.52 ± 0.62	0.56 ± 0.36

* Mean values ± SD.

trekking pain. Depending on the patient's group assignment, the PCA infuser was then attached to either the indwelling iv or to a 20-gauge catheter placed in the subcutaneous tissue on the medial aspect of the forearm. Patients were reminded of the instructions for use of the PCA infuser and allowed to self-administer hydromorphone for the duration of their PACU stay and while on the postoperative ward. Patients receiving iv-PCA used a 0.2-mg/ml solution of hydromorphone with an initial unit dose (the bolus dose administered on demand) of 1.0 ml and a lockout interval (minimum time between successive doses) of 10 min. Patients receiving SQ-PCA used a 1.0-mg/ml solution of hydromorphone with an initial unit dose of 0.2 ml and a lockout interval of 15 min. The more concentrated solution and smaller unit dose volumes were chosen to minimize the fluid volume administered at the SQ site. The bolus dose of analgesic medication was monitored and adjusted (*i.e.*, increased or decreased in increments of 50–100% of the initial dose) throughout the study to allow individual patients to achieve optimal analgesia with minimal sedation.

The patient's hydromorphone requirement was recorded in the PACU and at 4-h intervals during the first 48 h after the operation on the post-surgical ward. Patients were asked to assess their postoperative analgesia at 4-h intervals using a five-point scale: 1 = severe pain, 2 = moderate pain, 3 = slight pain, 4 = moderately comfortable, and 5 = very comfortable. Upon completion of their PCA therapy, patients were given a questionnaire to assess the incidence of side effects and their overall satisfaction with the PCA technique.

Data were analyzed by Chi-square analysis, Student's *t* test, and multivariate repeated measures analysis using the Systat® statistical package, with *P* < 0.05 considered significant. In addition to statistical comparisons between the iv-PCA and SQ-PCA groups, we compared hydromorphone usage in patients undergoing peripheral and intraabdominal operations.

RESULTS

Demographic data for the 30 patients are shown in table 1. The two study groups were comparable with respect to age, weight, gender, surgical procedures, the type and amount of intraoperative narcotics, and the amount of hydromorphone required to produce initial pain relief in the PACU (*i.e.*, loading dose). All patients were able to achieve satisfactory analgesia by self-administering hydromorphone in the dose and lockout ranges provided for in the protocol. Furthermore, there were no significant differences between the two groups with respect to their postoperative analgesia scores (table 2).

TABLE 2. Average Pain Severity Scores (Mean Values \pm SEM) during the First (0–24 h) and Second (24–48 h) Postoperative Periods in the Two Study Groups*

Treatment group†	Day of Surgery			Postoperative Day 1				Postoperative Day 2			
	0–4 h	4–8 h	8–12 h	0–4 h	4–8 h	8–12 h	12–16 h	0–4 h	4–8 h	8–12 h	12–16 h
iv	3.4 \pm 0.8	3.9 \pm 0.6	4.1 \pm 0.7	3.9 \pm 0.9	4.0 \pm 0.9	4.4 \pm 0.5	4.5 \pm 0.6	4.5 \pm 0.5	4.6 \pm 0.4	4.6 \pm 0.4	4.8 \pm 0.4
SQ	3.5 \pm 0.6	4.0 \pm 1.0	4.3 \pm 0.5	4.3 \pm 0.2	4.1 \pm 0.6	4.4 \pm 0.5	4.6 \pm 0.5	4.6 \pm 0.5	4.4 \pm 0.5	4.3 \pm 0.6	4.8 \pm 0.4

*Pain scale: 1 = severe pain, 2 = moderate pain, 3 = slight pain, 4 = moderately comfortable, and 5 = very comfortable.
† No significant difference between the two treatment groups.

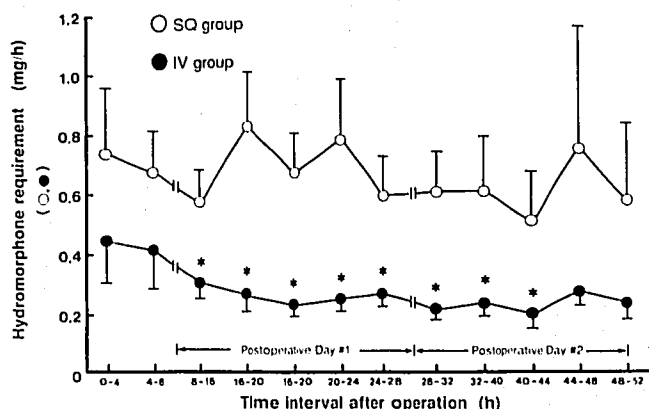


FIG. 1. Mean hourly hydromorphone requirement during the first 48 h after surgery (\pm SEM). Data points represent hourly requirement averaged for each of the 4-h observation periods. \bullet = iv-PCA group; \circ = SQ-PCA group. *Significant difference between treatment groups, $P < 0.05$.

The hydromorphone analgesic requirement and the frequency of bolus dose administration are summarized in figures 1 and 2, respectively. Patients receiving SQ-PCA had a significantly higher hydromorphone requirement than patients receiving iv-PCA (fig. 1). With SQ-PCA, the average hydromorphone requirement was 0.58 ± 0.36 and 0.57 ± 0.49 mg/h (mean \pm S.D.) for the first and second postoperative days, respectively, compared to 0.31 ± 0.21 and 0.21 ± 0.11 mg/h for the same time intervals with iv-PCA ($P < 0.01$). Although there was considerable interpatient variability, no significant changes in the hydromorphone requirement were noted for individual patients during the first 48 h after surgery in either study group. In addition, there were only minor differences between groups in the frequency of self-administered doses over the 48-h study

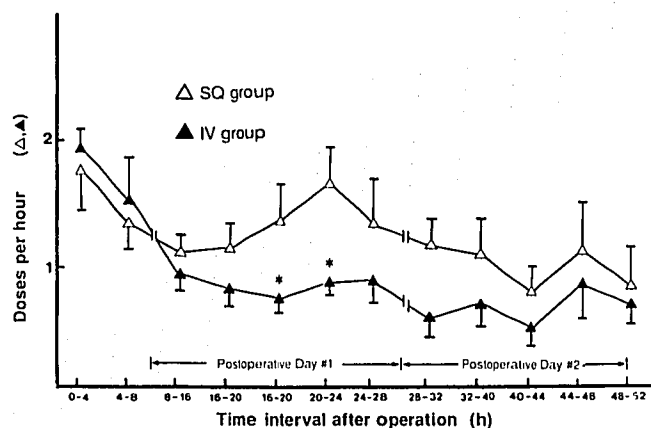


FIG. 2. Mean number of self-administered doses per hour during the 48-h study period (\pm SEM). Data points represent hourly doses averaged for each of the 4-h observation periods. \blacktriangle = iv-PCA; \triangle = SQ-PCA. *Significant difference between treatment groups, $P < 0.05$.

TABLE 3. Postoperative Hydromorphone Requirement (mg/h) during the First (0-24 h) and Second (24-48 h) Postoperative Periods

	Study group	Type of Operation		
		Peripheral Extremity	Lower Abdominal	Upper Abdominal
Number (N)	iv SQ	4 3	7 6	4 6
Usage 0-24 h*	iv SQ	0.23 (0.09) 0.47 (0.08)	0.34 (0.10) 0.53 (0.12)	0.34 (0.06) 0.69 (0.17)
Usage 24-48 h*	iv SQ	0.10 (0.02) 0.27 (0.05)	0.21 (0.04) 0.49 (0.16)	0.29 (0.06)† 0.83 (0.26)†

* Mean values (\pm SEM).

† Significant difference from the peripheral (extremity) group, $P < 0.05$.

period (fig. 2); however, the variability of both the hydromorphone dose requirement and the dosing frequency was higher in the SQ-PCA (versus iv-PCA) group.

The influence of the type of surgical procedure on the postoperative analgesic requirement is shown in table 3. As expected, patients undergoing more stressful procedures (e.g., upper abdominal surgery) required more hydromorphone than those undergoing superficial, peripheral procedures. The overall incidence of side effects reported during the 48-h study period is shown in table 4. No significant differences were found between the two study groups. However, patients complaining of pruritus had self-administered significantly more hydromorphone (0.67 ± 0.36 and 0.63 ± 0.6 mg/h for the first and second 24-h study periods, respectively) than patients who did not experience itching (0.35 ± 0.24 and 0.26 ± 0.15 mg/h, respectively). In contrast to pruritus, the incidences of sedation, dizziness, diplopia, nausea, and vomiting did not appear to be dose-related. Overall, SQ-PCA was well-tolerated by the patients without evidence of localized erythema, tenderness, or pruritus at the SQ injection site. No patient in either treatment group experienced clinically significant respiratory or hemodynamic depression.

Irrespective of the route of administration, patients were highly satisfied with PCA therapy. Twelve of 15 patients in the SQ group and ten of 15 patients in the iv group rated their overall pain control as "excellent." No patient rated it as less than "satisfactory," and all reported that they would choose to have PCA for postoperative pain relief in the future.

DISCUSSION

PCA is associated with good-to-excellent pain control and high patient acceptance when used for the treatment of postoperative pain.¹ Our results demonstrating the efficacy of PCA with hydromorphone are in agree-

ment with previous studies using morphine and meperidine.³⁻¹³ Analogous to previous PCA studies, patients in this study demonstrated wide variability in their individual analgesic requirements.^{1-11,18} This variability was related, in part, to the extent of the patient's surgical procedure.^{1,3,19}

This study was not designed to compare hydromorphone to other available opioid analgesics for PCA therapy. Indeed, the considerable interpatient variability and differences in study design make comparison of our results to studies with other analgesics of limited value. Nevertheless, the hydromorphone requirement for patients receiving iv-PCA was in close agreement with the equivalent dosage of morphine reported by other investigative groups.³⁻⁵ Assuming a potency ratio of 7:1, hourly requirement for iv hydromorphone in this study was equivalent to 2.2 and 1.5 mg/h of morphine during the first and second 24-h study periods, respectively. Bennett *et al.*⁵ reported a 2.4- and 1.5-mg/h average morphine requirement for the same time periods, while Tamsen *et al.*⁴ reported a mean morphine requirement of 2.7 mg/h during the first postoperative day. Previous studies at our institution have noted median hourly morphine requirements ranging from 1.1 to 2.6 mg/h during the first 48 h following major orthopedic or abdominal surgery.¹

Other investigators have demonstrated the efficacy of the SQ route of narcotic administration by either bolus injection or continuous infusion.¹⁴⁻¹⁷ Our study suggests that the administration of repeated small bolus doses of an opiate analgesic using a SQ-PCA delivery system is an effective approach to managing acute postoperative pain. Indeed, there was no difference in patients' rating of analgesia or overall satisfaction with their analgesic therapy between the iv-PCA and SQ-PCA treatment groups. All patients receiving SQ-PCA were able to achieve and maintain satisfactory postoperative analgesia with incremental hydromorphone dose volumes of 1 ml or less. The intermittent injection of this fluid volume into the SQ tissue was well-tolerated by all the SQ-PCA patients.

An unexpected finding was the significantly higher hydromorphone requirement during SQ-PCA (*versus* iv-PCA) therapy. The fact that the frequency of self-administered doses was similar for iv and SQ-PCA suggests that repeated administration of SQ hydromorphone did not produce a "depot" effect secondary to delayed absorption. The difference in narcotic dosage requirements in the two treatment groups may have been related to greater opioid bioavailability in the iv-PCA group, resulting in higher peak blood (and brain) hydromorphone concentrations. Unfortunately, pharmacokinetic data for the uptake of hydromorphone from the subcutaneous tissue are not available. A com-

TABLE 4. Overall Incidence of Postoperative Side Effects during the 48-h Study Period (%)

	iv	SQ	Overall
Sedation	20	27	23
Dizziness	13	27	20
Diplopia	0	20	10
Nausea	27	7	17
Vomiting	7	7	7
Pruritus	20	40	30
Hesitancy	7	13	10

No significant differences between the two treatment groups.

parison of minimum analgesic hydromorphone concentrations after iv and SQ administration would be necessary to determine if the observed difference between the two groups was due to pharmacokinetic or pharmacodynamic differences, or if it was simply an artifact due to the large interpatient variability and the relatively small number of patients in this study.

The ability to provide effective analgesia without intravenous or epidural access might allow more extensive surgical procedures to be performed on an ambulatory basis. The availability of a simplified parenteral analgesia delivery system could also lead to improved management of postoperative pain in the hospital setting. Although no problems were reported in this preliminary study, potential complications of SQ-PCA include pain secondary to the infiltration of opioid-containing fluid, the slow onset of analgesia and delayed respiratory depression secondary to decreased cutaneous blood flow, and infection at the injection site. Given the potential benefits of using a simplified approach to controlling postoperative pain, more in-depth studies involving larger numbers of patients are clearly needed.

In summary, PCA therapy with hydromorphone was highly effective for treating postoperative pain when administered by either the iv or SQ routes. SQ-PCA was associated with high patient acceptance and may offer advantages over conventional iv-PCA for patients in whom continuous iv access is either difficult or undesirable. Further studies evaluating the relative analgesic effectiveness and pharmacokinetic profiles for subcutaneously administered opioid analgesics of varying lipid solubility are needed to determine the optimal regimen for SQ-PCA.

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