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An Evaluation of Morphine and Oxymorphone Administered via *Patient-Controlled Analgesia (PCA) or PCA plus Basal Infusion in Postcesarean-Delivery Patients*

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The analgesic efficacy and adverse effects of morphine and oxymorphone in 32 patients who received traditional patient-controlled analgesia (PCA) following cesarean delivery were compared with those in 32 other patients receiving the same agents *via* PCA plus basal opioid infusion (PCA + BI). All patients were operated upon during epidural anesthesia with 2% lidocaine and 1:200,000 epinephrine to achieve a T4 sensory level. Upon first complaint of pain in the recovery room, patients were given a titrated iv loading dose of the assigned opioid until comfortable and were then provided with a programmable PCA device. Group I (PCA) consisted of two subsets in which incremental boluses of morphine (1.8 mg, n = 16) or oxymorphone (0.3 mg, n = 16) could be self-administered *via* conventional PCA. Patients in group II (PCA + BI) received a basal infusion of morphine (0.6 mg/hour, n = 16) or oxymorphone (0.1 mg/hour, n = 16) in addition to self-administered boluses of 1.8 and 0.3 mg, respectively. Patients were evaluated for 24 h following initiation of analgesic therapy, and 10-cm visual analog scales (VAS) were utilized at selected intervals to assess pain at rest, pain during movement, and satisfaction with therapy. The level of sedation and incidence of nausea/vomiting and pruritus were also recorded. Patients utilizing PCA + BI noted significant reductions in resting pain scores with oxymorphone and decreased pain during movement with both opioids when compared with individuals using PCA alone ($P < 0.05$). There were no significant differences between treatment groups in 24-h dose requirements or patient satisfaction with therapy (P = ns). The incidence of nausea was greatest in patients receiving PCA + BI oxymorphone, while level of sedation was highest in the morphine subsets ($P < 0.05$). We conclude that PCA + BI provides an effective form of intravenous analgesia in the postcesarean patient; however, further attempts to refine the technique and reduce the higher incidence of adverse effects are necessary. (Key words: Analgesics: morphine; oxymorphone. Anesthesia: obstetric. Pain: postoperative. Anesthetic techniques: patient-controlled analgesia; patient-controlled analgesia plus basal-opioid infusion.)

SEVERAL STUDIES have suggested that patient-controlled analgesia (PCA) provides superior postoperative pain relief and patient satisfaction than that associated with traditional pain therapy.[1,2] In controlled comparisons, however, the level of pain relief achieved with PCA has failed to reach that reported with epidural opioids,[3,4] and at times, it appears to be no better than that obtained with traditional parenteral therapy.[4] While reduction in overall effectiveness may be attributed in part to limitations of the opioid employed,[4–6] it more likely reflects reliance upon an awake and responsive patient for maintenance of adequate drug delivery.[7,8] In this regard, reductions in PCA dosing during sleep may result in subtherapeutic plasma levels upon awakening. Furthermore, patients may not effectively medicate themselves before unanticipated painful stimuli, such as coughing and movement. These deficiencies have prompted the addition of a basal infusion (BI) mode of opioid administration to further improve the uniformity of analgesia provided by conventional PCA. Although a number of programmable devices capable of combining PCA + BI have been developed and are actively marketed, little scientific information is presently available regarding optimal use and the overall merit of such therapy.[9,10]‡

We postulated that opioid analgesics commonly employed for PCA[1,2,5] would provide more effective postoperative pain relief without a greater incidence of adverse effects when administered *via* PCA plus a low-dose basal infusion (PCA + BI). One exception would be meperidine which has been restricted from use in continuous infusion or PCA + BI,§ as accumulation of its slowly eliminated metabolite, normeperidine, could predispose to overdosage and CNS toxicity.[11] We anticipated that the semisynthetic opioid oxymorphone would be particularly well-suited for this regimen, since it has been reported to provide rapid and effective analgesia with minimal sedation when self-administered by patients recovering from cesarean delivery[5] or general surgery.¶ The following randomized evaluation compared the analgesic effectiveness and incidence of adverse effects observed when oxymorphone and the more commonly utilized analgesic morphine were administered *via* traditional PCA or PCA + BI.

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‡ Ved SA, Dubois M, Lea D: PCA with sufentanil and alfentanil compared to morphine. Data presented at Georgetown University School of Medicine Acute Pain Service Seminar, September, 1988.

§ Callan C: Hospital Products Division, Abbott Laboratories, Abbott Park, Illinois, Personal Communication, May, 1988.

¶ Lampert BA, Sundstrom FD, Merrill J, Boyd-Long L: Oxymorphone in PCA. ANESTHESIOLOGY Review 15:35–39, 1988.

TABLE 1. PCA and PCA + BI Infusion Regimens

Subset	Agent	Basal Infusion ($mg \cdot h^{-1}$)	PCA Bolus Dose (mg)	Lockout Interval (min)	Max Number of Incremental Boluses/h*	Max Dose ($mg \cdot h^{-1}$)
I. PCA_{morph}	Morphine	0	1.8	8	6	10.8
II. PCA_{oxy}	Oxymorphone	0	0.3	8	6	1.8
III. PCA + BI_{morph}	Morphine	0.6	1.8	8	5	9.6
IV. PCA + BI_{oxy}	Oxymorphone	0.1	0.3	8	5	1.6

* Reductions in the maximum number of boluses/h reflects compensation for a potential increase in drug available to/or administered by patients in the PCA + BI subsets. During the study, no patient ever self-administered more than five boluses in a 1-h interval.

Materials and Methods

Following approval of the institutional Human Investigation Committee, written informed consent was obtained from 64 patients who had selected PCA for postoperative analgesia following elective cesarean delivery under continuous epidural anesthesia. Patients were free of any significant coexisting disease (ASA PS I or II) and had no history of substance abuse. All patients were instructed preoperatively in the use of a programmable PCA device (CADD-PCA®, Pharmacia-Deltec Inc.), and in the completion of both pain and satisfaction assessment scales. Intraoperative anesthesia was provided with 2% lidocaine plus epinephrine 1:200,000 in a volume sufficient to achieve a T_4 sensory level; this was supplemented as required with small increments of intravenous fentanyl (25–50 mcg) and/or diazepam (2.5 mg).

Patients were studied as two separate groups, each of which was randomized into two blinded subsets (table 1). The initial group consisted of two subsets that received opioids *via* PCA alone. Subset I received morphine sulfate (PCA_{morph}); subset II received oxymorphone hydrochloride (PCA_{oxy}). Results in this group prompted the evaluation of two additional subsets. Subsets in this second group received PCA plus a basal infusion of opioid at an hourly rate equivalent to one third of an incremental PCA bolus. Subset III received morphine (PCA + BI_{morph}), while subset IV received oxymorphone (PCA + BI_{oxy}). All study drugs were prepared by the investigational pharmacy and were delivered in unlabeled cassettes containing either morphine 1.5 mg/ml or oxymorphone 0.25 mg/ml. These formulations were reasoned to be equianalgesic as oxymorphone was found to be six times as potent as morphine in prior PCA studies.[5,¶]

As the epidural anesthetic resolved and patients first requested pain medication in the Postanesthetic Recovery Room (PAR), a 4-ml loading dose of either morphine (subsets I and III) or oxymorphone (subsets II and IV) was administered by an anesthesiologist who remained unaware of the opioid being used. The initial loading dose was supplemented with 1-ml increments of study drug solution as required. When adequate analgesia had been obtained (*i.e.*, patient reported that she was comfortable), the patient was connected *via* her iv catheter to the PCA infusion pump programmed for group assignment with respect to rate of basal infusion, incremental PCA dose, lockout interval, and maximum number of doses (table 1). Each patient otherwise received standard clinical care and was evaluated identically for the ensuing 24 h by one of four specially trained nurse observers.

Pain at rest and during movement was scored by the patient using a 10-cm visual analog scale (VAS): a score of 0 cm represented no pain, while 10 cm represented the worst pain imaginable. Pain at rest was scored upon arrival into the PAR, prior to initiation of the loading dose (first request for pain medication), and at 20 min (in the PAR), 2, 4, 8, 12, 16, 20, and 24 h (on the ward) following connection to the PCA pump. Pain during movement was evaluated at the 4-, 8-, 16-, and 24-h time periods, with VAS scores evaluated 5 min after the patient sat at the bedside and dangled her legs.

Patients also were asked to rate overall satisfaction with their analgesic regimen (on the ward at the same time pain at rest was assessed) using a modified VAS, where 0 cm indicated least satisfaction and 10 cm indicated highest satisfaction. Data collection also included the total amount of opioid administered, as well as the incidence of nausea/vomiting requiring treatment, pruritus, and significant respiratory depression (defined as a respiratory rate < 10/min). Sedation was assessed using the following four-point scale: (0) = alert, oriented, conversant; (1) = drowsy, oriented, conversant; (2) = drowsy, oriented, nonconversant; and (3) = very drowsy, disoriented, nonconversant.

Differences between subsets regarding patient demographics, pain, sedation, and satisfaction scores were assessed using analysis of covariance, with Tukey and unpaired *t* tests where appropriate. Differences in incidence of side effects were analyzed with chi-square tests. Data are expressed as mean ± standard deviation or percentage. A value of $P < 0.05$ was considered to be statistically significant.

Results

There were no significant differences among the four subsets with respect to demographic variables (table 2) or

TABLE 2. Demographics

Subset	% Previous C-Section	Age (yr)	Weight (kg)	Body Surface Area (M^2)
PCA_{morph}	0.69	30.1 ± 5.8	82.9 ± 12.9	1.72 ± 0.23
PCA_{oxy}	0.63	30.3 ± 2.9	77.4 ± 10.9	1.68 ± 0.15
$PCA + BI_{morph}$	0.63	29.8 ± 5.1	77.5 ± 12.0	1.67 ± 0.24
$PCA + BI_{oxy}$	0.69	31.3 ± 4.4	76.4 ± 9.9	1.59 ± 0.14

intraoperative anesthetic requirements; nor were there differences in VAS pain scores upon arrival into the PAR or at the time the loading dose was administered (fig. 1). There were no differences in amount of opioid administered (loading dose plus increments, table 3) or level of patient discomfort (as assessed by nurse observer) prior to initiating PCA. Although patients in the PCA subsets were allowed an additional incremental bolus (six boluses/h *versus* five in the PCA + BI subsets; table 1), no patient ever self-administered more than five boluses in an hour interval. All patients completed the study protocol without the need for additional (rescue) analgesics. Opioid dose requirements assessed at 12 and 24 h following initiation of PCA were similar for each subset (table 3).

With respect to resting pain (fig. 1), the addition of a basal infusion significantly reduced VAS pain scores in patients receiving oxymorphone ($P < 0.05$) but did not influence scores in the morphine subsets (P = ns). Resting pain scores in the PCA + BI_{oxy} subset were consistently less than 1.5 cm, and were significantly lower than scores noted in the PCA_{oxy} subset at 12-, 16-, and 24-h observation intervals ($P < 0.05$). Despite the fact that all patients were comfortable prior to initiating PCA, resting pain scores in both morphine subsets were higher than that observed with oxymorphone at the 20-min (PAR) and 2-h observation intervals ($P < 0.05$). This early superiority was not appreciated after 4 h, as pain scores in the morphine subsets were found to be comparable to that reported with PCA + BI_{oxy} and superior to PCA_{oxy}.

Movement-associated pain scores were significantly reduced in patients receiving PCA + BI (fig. 2). Reductions in VAS scores were noted at 8 and 16 h with morphine and at all observation intervals with oxymorphone when compared with that reported by patients utilizing PCA alone ($P < 0.05$).

With regard to adverse effects (table 4), a significantly higher incidence of nausea and vomiting ($P < 0.05$) was noted in the PCA + BI subsets. All cases of nausea and vomiting were successfully treated with small doses of droperidol (0.625 mg iv). Two patients in the PCA + BI_{oxy} subset experienced pruritus that was isolated to the face and neck and did not require treatment. The level of sedation, while not excessive in any treatment group, was highest in patients receiving morphine ($P < 0.05$). The addition of BI did not increase the level of sedation noted with either opioid (P = ns). Significant respiratory depression was not observed.

In all subsets, improvements in patient satisfaction paralleled reductions in pain scores at rest (fig. 3). Although higher satisfaction scores were noted in both oxymorphone subsets at early time intervals, high variability in VAS scores minimized differences between drugs or method of administration (P = ns).

Discussion

The addition of a continuous low-dose opioid infusion improved the analgesic effectiveness of conventional PCA and was not associated with increased sedation or evidence of significant respiratory depression. Such findings suggested a more efficient delivery and use of drug, and at the same time, reduced concerns that had been raised regarding risks of excessive drug delivery, increased somnolence, and major respiratory complications.[12,13]

McKenzie[12] correctly cautions that addition of a sizeable basal infusion (1–3 mg · h^{-1} of morphine) could compromise the intrinsic safety of PCA by maintaining opioid delivery in the overly sedated patient. For this reason, the present investigation employed a lower dose infusion

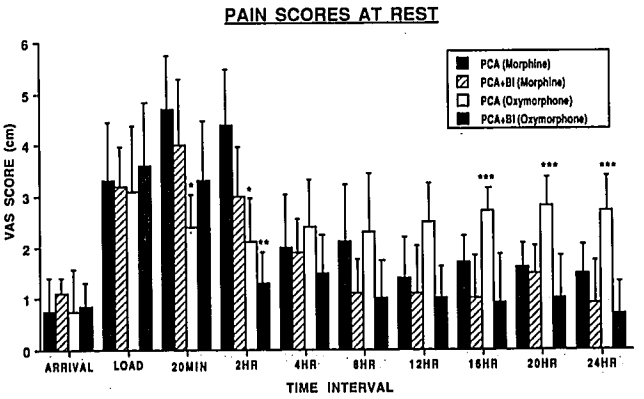

FIG. 1. Mean VAS scores (cm) reflecting pain at rest for patients receiving morphine or oxymorphone *via* PCA and PCA + BI. *Significant difference between PCA oxymorphone and PCA morphine. **Significant differences noted between PCA + BI oxymorphone and both PCA morphine and PCA + BI morphine ($P < 0.05$). ***Significant differences noted between PCA oxymorphone and PCA + BI oxymorphone, PCA + BI morphine, and PCA morphine ($P < 0.05$). Error bars reflect standard deviation.

TABLE 3. Opioid Requirements*

Subset	Opioid Administered (mgs) prior to PCA†	12-h dose (mgs)‡	24-h dose (mgs)‡
I. PCA_{morph}	7.2 ± 1.1	51.5 ± 12.7	87.45 ± 25.4
II. PCA_{oxy}	6.5 ± 0.3	57.3 ± 16.3	97.45 ± 28.3
III. PCA + BI_{morph}	7.5 ± 1.4	46.1 ± 12.3	79.32 ± 16.7
IV. PCA + BI_{oxy}	6.8 ± 0.8	45.5 ± 16.3	88.50 ± 21.6

* Opioid doses expressed as morphine equivalents (1 mg of oxymorphone equivalent to 6 mg of morphine[6,¶]). Values expressed as mean ± SD.

† Includes loading dose plus additional 1 ml increments of study drug required to achieve a subjective assessment of comfort.

‡ Includes opioid administered prior to initiating PCA.

than that utilized in preliminary evaluations of this combined form of analgesic therapy.[9,10] Despite the fact that patients utilizing PCA + BI continuously received either 0.1 mg oxymorphone or morphine 0.6 mg · h^{-1}, total drug administration noted at 12 and 24 h was comparable to amounts self-administered in the PCA groups. Mean hourly opioid requirements of 3.4 mg for morphine and 0.6 mg for oxymorphone were in close agreement with previously reported PCA potency ratios[5,¶] and dosages required to achieve minimum effective plasma concentrations.[14]

Patients recovering from cesarean delivery experience considerable incisional pain and uterine cramping during the first 24 postoperative hours.[4,15] The low pain scores especially during movement noted in both PCA + BI subsets represented the most consistent and effective level of parenteral analgesia we have observed in this setting, and suggested that the combination of PCA + BI is able to overcome deficiencies inherent in either continuous opioid infusions or PCA when each is used alone.[7,8] In this regard, continuous intravenous regimens provide superior pain relief than that following traditional IM dosing;[13,16] however, they have difficulty compensating for the well-known 2- to 3-fold differences in individual opioid requirements[2] and can predispose patients to underdosage or overdosage.[13] While PCA offers the psychologic benefit of increased control[1,2] and more effectively accommodates variations in pain thresholds, it nevertheless requires an awake patient to activate incremental boluses in order to avoid subtherapeutic plasma levels of opioid.

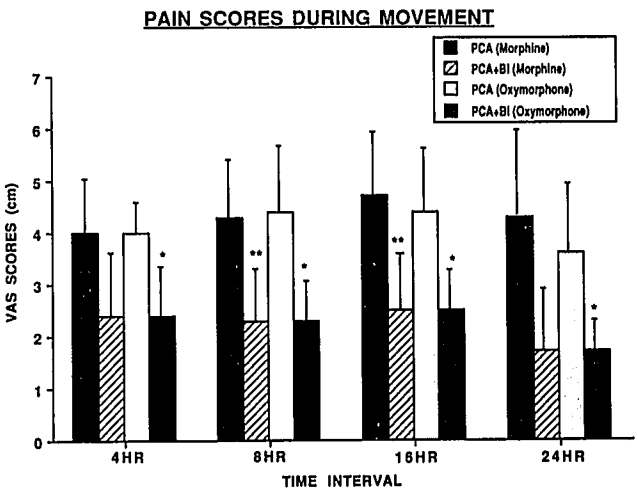

FIG. 2. Mean VAS scores (cm) reflecting pain scores during movement for patients receiving morphine or oxymorphone *via* PCA and PCA + BI. *Significant difference between PCA + BI oxymorphone and PCA oxymorphone ($P < 0.05$). **Significant difference between PCA + BI morphine and PCA morphine ($P < 0.05$). Error bars reflect standard deviation.

The potential benefits of combining PCA + BI were recently evaluated in postoperative[10,‡] and outpatient settings.[9] In their preliminary report, Ved *et al.*‡ noted that administration of the short-duration opioid alfentanil *via* PCA + BI reduced time to peak analgesic effect but did not lower resting VAS scores in patients recovering from abdominal surgery when compared with a similar group utilizing PCA alone. In our study, which employed opioids of longer duration, the addition of BI did not reduce time to peak effect or resting pain scores in the morphine subset. A similar lack of improvement was recently noted by Owen *et al.*,[10] who compared the effectiveness of morphine as administered *via* PCA or PCA + BI in patients recovering from gynecological surgery. It remains unclear why patients receiving oxymorphone *via* PCA + BI experienced significant improvements in resting pain when compared to PCA alone. The importance of this improvement was nevertheless minimized by the fact that scores were no better than those reported in the morphine subsets.

Patients self-administering oxymorphone did benefit from a superior level of analgesia during early observation intervals following initiation of PCA and experienced less overall sedation than either morphine subset. Morphine's latency in achieving peak analgesic effect with PCA has previously been described[5] and may be attributed to its hydrophilic properties that delay penetration across the blood-brain barrier.[17,18] In contrast, the higher lipid solubility[19] and binding affinity[20] of oxymorphone may facilitate both entry into CNS and activation of receptors. Thus, as the level of pain intensity increased (with further

TABLE 4. Side Effects

Subset	Pruritus*	Nausea requiring treatment*	Sedation score†
PCA_{morph}	1/16 (6.3%)	2/16 (12.5%)	0.9 ± 0.4
PCA_{oxy}	0/16 (0%)	3/16 (18.8%)	0.6 ± 0.3
$PCA + BI_{morph}$	0/16 (0%)	5/16 (31.3%)‡	0.9 ± 0.5
$PCA + BI_{oxy}$	2/16 (12.5%)	7/16 (43.5%)‡	0.2 ± 0.2§

* Data for pruritus and nausea presented as the number of patients reporting/total patients in the subset and percentage.

† Mean sedation scores over the 24-h study period ± standard deviation.

‡ Significantly greater than PCA_{morph}, ($P < 0.05$).

§ Significantly less than PCA_{morph} and $PCA + BI_{morph}$, ($P < 0.05$).

regression of the epidural anesthetic and increased patient activity during transfer to the ward), individuals self-administering oxymorphone appeared to catch up more quickly than those using morphine. In addition, an increased level of sedation noted with morphine was considered undesirable by the present patient population (as it compromised interactions with their newborn) and may have led to conscious reductions in early PCA dosing and subsequent increases in pain scores. The lower levels of drowziness noted with oxymorphone may be related to the fact that this semisynthetic opioid is a specific μ-receptor agonist[21] and, unlike morphine, is less likely to activate kappa receptors that mediate CNS sedation.[22]

A major test for any analgesic regimen is its ability to attenuate pain associated with movement. The significant reduction in movement-induced pain noted with PCA + BI may represent the most important finding of the present investigation and apparently reflects an ability of this form of therapy to minimize troughs in opioid plasma concentrations during periods of reduced self-administration.[7-9] While low doses of parenterally administered opioids may effectively blunt continuous (tonic) pain, higher plasma concentrations are required to attenuate intermittent sharp pain associated with activity or stimulation.[17] Thus, while sharp, movement-associated pain might be blunted by incremental PCA boluses administered prior to the attempt, lower opioid concentrations in patients who awaken from sleep or in individuals not anticipating movement may be less able to offset a sudden increase in pain stimulus. While not studied directly, we would anticipate that improvements noted with movement-associated pain may impact upon overall perioperative morbidity by facilitating coughing, deep breathing, and ambulation.

Benefits of improved postoperative analgesia were not achieved without cost, however, as PCA + BI was associated with a greater incidence of nausea and pruritus, especially in the $PCA + BI_{oxy}$ subset. While morphine is commonly associated with pruritus in the obstetrical population,[4] a higher percentage of patients complaining of pruritus was noted with $PCA + BI_{oxy}$. This finding was surprising since this agent has not been associated with significant histamine release in recent laboratory[23] and clinical[24] investigations. Fortunately, all cases of pruritus were mild in intensity and did not require treatment, and the nausea/vomiting was totally eliminated with 1–2 doses of antiemetic.

Overall, patient satisfaction paralleled improvements in resting pain scores; however, no significant differences were noted with respect to the agent used or mode of opioid delivery. Since satisfaction represents a composite of analgesic efficacy and adverse effects,[25,26] the superior analgesia noted in PCA + BI groups may have been tempered by the increased incidence of nausea observed with oxymorphone and a high level of sedation noted with morphine.

In conclusion, the addition of a basal opioid infusion improved the postoperative analgesic effectiveness of PCA, but was associated with an increased incidence of minor side effects. The excellent level of analgesia offered by this form of therapy, especially in blunting pain associated with movement, suggested an attractive form of intravenous analgesia in patients recovering from cesarean delivery. Further studies are necessary to refine PCA + BI and to determine whether increased analgesic effi-

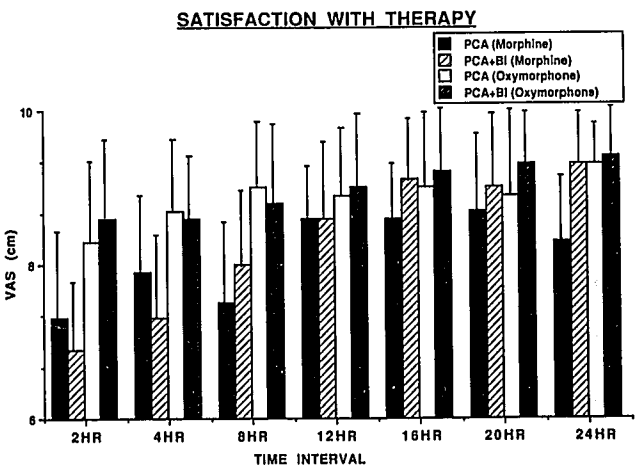

FIG. 3. Mean VAS scores (cm) reflecting satisfaction with therapy for patients receiving morphine or oxymorphone *via* PCA and PCA + BI. Error bars reflect standard deviation.

cacy can be provided in this and other patient populations without an unacceptably high level of adverse effects.

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