Oxyhemoglobin Saturation following Cesarean Section in Patients Receiving Epidural Morphine, PCA, or im Meperidine Analgesia

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The frequency and severity of oxyhemoglobin desaturation was compared in 49 patients receiving epidural morphine, 5 mg (n = 21); patient-controlled analgesia (PCA) using meperidine (n = 20); or intramuscular (im) meperidine (n = 8) for postoperative analgesia following elective cesarean section performed with epidural anesthesia. Oxygen saturation (SpO₂) was monitored for 24 h using a pulse oximeter; data were continuously collected and stored every 30 s via an interface connected to a computer. For analysis purposes, SpO₂ was divided into five categories: 96–100%, 91–95%, 86–90%, 81–85%, and ≤ 80%. Although SpO₂ remained above 95% for the majority of the monitored period, patients in all groups experienced periods of desaturation. PCA patients spent the longest cumulative time with SpO₂ between 91 and 95%, 231 ± 49 min (mean ± SEM), compared with only 112 ± 30 min and 152 ± 42 min for the epidural and im groups, respectively (P < 0.05 vs. epidural group). PCA patients also spent longest with SpO₂ at 86–90% (19 ± 10 min, vs. 6 ± 3 and 0.5 ± 0.3 min for the epidural and im groups, respectively), although this difference was not statistically significant. Severe desaturation episodes, defined as SpO₂ ≤ 85% for more than 30 s, occurred in 71% of patients in the epidural group, 30% in the PCA group, and 63% in the im group (P < 0.05 PCA vs. epidural and im). Mean minimum SpO₂ was lowest in the epidural group (83 ± 2%, vs. 88 ± 1% in the PCA, and 85 ± 2% in the im group; P < 0.05 epidural vs. PCA). In a group of ten women (not receiving opiates) studied in a similar fashion for 24 h following vaginal delivery, no severe desaturations occurred and SpO₂ decreased to 91–95% for only a brief period. The authors conclude that, following cesarean section, patients receiving all three opioid analgesic techniques potentially are at risk from respiratory depression. This is manifested by prolonged periods of mild desaturation following PCA, and a high incidence of brief periods of severe desaturation following epidural and im opioids. (Key words: Analgesia, postoperative: epidural narcotics; patient-controlled analgesia. Anesthesia: obstetric. Monitoring: oximetry. Oxygen: hemoglobin saturation.)

ADVANCES IN THE UNDERSTANDING OF spinal cord opiate receptors and improvements in drug administration technology have intensified interest in the treatment of postoperative pain. This has resulted in increased use of epidural opioids and patient-controlled analgesia (PCA) as alternatives to traditional intramuscular (im) administration of opioids. The greatest concern with these new therapies is the risk of respiratory depression. Although this can result from opioid administration by any route, epidural opioids may pose a special risk of respiratory depression due to cephalad spread of the drug in the neuraxis. Recent estimates of the incidence of this complication with epidural opioids range from 0.09–0.9%. However, little information exists regarding the incidence of life-threatening respiratory depression with PCA and im opioid administration.

In response to fears of respiratory arrest in patients receiving epidural opioids, many institutions have adopted special protocols mandating continuous or frequent respiratory monitoring of these individuals. In contrast, patients receiving PCA or im opioids generally are regarded as being at low risk, and have respiration monitored intermittently and often infrequently. A number of case reports in the literature and personal communication of several "near misses" with PCA led us to suspect that this technique was not without hazard. The goal of this study, therefore, was to document and compare the potential for ventilatory depression following epidural, PCA, and im opioids in women following cesarean section.

A variety of methods have been used to study the effects of opioids on respiration. The ventilatory response to CO₂ is depressed by relatively low doses of these agents, regardless of the route of administration. However, this test is not ideal for evaluating the risk of respiratory arrest in clinical practice because of its sensitivity, which may be too great, and the discontinuous nature of the measurements. Recording of PaCO₂ (or, more conveniently, end-tidal or transcutaneous CO₂) would be more useful, as an increase in these parameters indicates a more serious degree of respiratory depression. Unfortunately, these methods present technical difficulties in postoperative patients. We chose to monitor arterial oxygen saturation because significant ventilatory depression in individuals breathing room air results in hypoxemia. Using pulse oximetry to monitor oxyhemoglobin saturation (SpO₂), we documented the frequency with which clinically significant hypoxemia occurred in cesarean section patients receiving one of three methods of postoperative analgesia.

Materials and Methods

The protocol was approved by the Stanford Committee for the Use of Human Subjects in Research and all subjects provided written informed consent. The study population consisted of 49 parturients who had undergone elective

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cesarean section with lidocaine or bupivacaine epidural anesthesia. All participants had uncomplicated pregnancies, had no pre-existing medical disease, weighed less than 100 kg, were nonsmokers, and had no history of drug or alcohol abuse. In addition, patients denied any history of respiratory disease, neuromuscular disease, or sleep apnea.

For postoperative analgesia patients received either epidural morphine (Epidural group, n = 21); PCA meperidine, via the Abbott Lifecare® PCA Infusor (PCA group, n = 20); or intramuscular meperidine (im group, n = 8), according to their choice made before their enrollment in the study. Patients in the Epidural group were administered 5 mg of preservative-free morphine sulfate via an epidural catheter shortly following the birth of the baby. Subsequently, if additional analgesia was required, patients were treated with iv boluses of meperidine, 12.5–25 mg, and oral non-narcotic analgesics as soon as oral intake was tolerated (usually after 12 h). PCA patients initially were administered a loading dose of 50–100 mg of iv meperidine (titrated to patient comfort) in the recovery room and then were allowed to self-administer 10–20 mg iv meperidine boluses with a lockout interval of 10–15 min. Nursing personnel were allowed to increase or decrease the dose or lockout period in order to enhance patient comfort and minimize sedation or other side effects. However, a 4-h maximum dose of meperidine 300 mg could not be exceeded. Patients in the im group were given 50 mg im injections of meperidine every 2–4 h as needed. Nurses were instructed to disregard the monitoring equipment in the room and to administer analgesic medication as they would normally. In all groups, side effects, such as nausea, vomiting, or pruritus, were treated with small doses of promethazine, metoclopramide, or diphenhydramine, as appropriate.

Oxyhemoglobin saturation (SpO₂) was monitored for the first 24 h postoperatively in all patients using a Nellcor N-100 pulse oximeter with a sensor taped to the patient’s great toe. Monitoring was carried out continuously, except when the patient was ambulating, at which time either she or the nurse disconnected the sensor from the cable, leaving the former taped securely to her foot. All alarms on the oximeter were turned off, and patients were monitored according to standard hospital protocols, which dictated intermittent recording of respiratory rate (every 30 min with epidural morphine, and hourly with PCA and im meperidine). SpO₂ data were not made available to nursing personnel. Respiratory problems were not detected, and, thus, no patient received supplemental oxygen.

SpO₂ data were continuously collected and stored every 30 s via a Nellcor® N-8000 interface connected to a Compaq® 286 computer. Significant oxyhemoglobin desaturation episodes were defined as those lasting greater than 30 s. Plots of SpO₂ versus time were visually inspected in all patients and strict criteria applied to determine the number, duration, and severity of desaturation episodes. Artifacts were excluded after reviewing information provided on another computer printout of raw data that documented SpO₂, pulse amplitude, pulse rate, zero saturation (loss of signal), and a code for “connected” or “disconnected” status of the sensor. If examination of data relating to the observed desaturation or the period immediately adjacent to it cast doubt on its authenticity, it was rejected as being invalid. For the purposes of data analyses, SpO₂ measurements were divided into five categories: 96–100%, 91–95%, 86–90%, 81–85%, and ≤80%. Cumulative time spent in each saturation category was determined using a computer program. Again, specific error codes were employed to allow exclusion of invalid signals. The total duration of monitoring and the minimum saturation for each patient also were recorded using the computer program.

Initial review of SpO₂ data from the study groups revealed episodes of oxyhemoglobin desaturation in all treatment groups. This raised the question of whether this is a normal occurrence during the first 24 h postpartum. To answer this question, we studied an additional group of ten normal women following spontaneous vaginal delivery, none of whom received opioid analgesics during this period. Data from this group were collected and analyzed in a similar fashion to those from the other groups.

Statistical analyses were performed using one way ANOVA, Kruskal-Wallis, and Chi-square tests as appropriate. P < 0.05 was considered significant. Values are expressed as mean ± SEM.

**Results**

**Cesarean Section Patients**

The groups were similar with respect to age, height, weight, and total time each patient was monitored (table 1). The cumulative times spent in each SpO₂ category are presented in table 2. Although oxyhemoglobin saturation remained above 95% for the majority of the time, patients in each of the groups spent considerable periods of time

| Table 1. Demographic Data and Duration of Monitoring for Cesarean Section Groups |
|---------------------------------|---------------|---------------|-------|
| Age (yr)                        | EPI n = 21    | PCA n = 29    | im n = 8 |
|                                 | 33 ± 1        | 33 ± 1        | 30 ± 1 |
| Height (cm)                     | 163 ± 1       | 163 ± 1       | 165 ± 3 |
| Weight (kg)                     | 71 ± 2        | 76 ± 2        | 76 ± 6 |
| Total time monitored (min/patient) | 958 ± 45     | 1017 ± 36     | 1053 ± 77 |

Values are mean ± SEM. EPI = Epidural.
with SpO₂ between 91 and 95%. PCA patients spent the longest cumulative time in this category, i.e., 231 ± 49 min (representing 28% of the monitored period), as compared with only 112 ± 30 and 152 ± 42 min (14 and 16% of the monitored period), respectively, for the Epidural and im groups (P < 0.05 PCA vs. Epidural group). The longest cumulative time with SpO₂ between 86 and 90% also occurred in the PCA group; however, this did not differ statistically from values for the other groups.

Data on the incidence and severity of desaturation, which we defined as an SpO₂ ≤85% for more than 30 s, are presented in table 3. Such episodes occurred in all groups, but were significantly more frequent in patients in the epidural and im groups than in those in the PCA group (P < 0.05). The number of severe desaturation episodes per patient varied considerably within each group (table 3). One patient who received PCA experienced 35 such episodes! The mean minimum SpO₂ (obtained by calculating the mean for each group of the lowest saturation recorded in each patient) and range of values also are shown in table 3. Minimum SpO₂ was lowest in the Epidural group (P < 0.05 vs. PCA), with SpO₂ in one patient in this group decreasing to 65%. A prolonged desaturation of <85% occurred in one patient in each of the Epidural and PCA groups lasting for 3.5 min and 2.5 min, respectively. Respiratory rates of less than 10 were not recorded in any patient.

| Table 2. Cumulative Time in Minutes Spent in Each Saturation Category |
|-----------------------------|-----------------------------|-----------------------------|
| SpO₂ Category              | EPI (n = 21)                | PCA (n = 20)                | im (n = 8)                  |
| 96–100%                    | 858 ± 60                    | 784 ± 74                    | 900 ± 106                   |
| 91–95%                     | 112 ± 30                    | 231 ± 49*                   | 152 ± 42                    |
| 86–90%                     | 6 ± 3                       | 19 ± 10                     | 0.5 ± 0.3                   |
| 81–85%                     | 0.5 ± 0.2                   | 0.2 ± 0.2                   | 0 ± 0                       |
| ≤80%                       | 1.0 ± 0.6                   | 0 ± 0                       | 0 ± 0                       |

Values are mean ± SEM.

* P < 0.05 vs. EPI.

Total meperidine dosage was 532 ± 53 mg for the PCA group and 373 ± 44 mg for the im group (P = 0.08). Mean supplemental meperidine dosage for the epidural patients was considerably less at 16 ± 11 mg. However, this value represents data from only four patients, since the remainder of the group achieved good analgesia with the epidural dose alone. There was no correlation in any of the groups between total narcotic dosage in individual patients and either minimum saturation or the number of desaturation episodes to ≤85%. To determine whether hypoxic events occurred at a predictable time, desaturation episodes were plotted against both time from operation and real time. No pattern emerged in either case; episodes occurred in a random manner throughout the 24-h period and were distributed similarly among the groups. In the im group, severe desaturations occurred from 4 to 483 min following the last meperidine injection, with no consistent relationship between the two events.

NORMAL VAGINAL DELIVERY PATIENTS

Saturation remained at 96–100% for 90 ± 5% of the monitored period. Values decreased slightly to 91–95% for the remaining 10 ± 5% of the time. No patient experienced desaturation to ≤85% and minimum SpO₂ was 91 ± 1%. A notable difference between this group and the cesarean section groups was a shorter period of monitoring, i.e., 599 ± 65 min. As the reason for non-monitoring was usually amputation, it probably can be assumed that saturation during this activity was in the 96–100% category. Thus, the proportion of the first 24 h spent with saturation in the 91–95% category was likely less than the calculated 10%. Since the vaginal delivery group was not studied concurrently with the other groups, and since it differs in that patients did not have an operation, we did not consider it appropriate to include it in statistical comparisons of saturation data. Nevertheless, we believe our results indicate that women who have delivered vaginally do not normally experience significant oxyhemoglobin desaturation during the first 24 h postpartum, and thus differ from those who have undergone cesarean section.

**Tables**

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* P < 0.05 vs. im and EPI.
† P < 0.05 vs. PCA.
‡ Mean ± SEM.

**Discussion**

The current study revealed abnormalities of oxygen saturation following cesarean section with all three analgesic techniques. PCA patients spent the longest cumulative time with SpO₂ between 91 and 95% (i.e., with PaO₂ 60–70 mmHg) and between 86 and 90% (i.e., PaO₂ 50–60 mmHg), although the latter difference did not reach statistical significance. However, this group experienced the fewest number of severe desaturation episodes. In contrast, epidural and im patients experienced a greater number of severe desaturation episodes, but
spent the majority of the time with saturation above 95%. Although the mean minimum SpO₂ was lowest in the epidural group, values of 75% for one patient in the PCA group and 80% for one in the im group may be cause for concern.

We believe that our results accurately reflect differences among the groups, although subjects were not randomly assigned to treatments. Patients scheduled for elective cesarean section at our institution received written information about postoperative analgesia prior to admission, and have usually selected a technique before the preanesthetic interview. In spite of this, we believe that exclusion of obese individuals and smokers, and homogeneity of the population, resulted in groups with similar potential for respiratory problems. We did not employ a double-blinded study design because we did not consider it feasible to give all patients an epidural injection, a PCA pump, and intermittent im injections of what for two-thirds of patients would be a placebo. Since a physiologic variable was being measured, and data were collected and analyzed either by machine or by an investigator applying strict, predetermined criteria, bias is unlikely to have influenced our results.

The absence of SpO₂ below 90% in the vaginal delivery group suggests that postoperative hypoxemia in cesarean section patients was due to either opioid-induced respiratory depression, the effects of the operation itself, or a combination of the two. Unfortunately, so few postoperative patients (less than 1% in our practice) do not receive opioid analgesics that it was not possible to study such a group and thus separate the effects of analgesic drugs from those of lower abdominal surgery. In a recent report, Nishino et al.⁸ described abnormal breathing patterns (shallow, rapid respiration with decreased diaphragm activity) in the immediate postoperative period following abdominal hysterectomy performed with general anesthesia. Decreases in PaO₂ occurred, despite adequate analgesia with either epidural morphine, im morphine, or epidural lidocaine. These respiratory changes resemble those previously reported following upper abdominal operations performed with either general or epidural anesthesia.⁹-¹³ The underlying mechanism for the decrease in diaphragm activity remains to be elucidated. Although there are a number of differences between Nishino's study and the current work, enough common factors exist to suggest that similar abnormalities in cesarean section patients might partially explain the decreases in oxygen saturation found in all groups.

A completely different view is held by Ostman et al.,¹⁴ who believe that mild decreases in oxyhemoglobin saturation following cesarean section are physiologic, and occur in normal pregnant women during the sleeping state. This group measured oxyhemoglobin saturation in six patients the night prior to, and the night following, cesarean section during epidural morphine analgesia, documenting similar values for most patients during the two periods. Three patients spent considerable proportions of the time, both before and after operation, with SpO₂ of 91–95%. However, the applicability of their findings to our data is limited for a number of reasons: severe desaturations were never recorded (their lowest value for SpO₂ was 89%); the number of patients studied was small; patients were monitored only during the night (we found episodes of desaturation throughout the 24-h period); patients were not studied during PCA or im opioid analgesia; and term parturients may not be an appropriate control group for postpartum patients. With regard to the latter, in many women in late pregnancy, particularly in the supine position, airway closure results from the decreased functional residual capacity caused by cephalad displacement of the diaphragm by the pregnant uterus. As this resolves immediately after delivery, the propensity for postpartum women to develop hypoxemia during sleep should be less than that prior to delivery. Data obtained in our control group of nonoperated postpartum women suggest that neither severe desaturations nor prolonged periods of mild desaturation occur normally at this time.

If opioid administration contributes significantly to causing hypoxemia, then dosage is likely to be of importance. The fact that PCA patients received more meperidine (0.05 < P < 0.1) than im patients, and that the drug was administered in small, frequent doses, probably explains the longer periods of mild desaturation in the former group. As im patients received larger doses of meperidine, the greater frequency of severe desaturation episodes in this group might have been anticipated. However, since the expected temporal relationship between severe desaturations and time of opioid injection did not occur either in the im or the Epidural group, it suggests that other factors exert major influences on respiration.

The quality of analgesia might be important in this respect, with oversedation contributing to respiratory depression, and residual pain leading to stimulation of respiration. Although we did not specifically measure pain scores in this study, all subjects participated in an ongoing survey of cesarean section patients aimed at evaluating pain relief, patient satisfaction, and side effects with epidural, PCA, and im opioid analgesia. Questionnaires completed by patients in the current study revealed superior analgesia in the epidural morphine group for the first 8–16 h, but no differences among the groups thereafter. There were no significant differences between the PCA and im groups in the quality of analgesia at any time during the first 24 h. These results are representative of those in the entire survey population of approximately 700 patients (unpublished data) in which minimal differences in analgesia occurred in spite of a considerably higher meperidine dose in the PCA than in the im group.
In contrast to our findings, others\textsuperscript{15,14} have found a better correlation between opioid dosage and the quality of pain relief with PCA and im analgesia. Eisenach \textit{et al.}\textsuperscript{15} reported poorer analgesia with the lower doses administered an im versus a PCA group, whereas Harrison \textit{et al.}\textsuperscript{14} found comparable analgesia when the two groups received similar doses. While PCA and im patients in our study did not perceive major differences in the quality of analgesia, it is possible that, in the im group, a slightly greater degree of pain (not discernible by our method of evaluation) and, perhaps, greater variation in the level of pain relief, might have stimulated respiration. Although epidural morphine patients obtained the best analgesia, this state is seldom accompanied by significant sedation. Only one (5 mg) morphine dose was studied because lower doses produce inconsistent analgesia following cesarean section\textsuperscript{15,16} and larger doses have proved unnecessary.\textsuperscript{16}

Another important factor may be the presence of side effects, which could affect respiratory drive by increasing the level of consciousness. Questionnaire data revealed that, in this study, 95\% of patients in the epidural morphine group reported pruritus, compared with only 11–12\% in the im and PCA groups. Nausea and vomiting also occurred most frequently with epidural morphine, \textit{i.e.}, in 71\% and 47\% of patients, respectively; 50\% of patients receiving im opioids, and only 6\% of those receiving PCA, reported these complications. Because of the extremely low incidence of side effects in the PCA group, these patients may have lacked the arousals stimuli associated with scratching, vomiting, and treatment of complications.

How do our results relate to those previously reported in this area and what are their clinical implications? Our findings with epidural morphine support those of earlier studies reporting prolonged depression of CO\textsubscript{2} response\textsuperscript{17,18} and may help to explain the reports of delayed ventilatory arrests.\textsuperscript{19} The results with parenteral narcotics also are consistent with those of previous investigators.\textsuperscript{20–22} For example, Catley \textit{et al.}\textsuperscript{21} documented frequent severe desaturation episodes in a group of older patients receiving relatively large doses of iv morphine following major surgery; these were absent in a control group of patients who received regional analgesia. In a study of similar design to ours, Choi \textit{et al.}\textsuperscript{22} found no difference in oxyhemoglobin saturation between two groups of cesarean section patients receiving either epidural morphine or im meperidine. Only brief periods were spent with \textit{Sp}\textsubscript{O}_2 < 90\% (values are not provided for 90–95\%), with episodes of \textit{Sp}\textsubscript{O}_2 < 85\% occurring in about 50\% of all patients. Since the low alarm on the oximeter in that study was set at 85\%, episodes of severe desaturation might have been foreshortened.

We are not aware of reports of \textit{continuous} assessment of respiration during PCA, although normal arterial blood gases have been reported following intermittent sampling.\textsuperscript{4} In one study comparing epidural morphine, bupivacaine intercostal block, im morphine, and PCA fentanyl, capillary \textit{PCO}_2 at 24 h was elevated in more patients in the PCA group.\textsuperscript{25} Respiratory arrests with PCA have been reported, albeit infrequently, with the majority of such events in healthy patients being attributed to problems with programming, bolus administration during syringe change, or incorrect setup of the PCA tubing.\textsuperscript{4,6,7} Since our data show that PCA patients often are mildly desaturated (and therefore at the top of the steep portion of the oxyhemoglobin saturation curve), it is possible that a sudden additional bolus of an opioid could precipitate ventilatory failure.

With regard to the clinical relevance of our findings, we believe that cesarean section patients receiving opioids by any of the methods studied may be at risk for respiratory complications. Because the incidence of frank respiratory depression in a population of young healthy women (perhaps with increased ventilatory drive due to pregnancy) is very low, our numbers are too small to provide outcome data regarding life-threatening incidents. Thus, we cannot ascertain whether the relative risk with regard to desaturation episodes is indicative of the risk of respiratory arrest. Large scale epidemiologic studies are necessary to determine the relative risks of infrequently occurring complications. In the last few years, a number of such studies have been published relating to epidural opioids.\textsuperscript{1–3} For example, a recent Swedish survey of more than 14,000 patients receiving epidural opioids reported an incidence of respiratory depression of only 0.09\%.\textsuperscript{1} To date, comparable large-scale studies have not been performed in patients receiving either PCA or im opioids.

Our data do not support the use of unique protocols for the intensive respiratory monitoring of patients receiving epidural opiates. Until more reliable outcome data are available to guide the development of appropriate monitoring practices, we believe that all postoperative patients receiving opioid analgesics should be observed with reasonable frequency during the first 24 h. Ready \textit{et al.}\textsuperscript{24,25} suggest that repeatedly assessing level of consciousness by use of a sedation scale may be more helpful than measuring respiratory rate for purposes of detecting respiratory depression. The issue of where to care for patients receiving epidural opioids continues to provoke controversy.\textsuperscript{26} We believe, as do others,\textsuperscript{24} that cesarean section patients can receive epidural opioids and remain on normal patient wards. However, care of these and other postoperative patients necessitates adequate numbers of nursing personnel trained to recognize and treat respiratory depression. In this circumstance, pulse oximetry should prove useful for monitoring individuals with additional risk factors, or those who demonstrate low values for \textit{Sp}\textsubscript{O}_2.
intraoperatively or in the recovery room. Whether low-risk patients would benefit from pulse oximetry remains unclear. Although no patient in this study manifested an adverse outcome resulting from hypoxemia, this was not specifically investigated. It is of interest that routine pulse oximetry has been advocated for patients undergoing or recovering from anesthesia on the basis of data demonstrating desaturation episodes of similar severity and frequency to those reported here. 27

In summary, decreases in SpO2 to levels usually regarded as clinically significant occurred in the 24 h following cesarean section with all three opioid regimens. PCA resulted in prolonged periods of mild desaturation (and, thus, decreased respiratory reserve), while epidural and im opioids were associated with more frequent episodes of severe desaturation. These abnormalities likely are multifactorial in origin, and may be due in part to a common mechanism affecting diaphragm function following abdominal surgery. Differences among the groups may relate to differences in the dosage of the opioid, the incidence of side effects, and the quality of analgesia. In view of the apparent low morbidity in healthy women following cesarean section, we are not currently advocating major changes in monitoring practices, such as the routine use of pulse oximeters or apnea monitors. However, we believe that further large-scale studies are indicated to establish the relative risks of PCA and im opioid administration.

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References