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ORIGINAL ARTICLE

Retrospective evaluation of intravenous fentanyl patient-controlled analgesia during labor

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Abstract
Purpose Because the safety of intravenous fentanyl patient-controlled analgesia (iv-PCA) administered during labor remains unclear, we retrospectively examined the labor records from January 2005 to December 2007 in our institution, with a focus on both maternal and neonatal outcomes, as compared to no analgesia.
Methods Parturients over 35 weeks of gestational age who received fentanyl iv-PCA (iv-PCA group) or no analgesia (control group) during labor were enrolled. The former group received iv-PCA through a pump programmed to give a loading dose of 0.05 mg fentanyl, followed by bolus injection of 0.02 mg fentanyl, with a lock-out interval of 5 min. This analgesia was initiated at the parturient's request and was discontinued before the second stage of labor, to ensure neonatal safety. During labor, both maternal and fetal heart rates, maternal pulse oximeter oxygen saturation (SpO_2), respiratory rate, and sedation and nausea scores were continuously monitored, and the neonatal outcomes including umbilical arterial pH, Apgar scores, and other parameters were recorded.
Results The data of 129 of the 143 parturients who received fentanyl iv-PCA were analyzed, while 697 parturients delivered without any analgesia during the 3-year study period. While iv-PCA prolonged the duration of labor and increased oxytocin use, no obvious maternal or neonatal complications of fentanyl use were recorded. Except for the significantly lower rate of emergency cesarean section in the iv-PCA group, both the maternal and neonatal outcomes were comparable between the groups.
Conclusions As compared to no analgesia, fentanyl iv-PCA appears to be safe and clinically acceptable as analgesia during labor, particularly in nulliparous women.

Keywords Labor analgesia · Fentanyl · Intravenous patient-controlled analgesia

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Introduction

While regional block using epidural analgesia with or without subarachnoidal block has become a standard procedure for labor analgesia [1, 2], it is contraindicated in some pregnant women, such as those with coagulopathy, spinal abnormalities, or infection [3]. In addition, the provision of a 24-h epidural analgesia service for labor is not feasible in many institutions (including our hospital), owing to the limited availability of anesthesiologists. To resolve these issues in our institution, fentanyl intravenous patient-controlled analgesia (iv-PCA) has been implemented for parturients who requested labor pain relief. In our institution, while epidural analgesia for labor is restricted to those parturients who have accepted planned delivery, this systemic analgesia is offered to those who choose it rather than epidural analgesia, to those who do not accept planned delivery but accept some analgesia, and to those who show progress of labor before planned date of regional block. Among opioids, we chose fentanyl rather than the promising systemic opioid, remifentanil [4], because the latter was

relatively new and the staff of the obstetric ward were already familiar with the former as postoperative analgesia after cesarean section or laparoscopic surgery. Several studies have compared the analgesic efficacy of various opioids during labor. We reviewed the literature, but were unable to find any studies which addressed the effects of systemic administration of fentanyl or its congeners, as compared to no analgesia during labor [5, 6]. We, therefore, retrospectively examined the effects of fentanyl iv-PCA during spontaneous labor, as compared to no analgesia, on both the maternal and neonatal outcomes.

Patients, materials, and methods

With the approval of our institutional review board, we retrospectively reviewed all labor records of parturients between January 1, 2005, and December 31, 2007. Records of women who underwent elective cesarean section, those who received combined spinal-epidural analgesia as labor analgesia, those with earlier gestational age, and those with insufficient information were excluded. At our institution, a labor analgesia service, including epidural or intravenous analgesia, is provided for parturients who provide written informed consent in the routine prenatal visit, i.e., before the onset of labor. Because the risk of severe respiratory disorders has been shown to be markedly high until 34 weeks of gestation, possibly due to fetal lung maturation status [7], we enrolled only parturients over 35 weeks of gestational age at the time of labor in the present study, even in the control group, to match the substantial risk. The protocol for fentanyl iv-PCA was as follows: on the parturients' first request for analgesia during labor, 0.05 mg fentanyl was injected as a loading dose, followed by the application of an iv-PCA pump (i-Fusor; JMS, Tokyo, Japan) that did not deliver constant flow, but only bolus doses of 0.02 mg, with a lock-out interval of 5 min. The maximum dose of fentanyl per hour could be increased up to a maximum of 0.24 mg, in total. To minimize residual fentanyl effects on the neonate, this analgesia was terminated before the second stage of labor as assessed by the midwives, as reported previously [8]. The drug delivery/demand ratio automatically recorded in the PCA device was collected to evaluate the adequacy of our PCA protocol. The total fentanyl dose, PCA duration, and last PCA dose-to-delivery interval were recorded as the parameters related to the analgesic use. Both maternal and fetal heart rates were continuously monitored, and the parturients were cared for by midwives and obstetricians throughout the delivery. Concurrently, any maternal side effects, including sedation (0 = clear, 1 = calm, 2 = asleep but awakens easily, 3 = asleep and difficult to arouse) and nausea (0 = no nausea, 1 = mild nausea, 2 = nausea which needs antiemetics, 3 = vomiting), and the pulse oximeter oxygen saturation (SpO_2) and respiratory rate were monitored every 30 min and recorded by the attending midwives. In our protocol, oxygen supplementation by mask was initiated if the SpO_2 decreased to less than 90%, and the iv-PCA was terminated if the respiratory rate became less than 10 per min or the sedation level increased to more than 2.

In our obstetric ward, maternal demographic data and labor outcomes are routinely recorded, including the maternal and gestational ages, body mass index, labor duration, fetus presentation, oxytocin use, need for vacuum extraction, and conversion to emergency cesarean section. Decisions on oxytocin use are made by the attending obstetricians. Briefly, oxytocin is initiated when the first stage of labor is protracted because of inadequate uterine activity. It begins with oxytocin at 2 mU/min, followed by a 2 mU/min increase every 40 min to achieve adequate contraction. The decisions on emergency cesarean section are also made by the attending obstetricians, based on maternal and/or fetal indications. The birth weight, Apgar scores at 1 and 5 min, umbilical arterial blood gases, umbilical arterial base excess, neonatal resuscitation, and naloxone usage are recorded as neonatal outcomes. Because the umbilical arterial pH reflecting a healthy neonatal status is approximately 7.20 [9], the number of parturients with an umbilical arterial pH of less than 7.20 is also noted. To clarify the effects of parity, a major confounding factor in childbirth pain and outcomes, we divided the subjects into two subgroups, nulliparous versus parous women. The data are presented as means ± standard deviation, unless otherwise specified. Student's *t*-test and Fisher's exact test were applied for numerical data and the χ^2test was used where appropriate; p values of <0.05 were considered as denoting statistical significance.

Results

After excluding the records of women who underwent elective cesarean section ($n = 561$), those who received regional labor analgesia ($n = 80$), those who were of earlier gestational age ($n = 59$), and those with incomplete data ($n = 62$) from the 1,602 labor records examined, the records of 143 parturients who had received fentanyl iv-PCA (iv-PCA group) and the records of 697 parturients who received no analgesia (control group) were analyzed in the present study. The reasons that parturients received iv-PCA were varied: some requested iv-PCA analgesia rather than regional block, some did not want planned delivery, and others showed the progress of labor before planned date of regional block.

Of the 143 women in the iv-PCA group, 14 underwent emergency cesarean section; therefore, only the data of the

remaining 129 parturients were included for subsequent analyses of the iv-PCA group. All fetuses in the present study were in cephalic presentation and all were singletons. The main indications for emergency cesarean section in both the control and iv-PCA groups were prolonged labor or arrest of labor, and non-reassuring fetal status. The duration of the PCA use was 229 ± 216 min, the total fentanyl dose was 0.43 ± 0.38 mg, the fentanyl consumption rate was 3.6 ± 3.0 μg/kg/h, and the last dose-to-delivery interval was 82 ± 86 min. There were no cases of apparent respiratory depression or excessive sedation that needed prompt termination of the iv-PCA. Seven of the 129 parturients (5.4%) suffered from nausea (with nausea severity scores of 2 or 3), and the sedation score was more than 2 in 5 of the 129 (3.9%) parturients. There were no women with a sedation score of 3.

The drug delivery/demand ratio recorded in the PCA device was 0.43 ± 0.2, and there were no requests for alternative analgesia either during or after labor. Table 1 illustrates the maternal and neonatal demographic data and the labor outcomes. The iv-PCA group showed prolongation of the duration of the first and second stages of labor, and a higher rate of oxytocin use, accompanied by an apparent, but not statistically significant, increase in the frequency of instrumental delivery. At the same time, the rate of emergency cesarean section was significantly lower in the iv-PCA group. In regard to the neonatal outcomes, despite a lower mean umbilical arterial pH being found in the iv-PCA group, the percentages of infants with Apgar scores of less than 7 at 1 and 5 min, with an umbilical arterial pH of less than 7.20, and absolute values of base excess were comparable between the groups. No complications, including the need for naloxone reversal or bag-and-mask ventilation with oxygen, or fairly sedated newborns, were recorded in the iv-PCA group.

Because parity exerts a major influence on labor outcomes, we divided the parturients into two subgroups, the nulliparous versus parous women. The total fentanyl dose was greater in the nulliparous group than in the parous group (0.53 ± 0.46 vs. 0.28 ± 0.20 mg, $p = 0.003$). In the nulliparous women, the emergency cesarean rate was significantly lower in the iv-PCA group than in the control group, despite the higher rate of oxytocin use, more prolonged labor, and higher rate of instrument-assisted delivery in the former group (Table 2). The difference in the umbilical arterial pH between the control and iv-PCA groups did not reach statistical significance in the nulliparous women, whereas in the parous women the difference was trivial but statistically significant. There were no differences in the other neonatal outcomes, such as Apgar scores at 1 and 5 min of less than 7 and severe acidosis of the umbilical arterial blood, between the control and iv-PCA groups in the nulliparous women.

Table 1 Maternal and neonatal demographic variables and outcomes in control and iv-PCA groups

	Control	iv-PCA	*p* value
Maternal			
n	697	143	
Age (years)	34 ± 5	34 ± 4	0.584
Weight (kg)	62 ± 8	61 ± 8	0.405
BMI (kg/m^2)	24.3 ± 2.8	24.1 ± 3.0	0.479
Gestational age (weeks)	39 ± 1	40 ± 1	0.503
Infertility treatment, *n* (%)	107 (15.3%)	22 (15.3%)	0.982
First stage of labor (min)	474 ± 327	565 ± 358*	0.005
Second stage of labor (min)	46 ± 42	67 ± 51**	0.001
Nulliparous women, *n* (%)	486 (69.7%)	113 (79.0%)*	0.025
Oxytocin use, *n* (%)	314 (45.3%)	91 (63.6%)**	0.001
Vacuum-assisted delivery, *n* (%)	35 (5.0%)	13 (9.1%)	0.056
Emergency cesarean section, *n* (%)	117 (16.8%)	14 (9.8%)*	0.036
Neonatal			
n	580	129	
Birth weight (g)	2,967 ± 399	3,037 ± 414	0.075
Apgar score 1 min <7, *n* (%)	24 (4.1%)	10 (7.8%)	0.082
Apgar score 5 min <7, *n* (%)	6 (1.0%)	1 (0.8%)	1.000
Umbilical artery pH	7.31 ± 0.06	7.29 ± 0.06**	0.005
Umbilical artery pH <7.20, *n* (%)	27 (4.7%)	7 (5%)	0.711
Umbilical artery base excess	−4.1 ± 2.8	−4.2 ± 3.0	0.740

Data are expressed as means ± SD

iv-PCA intravenous patient-controlled analgesia, *BMI* body mass index

Significance: * $p < 0.05$, ** $p < 0.01$ versus control group

Table 2 Comparison of maternal and neonatal variables between control and iv-PCA groups based on parity

	Nulliparous			Parous		
	Control	iv-PCA	*p*	Control	iv-PCA	*p*
Maternal						
n	486	113		211	30	
Age (years)	33 ± 5	34 ± 4	0.133	34 ± 4	33 ± 5	0.160
Gestational age (weeks)	39.5 ± 1.4	39.7 ± 1.2	0.334	39.1 ± 1.4	38.9 ± 1.4	0.403
Infertility treatment, *n* (%)	94 (19.3%)	20 (14.7%)	0.840	13 (6.2%)	2 (6.7%)	0.767
First stage of labor (min)	540 ± 341	636 ± 367*	0.014	349 ± 256	332 ± 190	0.718
Second stage of labor (min)	58 ± 45	78 ± 51**	0.0002	22 ± 18	29 ± 28	0.207
Oxytocin use, *n* (%)	255 (52.5%)	81 (71.7%)*	0.002	59 (28.0%)	10 (33.3%)	0.543
Vacuum-assisted delivery, *n* (%)	33 (6.8%)	13 (11.5%)	0.090	2 (1.0%)	0	1.000
Emergency cesarean section, *n* (%)	106 (21.8%)	14 (12.4%)**	0.001	11 (5.2%)	0	0.368
Neonatal						
n	380	99		200	30	
Birth weight (g)	2,924 ± 392	3,041 ± 429*	0.01	3,048 ± 402	3,024 ± 367	0.753
Apgar score 1 min <7, *n* (%)	19 (5.0%)	7 (7.1%)	0.418	5 (2.5%)	3 (10%)	0.071
Apgar score 5 min <7, *n* (%)	4 (1.1%)	1 (1.0%)	1.000	2 (1.0%)	0	1.000
Umbilical arterial pH	7.30 ± 0.06	7.29 ± 0.06	0.056	7.32 ± 0.06	7.29 ± 0.08*	0.033
Umbilical arterial pH <7.20, *n* (%)	23 (6.1%)	5 (5.1%)	0.705	4 (2.0%)	2 (6.7%)	0.177
Umbilical artery base excess	−4.5 ± 2.7	−4.3 ± 2.8	0.540	−3.2 ± 2.7	−3.5 ± 3.5	0.606

Data are expressed as means ± SD

Significance: * $p < 0.05$, ** $p < 0.01$ versus control within each group

Discussion

The present study showed an apparently lower rate of emergency cesarean section in women administered fentanyl iv-PCA during the first stage of labor than in women who received no analgesia, especially in nulliparous women. At the same time, while there were no adverse effects of systemic fentanyl use on the neonatal outcomes, fentanyl iv-PCA evoked prolonged labor and increased the need for instrument-assisted delivery and oxytocin use. Although we enrolled only women with comparative gestational age in the control group, no clear explanations could be raised to account for the lower rate of emergency cesarean section in the fentanyl iv-PCA group. For example, the rate of infertility treatment, an independent risk factor for cesarean section [10], was similar in the two groups. Although the retrospective study design could not allow us to make conclusive comments on the the cause-and-effects aspect, one possibility is that the women receiving iv-PCA might have been able to better withstand prolonged labor, obviating the parturients' need to request a cesarean delivery. Nevertheless, fentanyl iv-PCA during the first stage of labor was not associated with a risk of emergency cesarean section even in nulliparous women. Labor pain is a complex phenomenon, with sensory, emotional, and perceptive components [11]; therefore, it is possible that the emotional relief obtained by holding a PCA button, in addition to the analgesic effects of fentanyl, could have obviated cesarean section on maternal request in this group of women.

A previous study indicated that both a loading dose of fentanyl of 0.05 mg and a 5-min lock-out interval could reduce excess demand and simultaneously match the lag-time between peak blood concentration and effect [12, 13]. Although the average drug delivery/demand ratio, which was less than 0.5 in the present study, did not appear to be high enough to satisfy the parturients, none of the parturients complained of insufficient analgesia during labor. Olofsson et al. [14] and Reynolds and Crowhurst [15] indicated that the use of systemic opioids to cause sedation alone was unethical and medically incorrect to meet nulliparous parturients' requests for pain relief. In the present study, however, only 3.9% of the parturients in the iv-PCA group showed even a moderate level of sedation. A recent report indicated that the systemic administration of meperidine or butorphanol, or a combination of the two, was effective to significantly reduce the intensity of labor pain in women with moderate to severe labor pain [16]. Besides, Liu and Sia [17] suggested that epidural analgesia in nulliparous women was not likely to increase the risk of cesarean section, but that it increased the frequency of instrument-assisted labor, possibly due to prolongation

of labor, as compared to systemic opioid analgesia. In other words, systemic opioid use was not apparently associated with unfavorable outcomes, except in terms of the analgesic efficiency, vis-à-vis the epidural approach [18], and may play a role in labor analgesia depending on its manner of usage, as previously described [4].

Another important finding of the present study was that there were no severe neonatal complications, including respiratory depression necessitating naloxone reversal or artificial ventilation, in the iv-PCA group. Rayburn et al. [19] demonstrated that, as compared to meperidine, the frequency of naloxone use was significantly lower in fentanyl-exposed infants (13 vs. 2%) at equivalent analgesic doses for labor. Although none of the women in our iv-PCA group showed apparent respiratory depression during labor, systemic opioid use increased the risk of maternal respiratory depression, resulting in lower umbilical arterial pH. In contrast, parturients with no or insufficient analgesia tend to hyperventilate and activate the sympathetic nervous system, consequently worsening placental perfusion and lowering the umbilical arterial pH. Accordingly, the cause of neonatal acidosis in the 7 cases in the present study cannot be entirely accounted for by the unfavorable effects of fentanyl iv-PCA alone. However, the difference in the umbilical arterial pH range between the groups was trivial, and the pH was apparently higher than 7.20, and, as stated earlier, a pH of approximately 7.20 reflects a healthy neonatal status [9], suggesting that the lower umbilical artery pH found in the iv-PCA group was not clinically relevant. In contrast, a previous study demonstrated that oxytocin use and hyperactive uterine contractions, both of which appeared to be higher in frequency in the iv-PCA group, were the most important risk factors for acidemia at birth [20]. In our study, we found that oxytocin use in the iv-PCA group was much higher than that in the parturients with no analgesia. Further study would be warranted to clarify the relationship between the systemic fentanyl concentration and uterine contractions. Morley-Forster and Weberpals [21] examined the effects of fentanyl iv-PCA and demonstrated that 3 (9.4%) of 32 infants were narcotized, which necessitated bag-and-mask ventilation and naloxone reversal. In contrast, none of our 129 neonates required any respiratory support, although other factors, such as the PCA duration and total fentanyl dose and consumption rate in such narcotized neonates were all comparable. Collectively, despite a number of factors being involved, the last dose-to-delivery interval, approximately 30 min in the study by Morley-Forster and Weberpals [21] versus 82 min in our protocol, could be the major factor preventing narcotization in the neonates. In either case, the adverse effects of fentanyl iv-PCA during the first stage of labor on neonates were considered to be negligible, although the long-term effects of fentanyl on the neurobehavioral scores of neonates remain to be determined.

There were some limitations to the data interpretation in this study. First, some may argue that parturients who would be expected to suffer from more prolonged and/or painful labor, possibly associated with oxytocin use, may request fentanyl iv-PCA. Besides, the initiation of iv-PCA during the first stage of labor, depending on the extent of cervical dilation, might vary depending on the time of the parturients' request. Even so, the neonatal outcomes in the fentanyl iv-PCA group were not different from those in the control group, and this approach could be conducted without serious complications. Because it would be unethical to perform a prospective randomized trial to examine the safety and efficacy of fentanyl iv-PCA as compared to non-medicated labor, only a retrospective study design can be used to unmask this issue. Another investigation is under way in our institution to prospectively examine maternal satisfaction and the degree of labor pain in parturients who have administered fentanyl iv-PCA. Second, the rate of emergency cesarean section of 21.8% in the control group, as shown in Table 2, appeared to be higher than that reported by other institutions [17, 22]. Owing to the high rate of infertility therapy, neither obstetricians nor parturients at our institution are inclined to allow prolonged labor with an increasing risk to neonates via vaginal delivery, and instead choose simple direct interventions [10]. Indeed, the total rate of either elective or emergency cesarean sections was up to 44.8% of all the deliveries during our study period. Due to the comparable rate of infertility therapy in both groups (Table 1), however, this confounding factor was unable to account for the lower rate of emergency cesarean section observed in the iv-PCA group in this study. Third, we did not examine the efficacy of other opioids, such as morphine or fentanyl congeners, for labor analgesia [23]. While a previous study showed that fentanyl iv-PCA was well tolerated for labor up to 5 h and there were no neonatal neurobehavioral complications [24], remifentanil could be a significant candidate for intravenous analgesia for labor, at least compared to non-medicated labor [8]. Finally, a retrospective study design such as that in the present study always has a substantial risk of bias. Therefore, we should be cautious in interpreting the data, although there is no way to compare the effects of iv-PCA with no labor analgesia in a prospective manner.

The data herein indicate that, as compared to non-medicated labor, fentanyl iv-PCA during the first stage of labor has no harmful effects on perinatal outcomes. Further examination, however, is necessary to obtain improved analgesic efficacy and to determine the optimal timing of the initiation and termination of fentanyl iv-PCA without increasing undesirable side-effects.

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