Abstract: Background: Remifentanil patient controlled intravenous analgesia (PCIA) during labor has rapidly gained popularity. Its pharmacological profile makes it suitable for this indication. However, remifentanil is a potent respiratory depressant that might cause serious maternal hypoventilation, respiratory arrest and desaturation.

Methods: In the present study we compared standard monitoring of parturients (saturation measurements and visual respiratory rate measurements at set times) with continuous monitoring. Data of patients in the standard monitoring group were collected from handwritten charts containing oxygen saturation and respiratory rate. The patients in the continuous monitoring group were connected to a device that measures the oxygen saturation and respiratory rate every two seconds and automatically saves the data. These data were analyzed retrospectively.

Results: In the standard monitoring group 1 patient (1%) had severe desaturation $SpO_2 < 80\%$, 22 patients (25%) had $SpO_2 < 94\%$ and in no patient a respiratory rate (RR) < 8/min was recorded. In the continuous monitoring group 20 patients (33%) showed $SpO_2 < 80\%$, 58 patients (97%) $SpO_2 < 94\%$ and 38 patients (63%) had bradypnea (RR < 8/min). The analysis of the data of the continuous monitoring group showed severe desaturations and serious respiratory depression.

Conclusion: The standard intermittent monitoring strategy dramatically underestimated the incidence of both bradypnea and oxygen desaturations with undetected hypoxemia and possible complications as a consequence. During use of remifentanil PCIA one-to-one midwifery care is advised. When obstetric caregivers are not present in the immediate vicinity of the parturient, high quality continuous monitoring, remote alarm notification and readiness for immediate corrective intervention are essential for safe use of this analgesic strategy.

Key words: Remifentanil; labor analgesia; patient-controlled intravenous analgesia; maternal opioids.

Introduction

Remifentanil patient controlled intravenous analgesia (PCIA) during labor has rapidly gained popularity in some countries. As an ultra-short acting opioid with a very short half-life (3-4 minutes), short elimination half time (10-20 minutes) and organ-independent metabolism in both adults and fetuses, remifentanil therefore seems suitable for systemic labor analgesia (1,2,3).

However, remifentanil is a potent respiratory depressant that might cause serious maternal hypoventilation, hypopnea and desaturations (4). The safety of the use of remifentanil PCIA during labor is heavily discussed in literature. Especially in situations without one-to-one midwifery care (5,6,7).

Standard monitoring (Philips Intellivue MP5 monitor) with pulse oximetry ($SpO_2$), heart rate (HR), respiratory rate (RR) and non-invasive blood pressure (NIBP) seems to be insufficient because of disturbances in saturation measurements which lead to frequent false alarms and alarm fatigue. Besides, measurements are not automatically saved and can’t thus be reliably analyzed.

In our hospital we use remifentanil only in cases with contra-indications for neuraxial analgesia or in multigravidous parturients with a relatively short time to delivery interval. One-to-one care is guaranteed for the first hour after starting remifentanil PCIA. Thereafter saturation monitoring is directly connected to an alarm system carried by one of the obstetric nurses. Intermittently midwives check the patient and fill in a checklist containing $SpO_2$, RR, NIBP and HR (8). Because of the before mentioned disturbances in our standard saturation monitoring we started using Masimo Radical-7 RRa monitoring. This monitor device measures respiratory rate continuously using an acoustic signal with a sensor in the neck of the parturient and saturation via a probe attached to a finger (9).
The goal of the present retrospective study was to compare both monitoring systems. Our hypothesis, based on clinical experience, was that conventional monitoring might significantly underestimate markers of hypoventilation and desaturation.

**METHODS**

Approval for this retrospective observational study was obtained from The Regional Committee for Medical and Health Research Ethics.

We started using remifentanil at the end of 2011. The data from handwritten charts of 2012 were used as control group because in this year the instruction to fill in the remifentanil checklist was best followed by caregivers. Only patients with completed checklists were included. From December 2014 until July 2015 data of remifentanil users were collected from the continuous monitoring device, which automatically records respiratory rate and peripheral saturation every two seconds. During this period patients were connected to both the standard saturation monitor and the continuous monitor, because the alarm system carried by a nurse only operated on the standard monitor. Included were patients of 18 years and older and with a gestational age above 24 weeks.

**Data collection and analysis**

Data from the checklist contained peripheral oxygen saturation, respiratory rate (counted by hand) and non-invasive blood pressure five minutes before start of remifentanil, at the moment of the first bolus, 15, 30, 45, 60 minutes after start and once every hour. Data from the continuous monitoring device were transferred and displayed in an excel file. They contained peripheral oxygen saturation and respiratory rate measured every two seconds. We retrospectively reviewed medical records of parturients who used remifentanil PCIA.

Our local protocol, adapted from national guidelines, prescribes interventions in case of saturations below 94% or respiratory rates below 8/min. We consider a saturation below 80% as potentially hazardous thus we analyzed our data for cut off points of \( \text{SpO}_2 < 80\% \), \( \text{SpO}_2 < 94\% \) and RR < 8 per minute. For safety reasons it is not allowed to administer oxygen to the patients when care givers are absent (8). Also continuous infusion is not allowed, only a bolus of 30 µg/bolus and a lockout of 3 minutes.

For the primary outcome results of standard monitoring and continuous monitoring were compared, based on a comparison of the number of desaturations and respiratory depressions. Statistical analysis of the data was performed by the program SPSS (Statistical Package for Social Sciences) version 23. The independent T-test was used to compare the baseline characteristics between the two groups. Fisher’s test was used for the comparison of the percentage of patients with desaturations and respiratory depressions per group. Results were evaluated at 95% confidence interval and \( p < 0.05 \) for significance.

The secondary outcome is an analysis of the results of the continuous monitoring which shows the course of the \( \text{SpO}_2 \) and RR during the use of remifentanil.

**RESULTS**

In 2012 there were 2307 childbirths above 24 weeks of gestational age. 142 parturients (6%) used remifentanil for labor analgesia. Only 89 checklists were filled in correctly and included in this research. The cause for this discrepancy was difficult to trace. We assume in most cases logistical obstacles (e.g. time constraints) were the reason.

From December 2014 – July 2015 there were 1400 childbirths above 24 weeks. 100 parturients (7%) used remifentanil. 60 patients were also connected to the continuous monitoring device and they were all included in the analysis. Except for age, which was significantly different (\( p < 0.05 \)), both groups were comparable in terms of parity, BMI, gestational age, Apgar scores and sex of the newborn child. Table 1 shows the baseline characteristics of the patient groups.

**Primary outcome**

In the standard monitoring group 1 patient (1%) had severe desaturation \( \text{SpO}_2 < 80\% \), 22 patients (25%) had \( \text{SpO}_2 < 94\% \) and in no patient a RR < 8/min was recorded. In the continuous monitoring group 20 patients (33%) showed \( \text{SpO}_2 < 80\% \), 58 patients (97%) \( \text{SpO}_2 < 94\% \) and 38 patients (63%) had bradypnea (RR < 8/min).

The difference between the number of patients with desaturations and respiratory depressions is found to be significant for all three cut-off points (\( P < 0.05 \)) (Table 2). It has not been reported whether the caregivers noted or intervened during the desaturations and bradypnoes.

No adverse events such as cardiorespiratory arrests were reported. In both groups one child had
Patient 31 (healthy, 30 years, BMI 24.1) used remifentanil PCIA for 6 hours and 40 minutes (Figure 2). She had 79 episodes with SpO$_2$ < 94%. The mean duration per hypoxemic episode was 35 seconds and the total duration of hypoxemia was 2778 seconds (46 minutes). She had 10 episodes with severe hypoxemia (SpO$_2$ < 80%). The mean duration per episode was 13 seconds and the total duration of severe hypoxemia was 128 seconds. She showed 24 periods of RR < 8/min. The mean duration of bradypnea was 14 seconds and the total duration was 342 seconds (6 minutes).

Patient 42 (healthy, 36 years, BMI 36.7) used remifentanil PCIA for 10 hours and 58 minutes (Figure 3). She had 252 periods of SpO$_2$ < 94%, with a mean duration per period of 23 seconds. The total duration for SpO$_2$ < 94% was 5728 seconds (96 minutes). She had 2 brief episodes of severe hypoxemia (SpO$_2$ < 80%) with a mean duration per episode of 23 seconds. The total duration of severe oxygen desaturation was 462 seconds (7.7 minutes).

Neonatal outcome was identical in both groups.

Secondary outcome

To get more insight in the course of the SpO$_2$ and RR during the use of remifentanil we describe three alarming cases in more detail below.

Patient 19 (healthy, 24 years, BMI 20.9) used remifentanil PCIA for 1 hour and 44 minutes (Figure 1). She had 11 episodes with SpO$_2$ < 94%. The mean duration per hypoxemic episode was 32 seconds and the total duration of hypoxemia was 348 seconds (6 minutes). She had 3 episodes with SpO$_2$ < 80%, with a mean duration per episode of 23 seconds and a total duration of 68 seconds. What makes this case alarming is that the patient had a SpO$_2$ < 50% for 26 seconds in a row.

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hypoxemia of SpO₂ < 80%. The mean duration per period was 9 seconds and the total duration was 18 seconds. She had 199 periods with a RR < 8/min. The mean duration per bradypneic period was 36 seconds. The total duration of RR < 8/min was 7225 seconds (120 minutes).

**DISCUSSION**

In The Netherlands the use of remifentanil PCIA for labor analgesia is a favorite method in many hospitals. The reason for this widespread use is a logistic problem to provide epidurals at all times and the ease for the obstetric ward to propose this way of pain treatment. Although pain relief and satisfaction are insufficient in comparison with epidural analgesia, many women prefer this less invasive treatment (10). We are aware of the discussion concerning the safety of the use of remifentanil PCIA during labor (4,11). Several reports about respiratory and cardiac arrests have been published in recent years (12-16). Although it is advised to practice one-to-one care during remifentanil PCIA use for labor analgesia, this is not always possible due to logistic reasons. During the absence of a midwifery nurse the staff has to rely on adequate monitoring, an adequate alarming system and the opportunity to react directly.

With our standard SpO₂ monitor we noted that many disturbances occur and because of frequent false alarms alarm fatigue arises. Desaturations and respiratory depressions during absence of midwifery nurses are often not noticed. According to experiences of our caregivers the measurements of the Masimo RRa Radical-7 are accurate and fewer disturbances occur (9). The Masimo RRa Radical-7 was not connected to the alarm system cared by nurses thus we can not compare the number of false alarms between the two groups. Corrective interventions during the use of remifentanil were not registered.

In this retrospective study we observed that patients receiving obstetric analgesia with remifentanil PCIA were inadequately monitored for potential respiratory depression and desaturations. Van de Velde et al. concluded in their review on remifentanil use during labor that remifentanil PCIA should not be considered a routine analgesia technique during labor and that its safety is not well known. They state that continuous and careful monitoring is required to provide safe care of mother and unborn child (17). Our study supports these conclusions. Our small series had insufficient
controlled study with a larger patient sample would be necessary to demonstrate such effects. Our data show that monitoring needs to be improved in the future.

CONCLUSION

We analyzed monitoring practices during remifentanil PCIA for labor and compared the standard approach (a pulse oximeter, RR counted intermittently by hand and NIBP) with automated continuous monitoring of RR and saturation.

The standard intermittent monitoring strategy dramatically underestimated the incidence of both bradypnea and oxygen desaturations. This could lead to undetected severe hypoxemia with possible complications. During use of remifentanil PCIA one-to-one midwifery care is advised. When obstetric caregivers are not present in the immediate vicinity of the parturient, high quality continuous monitoring, remote alarm notification and readiness for immediate corrective intervention are essential for safe use of this analgesic strategy.

REFERENCES