International Journal of Obstetric Anesthesia (2019) 39, 12–21
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https://doi.org/10.1016/j.ijoa.2018.12.004

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ORIGINAL ARTICLE

Remifentanil patient-controlled analgesia in labour: six-year audit of outcome data of the RemiPCA SAFE Network (2010–2015)

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ABSTRACT

Background: The RemiPCA SAFE Network was established to set standards and monitor maternal and neonatal outcomes when using remifentanil for labour analgesia. The aim of this analysis was to describe the development of the network standard and to report maternal and neonatal outcome data, including severe adverse events.

Methods: Data sets of the RemiPCA SAFE Network database from the initial six consecutive years (2010–2015) were retrospectively analysed. The data were analysed on an annual basis and set in context with changes of the network standard, i.e. adaptations of the network's standard operating procedure. Main outcomes reported are maternal and neonatal data regarding effectiveness and safety, such as satisfaction, need for bag/mask ventilation and/or cardiopulmonary resuscitation.

Results: Among 5740 data sets, no need for maternal ventilation or cardiopulmonary resuscitation was registered. Neonatal cardiopulmonary resuscitations, potentially related to remifentanil, occurred in 0.3%. In parallel with adaptations of the network standard, a moderate rate of maternal hypoxia (oxygen saturation <94% in 24.7%) was found, together with a low rate of supplemental oxygen requirement in neonates (5.0%).

Conclusion: The RemiPCA SAFE Network data show that remifentanil patient-controlled analgesia can be applied safely. There is bias when data from real clinical settings are analysed retrospectively. Notwithstanding, the approach taken by the RemiPCA SAFE Network, with constant, systematic and standardised evaluation of multiple parameters during the course of labour, might identify trends and anomalies and guide the development and application of safety standards, when translating knowledge from scientific trials into clinical practice.

Keywords: Remifentanil; Labour analgesia; Obstetric; Patient controlled analgesia

Introduction

Remifentanil patient-controlled analgesia (PCA) as a method of labour analgesia was first used by Jones and colleagues in 1999 to circumvent epidural puncture in thrombocytopenic patients.[1] In 2008, it had already been proposed as a routine alternative labour analgesic method.[2] Since then, remifentanil PCA has been utilised on labour wards in many countries, either on a regular basis or when neuraxial analgesia is not feasible. Although parturients show high satisfaction rates with remifentanil PCA,[3] it can be accompanied by considerable side effects, mainly respiratory complications such as hypoxia and hypercapnia, or effects of remifentanil on cardiac function and circulation.[4–8] In Switzerland, remifentanil PCA was introduced into clinical practice in 2009. Being a new analgesic method in obstetrics, it was controversial from the very beginning. Therefore, in 2009, the platform RemiPCA SAFE Network (www.remipca.org) was developed to monitor the

Accepted December 2018
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clinical application and evaluate maternal and neonatal outcomes, to assist future safe administration based on the basic principle "do no harm".[9] Every delivery unit in Switzerland, and later on in other countries, was welcome to join the RemiPCA SAFE Network.

In spite of the numerous advantages of controlled trials, their portability to daily clinical life is limited and patient numbers may be too low to discover infrequent complications or to find suitable recommendations for a wide variety of patients. This is where large scale registries may complement information from clinical trials. The RemiPCA SAFE Network allows the individual hospital to monitor its performance (individual quality management), and it provides data to the network steering committee about the overall performance of the method (overall quality management).

The RemiPCA SAFE Network developed quickly and was established under the patronage of the Swiss Association of Obstetric Anaesthesia (SAOA) in 2013. If deemed necessary, for example as a result of adverse events reported, the network standard operating procedure (SOP) is adapted to reduce or avoid such complications in the future and the members of the network are informed. Further measures, such as network training sessions and annual evaluations, contribute to a continuous improvement of the application of remifentanil PCA.

The aim of this analysis was to describe the quality assurance system, to examine the maternal and neonatal outcome data collected regarding effectiveness and safety, and to report modifications made to the protocol.

Methods

Following approval by the Ethical Committee of the Canton of Berne, Switzerland (KEK Nr. 2016-01855), data of the RemiPCA SAFE Network database from 1st January 2010 to 31st December 2015 were analysed. This time period reflects the development of the network SOP, with all participating hospitals using the same application standard. For this retrospective audit no specific additional patient consent was required by the Ethical Committee.

Hospitals participating in the RemiPCA SAFE Network agreed to follow the SOP of the network and to submit the outcome data of all their remifentanil PCA applications. With participation in the network, expectant mothers were informed about the off-label use of remifentanil PCA and the collection of their outcome data. Data were obtained prospectively after written informed consent had been given. It was possible to include parturients more than once, but not from the same delivery.

The administration of remifentanil PCA was implemented according to the network SOP. Contraindications to remifentanil PCA were intrauterine fetal death (IUFD), opioid drug abuse, known allergic reactions to remifentanil, prematurity (<36 weeks-of-gestation), pre-eclampsia, intravenous magnesium therapy, morbid obesity (body mass index [BMI] >40 kg/m^2), obstructive sleep apnoea, severe airway abnormality and serious cardiac disease.

Data were submitted from various hospitals in Switzerland and Germany, including teaching hospitals, regional hospitals, private hospitals and university hospitals. Data were gathered via a standardised online questionnaire, which all participating hospitals had agreed to complete for every remifentanil PCA application.

In 2012, the questionnaire was extended to ascertain maternal and neonatal severe adverse events (SAEs), the highest remifentanil bolus dose, supplemental oxygen administration and bag/mask-ventilation of the newborn. From 2014 onwards, severe adverse events resulted in an automatically triggered request for a detailed description of the case. Since 2014, the Network provided an alert function for severe adverse events, the so-called RemiPCA Alert. Every such case is analysed for a potential contribution of remifentanil to the severe adverse event.

General data consisted of the total number of remifentanil PCA applications, parturient parity and weeks-of-gestation, and her cervical dilatation at the start of remifentanil PCA. Use of other opioids than remifentanil, including their timing prior to remifentanil PCA, the indication for remifentanil PCA, the total amount of remifentanil given, and the duration of remifentanil PCA were recorded. So was the reason for, and rate of conversion to, epidural analgesia and the mode of delivery. From 2012 onwards, the highest applied bolus dose was recorded.

The change of the bolus dose over the years was analysed. Regarding the mode of delivery two subgroups were analysed; parturients with and without conversion to epidural analgesia. The duration of remifentanil PCA, depending on the cervical dilatation at initiation of remifentanil PCA, was analysed for nulliparous and multiparous women.

Pain was rated by the mother on an 11-point numerical rating scale (NRS, 0 indicating no pain, 10 indicating worst pain imaginable) before the use of remifentanil and one hour after its start. The difference between these two values was defined as the outcome 'pain reduction'. Overall maternal satisfaction with remifentanil PCA was rated after delivery on a 5-point Likert scale (very satisfied (=1), satisfied, undecided, unsatisfied and very unsatisfied (=5)). Dichotomous outcomes included side effects such as pruritus, sedation, nausea and vomiting. Oxygen saturation was monitored continuously during the administration of remifentanil PCA and the lowest reading over the prior 30-minute period was recorded

by the midwife caring for the parturient 30 minutely. The lowest of these recorded values of peripheral oxygen saturation (hypoxia being defined as a peripheral oxygen saturation (SpO_2, <94%) during the course of remifentanil PCA was analysed.

Neonatal outcome data consisted of mode of birth, Apgar score <7 at 1- and 5-min, umbilical cord pH <7.1 (arterial and/or venous cord pH were done routinely immediately after delivery), the application of supplemental oxygen or bag/mask-ventilation, and initial feeding success (suckling within two hours of delivery). If the mother converted to epidural analgesia or had caesarean delivery, neonatal data were excluded from analysis.

Maternal severe adverse events were defined as the need for bag/mask ventilation and/or cardiopulmonary resuscitation. Neonatal severe adverse events were defined as the need for cardiopulmonary resuscitation. From 2014 onwards, all severe adverse events were evaluated by the network steering committee on the basis of the RemiPCA Alert and the submitted case report.

All data were analysed in total and on an annual basis. Descriptive analyses for categorical data, count and percentage values were used. For continuous parameters, sample size, mean, and standard deviation were calculated. Bar charts and mean-plots with 95% confidence intervals were used for graphical representation. For all analyses the pairwise complete data were used. Statistical analyses were conducted with IBM SPSS 24 [IBM Corp.; Armonk, NY, USA] and Microsoft Excel [Microsoft Corp., Redmond, WA, USA].

Results

A total of 5740 remifentanil PCA data sets were submitted to the RemiPCA SAFE Network from 1st January 2010 to 31st December 2015 (Fig. 1). The number of participating hospitals (including teaching, regional, private, and university hospitals) increased from 3 in 2010 to 31 in 2015. Baseline data are depicted in Table 1.

Annual evaluations of the outcome data and emerging literature led to SOP changes which are shown in Table 2. The changing topics included a reduction of the recommended remifentanil bolus doses, the threshold for supplemental oxygen administered to the parturient, the time interval deemed necessary between other opioids and the start of remifentanil PCA, and the stopping time of remifentanil PCA prior to cord clamping. The remifentanil PCA lockout interval was two minutes and did not change over the years. There was no restriction of the maximal dose over a specific amount of time. No background infusion of remifentanil, no additional use of nitrous oxide, and no other analgesics were allowed once remifentanil PCA had commenced. The maternal SpO_2 was monitored continuously and there was dedicated 1:1 midwifery care at all times. The recommendation for remifentanil bolus dosing was 20–40 µg until 2013, when it was reduced

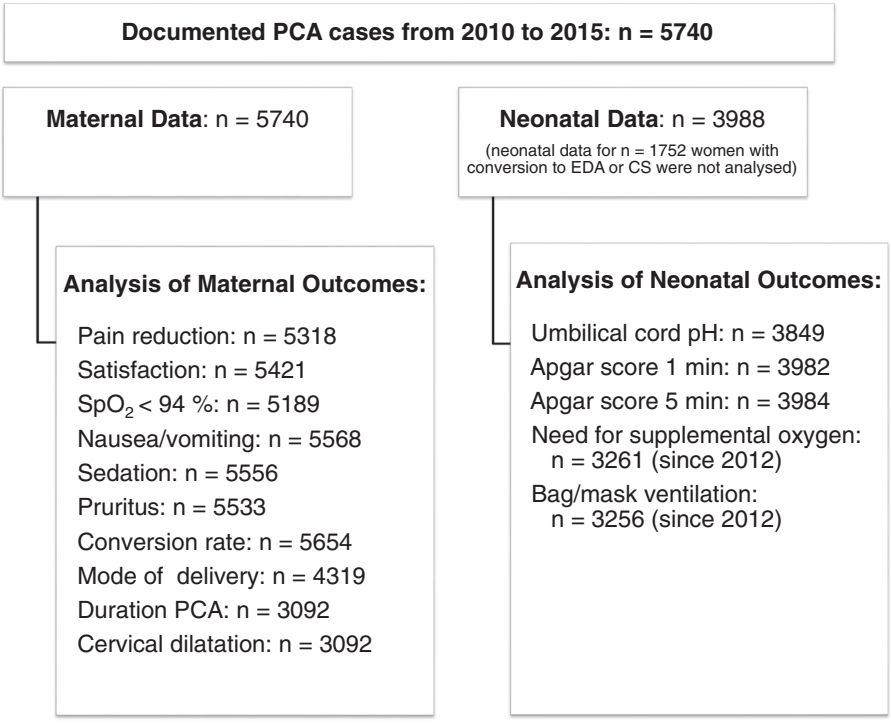

Fig. 1 Flow diagram of remifentanil patient-controlled analgesia cases and outcome parameters. PCA: patient-controlled analgesia. EDA: epidural analgesia. CS: caesarean section. SpO_2: oxygen saturation

Table 1 Baseline data

	2010	2011	2012	2013	2014	2015	Total
Participating hospitals (n)	3	10	12	18	23	31	31
Reported RemiPCA cases (n)	438	662	855	1033	1386	1366	5740
Nullipara in % (n)	65.8 (438)	59.4 (662)	60.5 (827)	59.1 (1028)	57.2 (1386)	59.0 (1366)	59.4 (5707)
Conversion rate in % (n)	31.5 (438)	16.8 (662)	16.7 (820)	19.0 (983)	19.3 (1385)	21.3 (1366)	21.0 (5654)
Mode of delivery without conversion to epidural (%)							
(n)	(294)	(517)	(522)	(793)	(1118)	(1075)	(4319)
Spontaneous	84.3	75.4	85.0	82.9	80.1	78.6	80.6
Instrumental	9.9	11.8	9.4	10.1	12.4	13.9	11.8
CS	5.8	12.8	5.6	7.1	7.4	7.4	7.7
Remifentanil bolus dose as mean [μg] (SD, n)	NA	NA	27 (7.9, 410)	20 (6.7, 715)	19 (6.3, 1017)	18 (5.9, 987)	20 (7.1, 3129)
Total amount of remifentanil given per application as mean [μg] (SD, n)	1074 (759, 388)	996 (1167, 653)	1008 (842, 760)	824 (1357, 961)	730 (865, 1293)	727 (908, 1277)	843 (1018, 5332)
Opioid use prior to PCA (%)							
Pethidine (n)	3.2 (435)	2.3 (660)	2.5 (811)	4.3 (959)	4.6 (1316)	4.1 (1295)	3.7 (5476)
Tramadol (n)	10.6 (435)	7.4 (658)	13.1 (770)	14.4 (968)	16.8 (1329)	8.4 (1298)	12.2 (5458)
Other (n)	0 (438)	0.2 (662)	0.6 (855)	0.3 (1033)	0.4 (1386)	1.3 (1366)	0.6 (5740)
Time in hours between use of other opioids to PCA (mean)							
Pethidine (SD, n)	4.2 (1.9, 13)	6.4 (1.6, 15)	7.3 (5.8, 20)	5.0 (6.2, 60)	5.7 (7.5, 73)	6.9 (10.4, 68)	5.9 (7.6, 249)
Tramadol (SD, n)	2.9 (1.6, 43)	5.1 (1.7, 43)	4.7 (5.8, 96)	4.2 (7.6, 158)	4.8 (9.1, 233)	4.4 (4.4, 116)	4.5 (7.0, 689)
Others (SD, n)	-	4.9 (1.6, 7)	3.5 (0.4, 10)	1.2 (3.3, 30)	1.9 (4.1, 26)	3.2 (6.2, 37)	2.5 (4.7, 110)

Numbers are percentages or mean (SD) if not otherwise indicated. NA: not available (exact maximum dose was not included in the first questionnaire); CS: caesarean section; PCA: patient-controlled analgesia; SD: standard deviation.

Table 2 Changes to the standard operating procedure

	2010	2011	2012	2013	2014	2015
Recommended bolus dose (μg)	20–40	20–40	20–40	10–30†	10–30†	10–30†
Recommended SpO_2 threshold for supplemental oxygen	<92%	<92%	<92%	<92%	<94%	<94%†
Recommended interval between other opioids prior to PCA and start of PCA (h)	NA	NA	NA	>4	>4	>4†
Recommended time to stop PCA prior to cord clamping (min)	NA	NA	NA	>5–10	>5–10	>5–10†
Standardised documentation of severe incidents	NA	NA	yes	yes	yes	yes
RemiPCA Alert function (with detailed report)	NA	NA	NA	NA	yes	yes

†Mandatory guideline. NA: not applicable; PCA: patient-controlled analgesia; SpO_2: oxygen saturation.

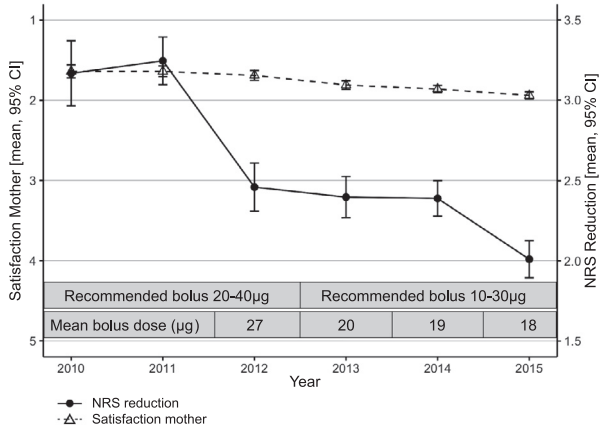

Fig. 2 Maternal satisfaction and pain reduction in the first hour of treatment (recommended and administered bolus dose). Maternal satisfaction: 1–5 (1 = very satisfied, 2 = satisfied, 3 = undecided, 4 = unsatisfied, 5 = very unsatisfied). CI: confidence interval. NRS: numerical rating scale. The question about the highest bolus dose was not included in the first questionnaire used in 2010 and 2011 (no analysis for these years)

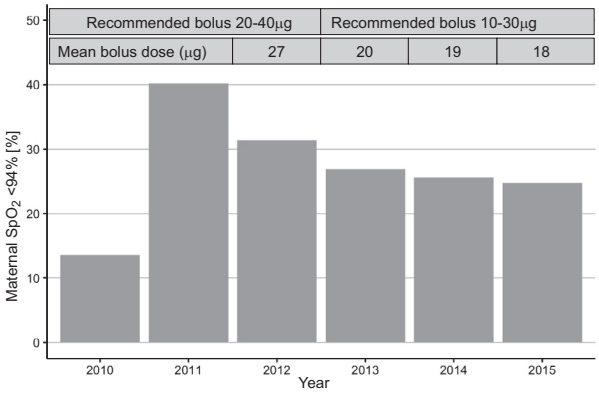

Fig. 3 Maternal hypoxia (SpO_2 <94%). Data reflect percentages when not indicated otherwise. The question about the highest bolus dose was not included in the first questionnaire used in 2010 and 2011 (no analysis for these years)

to 10–30 μg (maximum 30 μg). Following the recommendation of this bolus dose reduction in 2013, the mean bolus dose used subsequently reduced from approximately 27 to 18 μg (Table 1).

Fig. 2 correlates the remifentanil doses (recommended and actually applied) with the satisfaction scores and the pain reduction. The key observation was that during the stepwise decrease in the dose, pain reduction decreased (NRS change from −3.2 vs. −2) but satisfaction was only slightly affected.

Table 3 shows the incidence of maternal side effects. The incidence of maternal hypoxia in relation to the recommended and actually administered remifentanil bolus dose is illustrated in Fig. 3. The incidence of maternal hypoxia decreased from 40.2% in 2011 to 24.7% in 2015.

The mode of delivery of parturients, with or without conversion to epidural analgesia, is shown in Table 4.

Table 3 Maternal side effects

	2010	2011	2012	2013	2014	2015	Total
SpO_2 < 94%	56/423 (13.6%)	254/632 (40.2%)	239/762 (31.4%)	238/885 (26.9%)	322/1256 (25.6%)	306/1241 (24.7%)	1415/5189 (27.3%)
Sedation	97/435 (22.3%)	150/659 (22.8%)	231/798 (28.9%)	276/975 (28.3%)	371/1355 (27.4%)	309/1334 (23.2%)	1434/5556 (25.8%)
Nausea/Vomiting	89/435 (20.5%)	126/659 (19.1%)	160/798 (20.1%)	175/980 (17.9%)	185/1361 (13.6%)	206/1335 (15.4%)	941/5568 (16.9%)
Pruritus	20/435 (4.6%)	14/659 (2.1%)	20/786 (2.5%)	38/972 (3.9%)	33/1354 (2.4%)	31/1327 (2.3%)	156/5533 (2.8%)

Data are number/number of cases included (%). SpO_2: oxygen saturation.

Table 4 Mode of delivery of parturients not changing from remifentanil patient-controlled analgesia; and having converted to epidural analgesia prior to delivery

Mode of delivery	Analgesia for delivery		Total n=5400
	Remifentanil PCA until delivery n=4319	Remifentanil PCA with conversion to epidural analgesia n=1081	
Spontaneous vaginal	3480 (80.6%)	416 (38.5%)	3896
Instrumental	508 (11.7%)	305 (28.2%)	813
Caesarean section	331 (7.7%)	360 (33.3%)	691

Data are numbers (%). PCA: patient-controlled analgesia.

Table 5 Duration of remifentanil patient-controlled analgesia, dependent on cervical dilatation, in nulliparous compared with multiparous women who delivered vaginally

Cervical dilatation	Nullipara n=1717		Multipara n=1375	
	Number (%)	Duration [h]	Number (%)	Duration [h]
less than 1 cm	74 (4%)	5.0 (1.3, 13.0)	44 (3%)	2.6 (1.3, 10.7)
1–4 cm	595 (35%)	4.3 (0.2, 13.2)	511 (37%)	2.3 (0.3, 10.2)
5–9 cm	865 (50%)	3.0 (0.3, 16.0)	722 (53%)	1.7 (0.2, 16.8)
fully dilated	183 (11%)	1.7 (0.1, 5.2)	98 (7%)	1.1 (0.0, 11.2)
Total	**1717** (100%)	**3.3** (0.1, 16.0)	**1375** (100%)	**1.8** (0.0, 16.8)

Data are numbers (%) and duration is stated as median (minimum, maximum).

Table 6 Neonatal outcomes

	2010	2011	2012	2013	2014	2015	Total
Oxygen supplementation	NA	NA	54/486 (11.1%)	64/737 (8.7%)	80/1034 (7.7%)	50/995 (5.0%)	248/3261 (7.6%)
Bag/mask ventilation	NA	NA	25/481 (5.2%)	31/737 (4.2%)	46/1034 (4.4%)	27/995 (2.7%)	129/3256 (4.0%)
Umbilical cord pH <7.1	11/257 (4.3%)	30/434 (6.9%)	25/489 (5.1%)	26/714 (3.6%)	32/1004 (3.2%)	29/951 (3.0%)	153/3849 (4.0%)
Apgar score <7 at 1-min	36/276 (13.0%)	58/446 (13.0%)	54/493 (11.0%)	70/737 (9.5%)	96/1035 (9.3%)	75/995 (7.5%)	389/3982 (9.8%)
Apgar score <7 at 5-min	7/276 (2.5%)	14/448 (3.1%)	14/493 (2.8%)	8/737 (1.1%)	26/1035 (2.5%)	18/995 (1.8%)	87/3984 (2.2%)

Data are numbers/number of cases included (%). NA: not available (question was not included in the first questionnaire).

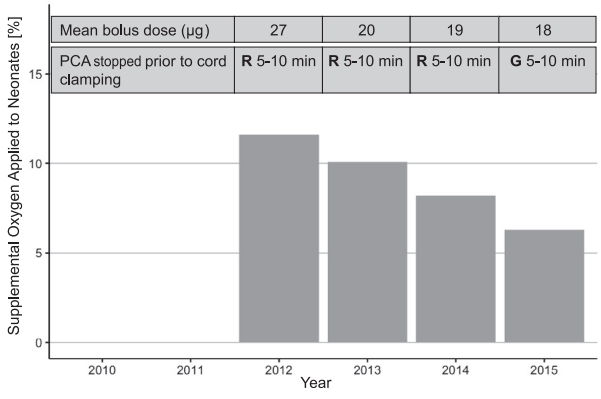

Fig. 4 Supplemental oxygen applied to neonates. Data reflect percentages when not indicated otherwise. R: Recommendation. G: Guideline (set as a mandatory standard in the network standard operating procedure)

The duration of remifentanil PCA, depending on cervical dilatation at initiation of remifentanil, is depicted in Table 5.

Neonatal outcomes and side effects are displayed in Table 6. Oxygen supplementation and bag/mask ventilation of the neonate was documented from 2012 onwards. The need for supplemental oxygen decreased steadily over the years (Fig. 4). The need for bag/mask ventilation showed a declining trend. The proportion of neonates with umbilical cord pH <7.1 showed a reduction from 2011 onwards. The proportion of neonates with an Apgar score <7 at 1-minute showed a decreasing trend, in contrast to the 5-minute Apgar score which did not. The success rate of feeding (breast or bottle) within the first two hours of delivery did not change over the years.

A summary of all severe adverse events is shown in Table 7. No maternal severe adverse event was reported.

Table 7 Severe maternal and neonatal adverse events

		2010	2011	2012	2013	2014	2015	Total
Total number of cases		(438)[†]	(662)[†]	855	1033	1386	1366	4640
Ventilation mother		–	–	0	0	0	0	0
CPR mother		–	–	0	0	0	0	0
CPR neonate (n=4559)	Alerts unrelated to PCA[‡]	–	–	7	7	22	13	49 (1.1 %)
	Alerts potentially related	–	–	3[¶]	8[¶]	1	1	13 (0.3 %)
	Total RemiPCA alerts	–	–	10	15	23	14	62 (1.4 %)

Data present absolute numbers when not otherwise indicated. PCA: patient-controlled analgesia. CPR: cardiopulmonary resuscitation.
[†]In 2010 and 2011 severe events were not specifically addressed in the questionnaire, but hospitals exchanged experience through direct contact. These cases are not included in the overall number of cases.
[‡]Unrelated to remifentanil PCA if (a) conversion to epidural analgesia, (b) delivery via caesarean section, (c) remifentanil PCA was stopped >15 min prior to delivery, (d) severe neonatal pathology or pathological course of delivery was already known or present.
[¶]In 2012 and 2013, it was not possible to evaluate the event regarding the relation to remifentanil PCA. The RemiPCA Alert function, including detailed reporting for the evaluation of severe events, was established in 2014.

Only one critical maternal incident was reported. In this case, the parturient suffered a short-term apnoeic period without the need for bag/mask ventilation. This incident was caused by a manipulation on the syringe without closing the three-way-tap, leading to an uncontrolled remifentanil bolus. After prompt verbal and physical stimulation by the midwife, the patient immediately started breathing and respiration returned to normal. The rate of neonatal severe adverse events was 62 out of 4559 (1.4%), of which 13 (0.3% overall) were considered to be potentially related to remifentanil PCA administration.

Discussion

This audit investigates the use of remifentanil PCA for labour analgesia in hospitals in Switzerland and Germany participating in the RemiPCA SAFE Network. The network, with its central database, was initiated in 2009 to support the safe use of remifentanil PCA in labour by collecting data about applications, and by disseminating warnings and modifications to the protocol emerging as a result of annual data analyses and critical appraisal of the literature.

This large database audit analyses the quality of remifentanil PCA usage for labour analgesia outside the controlled environment of clinical trials.

The main finding of the study is that remifentanil PCA can be used safely within the framework of supporting measures from the network. Approximately 80% of parturients delivered without converting to epidural analgesia, which is similar to the findings of the RESPITE trial.[10] No maternal and 13 (0.3%) neonatal severe adverse events, potentially related to the application of remifentanil PCA, were reported during the observation period.

The most recent Cochrane review on remifentanil PCA emphasises that reliable data on efficacy, and explicitly on safety, are still lacking,[11] and some authors have criticised remifentanil PCA for labour analgesia because of safety issues.[12] Safety issues consist of severe life-threatening events and side effects that may be either short-lived (e.g. nausea in the mother, short-lived respiratory depression only needing tactile stimulation) or long-lasting (e.g. problems to initiate breastfeeding).

This audit showed that severe events related to remifentanil PCA were extremely rare and typically short-lasting. Among 5740 reported administrations, no maternal bag/mask ventilation or cardiopulmonary resuscitation was registered. A single critical maternal incident was reported when the manipulation of the PCA pump led to an inadvertent manual bolus dose, causing short-term maternal apnoea, with immediate recovery after stimulation. The root-cause analysis of this event identified an open three-way tap during the manipulation of the pump as a contributor. Subsequently a note of caution was added to the respective section of the SOP, participating hospitals were informed and this information was specifically used for training. This event adds to previous ones where an unintentional large bolus dose was applied.[4,5] Out of data from 4559 neonates, severe adverse events potentially related to remifentanil were documented in 13 (0.3%), with other large retrospective studies showing that neonatal resuscitation was necessary in 0.08%[13] to 1.48%[14] of live births without remifentanil PCA.

In 2012 and 2013, severe adverse events were registered in the RemiPCA SAFE Network without further details, but after 2014 it became possible to judge the causal role of remifentanil on the basis of a detailed report triggered by the RemiPCA Alert function. It was reassuring that not only minor events but also severe or critical ones were reported. However, we cannot exclude underreporting of critical events due to the voluntary nature of the report.

Current literature indicates that maternal adverse events are associated with remifentanil bolus doses of 40 µg and above or with the concomitant use of long-acting opioids.[4–7] This led to three changes of the Network SOP, starting in 2013. The first was to have a minimum time interval of four hours between long-acting opioids and the start of remifentanil PCA; the

second to reduce the bolus dose from a maximum of 40 μg to a maximum of 30 μg; and the third to increase the threshold for supplemental oxygen administration from SpO_2 <92% to <94%.

The audit data show adherence to these recommendations. The mean bolus dose given reduced after 2012, as did the incidence of maternal hypoxia. The reduction of bolus dose was associated with less pain relief and lower maternal satisfaction. However, in 2015, more than 85% of the parturients remained either "very satisfied" or "satisfied". The other maternal side effects in our audit did not follow such an apparent trend. Pain was assessed before and one hour after the start of remifentanil analgesia, as suggested in previous trials.[3,15] From these data, however, we cannot conclude how stable these effects are, as previous reports suggest that analgesia decreases over time.[3,15] Assessment of sedation and nausea or vomiting was not standardised. We plan to establish assessment standards in a future release of the database questionnaire. Additionally, in parallel to the reduction in bolus dose, the conversion rate to epidural analgesia increased from 2011 to 2015. Despite using a lower bolus dose, the overall conversion rate of 21% in this audit is similar to the conversion rate of 19% found in the RESPITE trial.[10] Parturients who converted to epidural analgesia had substantially more instrumental and caesarean deliveries. Insufficient analgesia with remifentanil and conversion to epidural analgesia could be a predictor for the need of assisted or operative delivery.

In 2013 the network recommended stopping remifentanil PCA 5–10 min prior to cord clamping. Altogether, only a small proportion of neonates required interventions, such as supplemental oxygen or bag/mask ventilation, with a trend towards fewer interventions over the years. The same is true for improved 1-min, but not 5-min Apgar scores. This might reflect the very short-lasting effect of remifentanil in the newborn. The proportion of neonates with umbilical cord pH <7.1 also fell between 2011 and 2015.

There are clear limitations to this analysis. First, underreporting of severe events cannot be excluded. Second, the maternal outcomes "pain" and "satisfaction", as well as most side-effects, were recorded by midwives, which may favour a certain bias. Neonatal interventions and outcome measurements (such as measurement of arterial or venous umbilical cord pH) were dependent on the individual labour ward practices.

Some other aspects need to be taken into account. The introductory year 2010 differed from the following years: there was little familiarity with the method and data were generated predominantly by a single hospital (86% of all data in 2010). The high conversion rate to epidural analgesia in 2010 may be due to the lack of experience. In addition, the relatively few reports of desaturation (SpO_2 <94%) probably reflect underreporting due to the process of transferring the standards of correct documentation into clinical practice. Therefore conversion rate and maternal hypoxia for the year 2010 need to be interpreted with caution.

There are multiple causes for the changes observed over the time period studied. First, this network started with three centres and 438 remifentanil PCA cases in 2010. The number of participating hospitals increased rapidly to a total of 31 centres and 1366 documented annual cases in 2015. There were changes of recommendations and an increase in familiarity with the use of remifentanil PCA, together with dedicated training sessions either from internal personnel or the network operating team. Finally, generalisation of these data is limited to institutions participating in the RemiPCA SAFE Network, as the flow of information and continuous process of improvement from the centres (application reports, severe event case reports) and back to the centres (changes of SOP, benchmarks) can only be assured within the network.

In summary, the RemiPCA SAFE Network is able to set standards and transfer them into safe clinical practice, while simultaneously monitoring this process. This audit shows that it is possible to safely apply remifentanil PCA in labour, as long as strict safety standards are applied and the compliance to these standards is controlled. The network can offer guidance and support to hospitals and functions as a monitoring and steering instrument of pain management.[16] In addition to clinical trials, it gives a view on the course of labour and the influence of labour analgesics in the routine labour ward setting and bundles outcome data from various hospitals. The results gained from this audit have clear limitations but might detect trends and pitfalls in the clinical application of remifentanil PCA for labour analgesia. One consequence of this analysis is to further improve standardisation in terms of outcome measurements, SOPs and guidelines.

Since 2016 the network has been open to international hospitals which use different protocols. This will increase the data bias and pose more challenges to analysis. If as a consequence of the RESPITE trial, remifentanil PCA is used on a larger scale[10] it will be even more important to monitor outcomes and improve regimens and safety procedures in a common effort.

Disclosure

A.M. and T.G. are board members of the Swiss Association of Obstetric Anaesthesia (SAOA). A.M. and M.H. are founding members of the RemiPCA SAFE Network.

Funding

This study was supported by an external grant for statistical analysis from the Obstetric Anaesthetists' Association (2017) in addition to departmental funding by the

Department of Anaesthesiology, University Hospital Würzburg, Department of Anaesthesiology University Hospital Basel, Department of Anaesthesiology, Spital Münsingen Inselgruppe AG, Institute for Anaesthesia and Intensive Care Medicine, Spital Thurgau Frauenfeld; Condesys Consulting GmbH contributed all development work for the RemiPCA database and website on a voluntary basis.

Acknowledgement

We are very grateful to Stephan Blumenthal for his support by initialising the audit and Petri Volmanen for his valuable inputs to the manuscript. We would like to thank the RemiPCA SAFE Network Group and all midwifery and medical staff for their continuous participation and data entry.

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Appendix A. RemiPCA SAFE Network Group

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