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ORIGINAL ARTICLE

Remifentanil patient-controlled intravenous analgesia during labour: a retrospective observational study of 10 years' experience

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ABSTRACT
Background: Intravenous remifentanil patient-controlled analgesia (PCA) has been routinely available for labouring women in our unit since 2004, the regimen using a 40 μg bolus available two minutely on demand, continuous pulse oximetry and mandatory one-to-one care. We examined remifentanil use and compared, with the other analgesic options available in our unit, outcomes such as mode of delivery, Apgar scores, neonatal resuscitation and admission to the neonatal intensive care unit.
Methods: We retrospectively identified women who delivered in our unit between 2005 and 2014 and received remifentanil, diamorphine or epidural analgesia during labour. Data were drawn from the Northern Ireland Maternity System electronic database, which records birth details from all obstetric units in Northern Ireland. Additional data were identified from paper survey forms, completed by the midwife post delivery for all women who received remifentanil in our unit. Outcomes were compared between women who received remifentanil, diamorphine or an epidural technique for labour analgesia.
Results: Over the 10-year period, remifentanil was the most popular form of analgesia, being selected by 31.9% (8170/25617) women. Compared with women selecting diamorphine or epidural analgesia, those having remifentanil had similar rates of instrumental and operative delivery. Neonatal Apgar scores were also similar. Neonatal resuscitation or neonatal unit admission were not more likely in women choosing remifentanil PCA.
Conclusion: We found remifentanil PCA to be neither less safe nor associated with poorer outcomes than other analgesic options offered in our unit, when used within our guidelines for more than a 10-year period.

Keywords: Labour analgesia; Maternal outcomes; Neonatal outcomes; Patient-controlled analgesia; Remifentanil; Safety

Introduction

Intravenous remifentanil patient-controlled analgesia (PCA) was first used in our unit in 2001 following a feasibility study and has been routinely available on request as an analgesic option for labouring women since 2004.[1] Since then, remifentanil PCA has become a popular choice, resulting in a one-third decline in our unit's epidural analgesia rate from 41% to 25%.

Epidural analgesia is the gold standard for labour pain relief because of its superior efficacy. While remifentanil PCA does not match labour epidural analgesia in satisfaction ratings, it appears to have an adequate analgesic effect.[2–4] Remifentanil PCA for labour analgesia may therefore be a feasible option for women who wish to avoid neuraxial analgesia or for those with physiological, pharmacological or anatomical contraindications to neuraxial block. However, respiratory arrest has been reported.[5–8]

We aimed to determine the safety of remifentanil PCA and the associated delivery outcomes, compared with intramuscular diamorphine and epidural analgesia administered in our unit, over a 10-year period. Safety outcomes included the need for neonatal resuscitation in the form of positive pressure ventilation (PPV), the rate of admission to the neonatal intensive care unit (NICU), and adverse incident reports associated with each method of analgesia. Delivery outcomes included mode of delivery (normal, instrumental or caesarean delivery) and the frequency of Apgar scores <7 at one and five minutes post delivery.

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Methods

This is a single-centre retrospective study of data collected during the period from 1st January 2005 to 31st December 2014. Approval for this study was sought and granted by the audit committee and trust Caldicott guardian. Database use and anonymised patient surveys form part of our routine care, so local research ethical approval was not required.

Inclusion criteria were all women delivering in our unit who had received remifentanil PCA, intramuscular diamorphine or epidural analgesia for labour analgesia. Exclusion criteria were women undergoing elective caesarean delivery and women receiving only Entonox® or oral analgesics such as paracetamol and codeine. Women receiving combined-spinal epidural (CSE) analgesia were also excluded as they comprised fewer than 1% of all deliveries per annum.

Remifentanil PCA in our unit has a single administration programme: 1 mL (40 μg) bolus, delivered over approximately six seconds and with a two-minute lockout period, and no background infusion. Continuous pulse oximetry is established before the PCA is initiated, with supplementary oxygen provided via nasal cannula if oxygen saturation falls below 95%. A midwife with training and expertise in the use of remifentanil provides continuous one-to-one care. The criteria for remifentanil PCA eligibility, the dosing regimen and the monitoring mandated are presented in e-Supplements A–C.

Intramuscular (IM) diamorphine 5 mg may be administered, without a physician order, by midwives for up to two doses every four hours. Subsequent doses must be prescribed by a physician. Labour epidural analgesia is provided by patient-controlled epidural analgesia (PCEA) using a continuous infusion of 0.1% levobupivacaine with 2 μg/mL fentanyl at a rate of 2–12 mL/h, plus demand boluses of 3 mL every 20 minutes.

We retrieved data from four sources: 1. Paper survey. All women using remifentanil PCA complete a post-delivery survey asked by their midwife. This records the overall pain intensity and satisfaction scores defined by the patient, maternal side effects experienced and details about additional analgesia used (e-Supplement D). These surveys are subject to regular hospital audit and outcomes have been published.[9–11] 2. The Northern Ireland Maternity System (NIMATS). This electronic database records all deliveries in obstetric units in Northern Ireland and data are completed at the time of delivery by a midwife involved in the woman's care. Our outcome data were accessed retrospectively from the NIMATS database and analysed both cumulatively and in discrete yearly intervals. 3. Trust incident reporting (IR1) system. This records any adverse events and was reviewed for the study time period. 4. Electronic patient administration system (PAS). This records inpatient and outpatient activity and was used to identify NICU admissions for the period 2011 to 2014 inclusive, when these data have been available in our unit.

Study outcomes measured were mode of delivery (vaginal, instrumental or caesarean); Apgar scores <7 at one and five minutes; the need for neonatal resuscitation (PPV); and the rate of admission to the NICU. The analgesia received at the time of delivery was analysed, without adjustment for any previous crossover between analgesia modalities (e.g. remifentanil PCA changed to epidural analgesia).

Statistical analysis was performed using SPSS (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp) and Stata (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP.) software packages. Fisher's exact test was used to compare Apgar scores and neonatal admission rates between the three analgesic options. Pearson's chi-squared test was used to compare mode of delivery between remifentanil and other analgesic groups. Odds ratios (OR) were calculated to compare the likelihood of requiring neonatal PPV between analgesic modes.

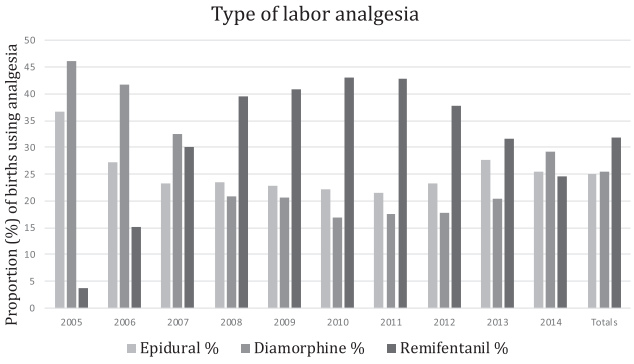
Results

In the study period, over 35 000 live babies were delivered in our unit. Other than Entonox®, which was used both as a sole agent and for supplementation of other analgesic options, remifentanil PCA was the most popular form of labour analgesia, selected by 31.9% of women, while 25.0% received labour epidural analgesia (Fig. 1).

Among women selecting remifentanil PCA, there was a higher proportion of normal deliveries compared with a higher proportion of instrumental deliveries and caesarean deliveries among women receiving labour epidural analgesia (Fig. 2). Women receiving epidural analgesia had a significantly higher rate of instrumental or operative delivery, in each of the years reported, when compared with women selecting remifentanil PCA (Fig. 2). There was no significant difference in delivery mode outcomes when comparing remifentanil PCA with IM diamorphine (Fig. 2).

The proportion of neonates with Apgar scores <7 at one and five minutes in each year are displayed according to the method of analgesia administered in Fig. 3. Apgar scores of neonates delivered by women who selected remifentanil PCA or IM diamorphine were similar. There was usually a higher proportion of one- and five-minute Apgar scores <7 among women receiving epidural analgesia. This reached significance in one year (2011) when compared to women selecting remifentanil PCA or IM diamorphine (Fig. 3).

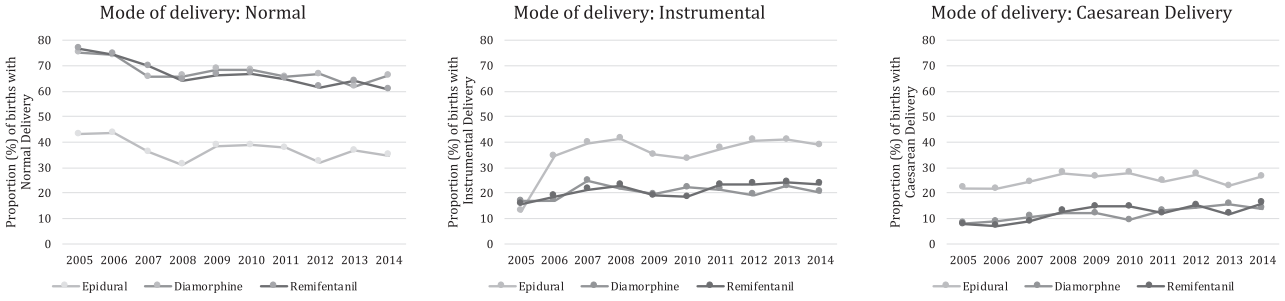
The incidence of neonatal PPV was consistently higher among women receiving epidural analgesia in each year, whereas remifentanil PCA and IM diamor-



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	**Totals**
Epidural n (%)*	751 (36.6)	589 (27.3)	533 (23.2)	613 (23.4)	599 (22.9)	568 (22.1)	624 (21.6)	668 (23.2)	740 (27.7)	731 (25.5)	6416 (25.0)
Diamorphine n (%)	949 (46.2)	899 (41.7)	745 (32.4)	548 (20.9)	540 (20.7)	435 (16.9)	510 (17.6)	510 (17.7)	545 (20.4)	833 (29.1)	6514 (25.4)
Remifentanil n (%)	77 (3.7)	328 (15.2)	688 (30)	1037 (39.5)	1066 (40.8)	1108 (43)	1240 (42.8)	1084 (37.7)	842 (31.6)	700 (24.5)	8170 (31.9)

* Values are number (proportion) of live births with each form of analgesia

Fig. 1 Choice of labour analgesia (epidural, intramuscular diamorphine or remifentanil intravenous patient-controlled analgesia) in each year for births from 2005 to 2014, including 10-year totals

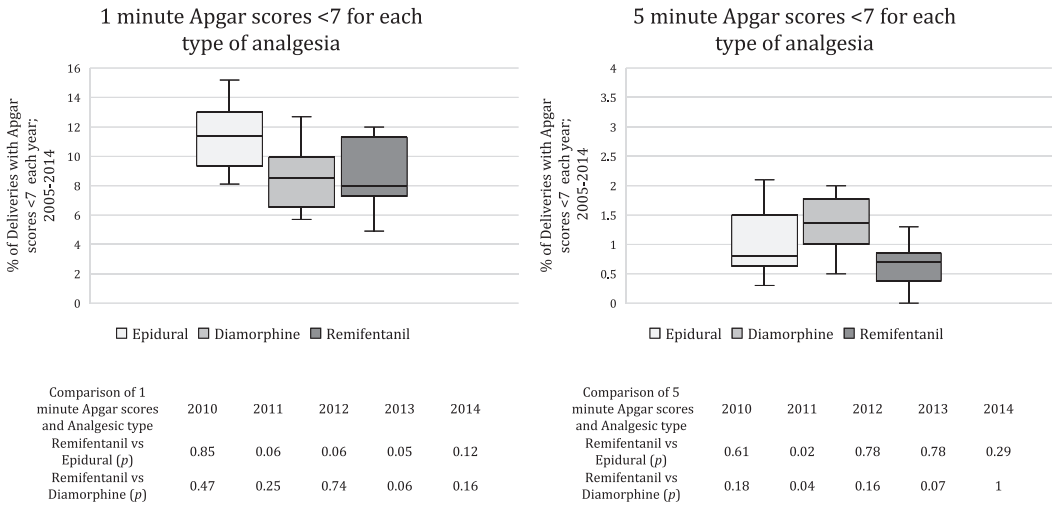


Comparison of Mode of Delivery and Analgesic Type	2010	2011	2012	2013	2014
Remifentanil vs Epidural (p)	0.00	0.00	0.00	0.00	0.00
Remifentanil vs Diamorphine (p)	0.01	0.58	0.11	0.12	0.09

Fig. 2 Proportion of births which were normal, instrumental or by caesarean delivery in each year from 2005 to 2014, according to the method of analgesia used. This includes comparison of remifentanil intravenous patient-controlled analgesia with intramuscular diamorphine and with epidural analgesia for the incidence of normal, instrumental or operative delivery

phine had similar frequencies (Table 1). No neonates required treatment with naloxone following delivery. Mean annual NICU admission rates were approximately 13%, with 3% admitted on the day of birth. Women selecting remifentanil PCA had the lowest proportion of neonatal NICU admissions when compared to women receiving either epidural analgesia or IM diamorphine (Table 1).

In our review of paper survey forms, the trends in parity, spontaneous or induced labour, analgesia and satisfaction scores for remifentanil PCA were largely unchanged over the past 10 years from those previously reported.[10,11] Supplemental oxygen was used in approximately 22% of women in 2011, however as the result of policy change, the 2014 audit showed an increase in use to 53.6% of women (Table 2). Prior to October 2012 remifentanil had been discontinued if desaturation occurred to an oxyhaemoglobin saturation (SpO_2) of <90%, but thereafter this was practised if SpO_2 was <95% (Table 3). Analysis of our institution's incident



Comparison of 1 minute Apgar scores and Analgesic type	2010	2011	2012	2013	2014
Remifentanil vs Epidural (p)	0.85	0.06	0.06	0.05	0.12
Remifentanil vs Diamorphine (p)	0.47	0.25	0.74	0.06	0.16

Comparison of 5 minute Apgar scores and Analgesic type	2010	2011	2012	2013	2014
Remifentanil vs Epidural (p)	0.61	0.02	0.78	0.78	0.29
Remifentanil vs Diamorphine (p)	0.18	0.04	0.16	0.07	1

Fig. 3 Proportion of Apgar scores <7 at one and five minutes post delivery according to the method of analgesia, showing median and interquartile range data points; and including a comparison of the incidence of low Apgar scores between remifentanil intravenous patient-controlled analgesia, intramuscular diamorphine and epidural analgesia

Table 1 Neonatal resuscitation requirement and neonatal intensive care unit admission* according to method of labour analgesia

	2010	2011	2012	2013	2014	Total
Epidural group PPV n (%)	75 (13.2)	111 (17.8)	115 (17.2)	122 (16.5)	110 (15.0)	533 (16.0)
IM diamorphine group PPV n (%)	63 (14.5)	66 (12.9)	70 (13.7)	84 (15.4)	118 (14.2)	401 (14.2)
Remifentanil PCA group PPV n (%)	132 (11.9)	194 (15.6)	151 (13.9)	109 (12.9)	102 (14.6)	688 (13.8)
Remifentanil vs epidural OR (95% CI)	0.89 (0.65 to 1.22)	0.86 (0.70 to 1.12)	0.78 (0.59 to 1.02)	0.75 (0.56 to 1.01)	0.96 (0.71 to 1.30)	
Remifentanil vs IM diamorphine OR (95% CI)	0.80 (0.57 to 1.12)	1.25 (0.92 to 1.71)	1.02 (0.74 to 1.40)	0.82 (0.59 to 1.13)	1.03 (0.77 to 1.39)	
Epidural group NICU admission n (%)	+	24 (3.9)	25 (3.7)	29 (3.9)	22 (3.0)	100 (3.6)
Diamorphine group NICU admission n (%)	+	18 (3.5)	21 (4.1)	10 (1.8)	16 (1.9)	65 (2.7)
Remifentanil PCA group NICU admission n (%)	+	14 (1.1)	19 (1.8)	14 (1.7)	16 (2.3)	63 (1.6)
Remifentanil vs epidural (P-value)		0.000	0.012	0.008	0.416	
Remifentanil vs IM diamorphine (P-value)		0.001	0.009	0.835	0.721	

Values are number (percentage) of neonates requiring positive pressure mask ventilation (PPV) and admission to the neonatal intensive care unit (NICU) after birth in each analgesic group, for each year; PCA: patient-controlled analgesia; OR: odds ratio; CI: confidence interval.
*Excludes births with admission to NICU after day of birth.
+Data on NICU admissions were not available on PAS system until 2011.

reporting (IR1) system revealed no additional incidents (of adverse maternal or neonatal outcomes) with remifentanil PCA use.

Discussion

In the current study we reported remifentanil PCA use in over 8100 labouring women and found no greater likelihood of instrumental or operative delivery, and similar neonatal status post delivery, compared to babies born to women in our unit receiving other methods of labour analgesia (IM diamorphine or epidural analgesia).

Without adjustment for other contributing factors, the favourable results regarding non-operative delivery and Apgar scores with remifentanil PCA potentially reflect that more complicated labours may require epidural analgesia to assist in their management. As

Table 2 Supplemental oxygen use with remifentanil patient-controlled analgesia

Supplemental oxygen required	2011[+] n (%)	2014 n (%)
Yes	215 (21.9)	221 (53.6)
No	766 (78.1)	106 (25.7)
Unknown	0 (0)	85 (20.6)
Total	981	412

[+]2011 data drawn from previously published data.[10] 2009 local audit reported supplemental oxygen use in 21% of women using remifentanil patient-controlled analgesia.

women with low-risk deliveries were more likely to use opioid analgesic options, this may explain the greater need for neonatal resuscitation among women receiving epidural analgesia.

Remifentanil PCA is less invasive than epidural analgesia and provides an element of personal control over labour pain. From our paper survey forms, we know that concomitant use of nitrous oxide (Entonox®) remains high and has increased progressively, with over 93% of women choosing to supplement their remifentanil PCA, particularly in the later stages of labour. The effect of Entonox® usage on total consumption of remifentanil was not measured. While the rates of women experiencing adverse effects appears high (53–56% experiencing one or more side effect), these rates are similar to those reported in earlier studies;[1,2,12,13] and more than 87% of women each year stated that they would consider using remifentanil PCA for future labour analgesia. Nausea was the predominant side effect reported, however this is unlikely to be solely attributable to remifentanil alone, as the use of Entonox®, and labour itself, are also highly emetogenic in isolation.[14]

The proportion of women requiring supplemental oxygen in our unit has more than doubled, from 22% in 2011 to 54% in 2014, as a result of a change in policy in response to literature reports of severe adverse incidents and our own increasing experience with remifentanil.[5–8,10] Furthermore, our current protocol dictates discontinuation of remifentanil PCA if there is failure to maintain oxygen saturation at 95% or more with supplemental oxygen. Previous studies have demonstrated maternal desaturation in 40–70% of women using remifentanil PCA, with supplemental oxygen reducing the overall number but not the severity of episodes.[2,15] Somewhat encouragingly, poorer Apgar scores or lower neonatal pH have not been found to correlate with episodes of maternal desaturation.[16,17]

Recent reviews have suggested the use of capnography should be mandatory in all cases of remifentanil PCA during labour,[18] however that is not a form of monitoring we currently utilise. Interpretation of capnography in the setting of labour may be complicated by wide variations in respiratory patterns, diffusion hypoxia and dilution of end-tidal carbon dioxide (CO_2) with Entonox® or supplemental nasal oxygen. One study involving capnography using an oral-nasal cannula described compliance issues and multiple complexities in analysing episodes of apnoea.[19] The potential safety concern of alarm fatigue and desensitisation are also important as these factors have been attributed to patient deaths.[20]

In our unit, women are monitored with the constant presence of a midwife, which enables a prompt response to clinically significant hypoventilation. This may not be a universally feasible option due to increasing midwifery vacancies and a rise in the proportion of units which report insufficient funding to meet even the current demands on service.[21,22] A 2011 survey in the United Kingdom (UK) reported that 50% of units planned to use remifentanil PCA, however of the 14% of units that did not, a main reason was difficulty in adequately monitoring recipients.[23]

Although labour epidural analgesia provides superior pain relief, in our unit remifentanil PCA appears to provide a satisfactory experience, as demonstrated by the low conversion rate to epidural analgesia of 8–9% across the past 10 years. This finding is echoed in other literature.[4,12] Wilson et al. reported a conversion rate of 19% from remifentanil PCA. While we did not examine reasons for conversion to epidural analgesia, this difference in incidence may be attributable to the free choice of remifentanil in our unit, whereas in the randomised

Table 3 Trends in reasons for discontinuing remifentanil patient-controlled analgesia

Reason for stopping remifentanil PCA	2008[*] n (% of 603)	2011[+] n (% of 981)	2014 n (% of 412)
Desaturation	4 (0.66)	3 (0.31)	1 (0.24)
Drowsiness	5 (0.83)	5 (0.51)	1 (0.24)
Other side effect	4 (0.66)	7 (0.71)	0 (0)
Inadequate analgesia	24 (3.98)	83 (8.46)	32 (7.77)
Pushing	0 (0)	307 (31.29)	172 (41.75)
Technical problem	5 (0.83)	7 (0.71)	2 (0.49)
Instrumental or CD	65 (10.78)	116 (11.82)	40 (9.71)
Total no. stopped	107 (17.74)	528 (53.82)	248 (60.19)

PCA: patient-controlled analgesia; CD: caesarean delivery. [*]2008 and [+]2011 data drawn from previously published data.[9,10] Values are number (percentage) of all remifentanil users that were discontinued.

controlled trial by Wilson et al. 11% of women randomised to receive pethidine requested epidural analgesia instead.[24]

Limitations of our study include the single-centre experience that reduces generalisability, and its retrospective nature. Paper survey forms are not routinely completed for other forms of analgesia so no comparison of these could be made with remifentanil PCA. In addition, an element of partiality exists, as women scored their satisfaction after selecting remifentanil PCA. Descriptive statistics, rather than *P*-values, were predominantly used throughout this paper. As our data were analysed retrospectively, and involved multiple outcomes and time points, further exploratory analysis might lead to spurious results. Although these data provide low-quality evidence on maternal and neonatal safety outcomes, we report a large volume of cases with 8100 labouring women. We are now recording our data in a broader database which can be analysed and compared with other centres worldwide.

In conclusion, in this retrospective study neonatal outcomes associated with remifentanil PCA were favourable and similar to other modes of analgesia. This suggests that remifentanil may be safe for the mother and baby and that outcomes may be comparable to other labour analgesic options available in our unit. We advocate for remifentanil PCA to be offered routinely as a labour analgesic option, provided rigorous adherence to protocols and regular staff training are ensured. The constant presence of a midwife is essential for uninterrupted monitoring and timely management of respiratory depression or other severe adverse events. More high-quality research on safety outcomes is required and further trials investigating the use of capnography, particularly in combination with Entonox®, would be welcome.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijoa.2019.05.012.