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ORIGINAL ARTICLE

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Effect-site concentration of remifentanil during patient-controlled analgesia in labour

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ABSTRACT
Background: Intravenous remifentanil has been described for patient-controlled analgesia in labour. Recently, the application of target-controlled infusion pumps with Minto's pharmacokinetic/pharmacodynamic model has been reported. Hypothetical effect-site remifentanil concentration during patient-controlled analgesia for labour has yet to be examined. The aim of this concept study was to explore characteristics of this parameter.
Methods: We performed a historical cohort study based on our previous randomised cross-over clinical trial and analysed hypothetical effect-site remifentanil concentration. Values at spontaneous vaginal delivery and Apgar scores were tested for correlation. The association between pain score and the corresponding effect-site remifentanil concentration before and after bolus administration, and their relative difference, was examined with a linear mixed-effects model, adjusted for other variables.
Results: A series of 23 parturients with uncomplicated singleton pregnancies were included. On average, effect-site remifentanil concentration was highest during the third quarter throughout our recordings (5.5 ng/mL; maximum 15.8 ng/mL). The mean (median) {IQR} [range] at spontaneous vaginal delivery (n=14) was 2.52 (1.32) {0.95–4.28} [0.65–6.88] ng/mL, all Apgar scores were >7, and no correlation was confirmed. A negative association between effect-site remifentanil concentration before bolus administration and pain score (scale 0–100) was observed (−3.9, 95% CI −5.16 to −2.61, P <0.01).
Conclusions: The residual value of hypothetical effect-site remifentanil concentration before uterine contraction, at the beginning of bolus administration, predicted lower pain scores. Monitoring effect-site remifentanil concentration may be potentially useful when remifentanil is administered for labour analgesia. However, our results need to be confirmed with a pharmacokinetic model optimized for pregnant patients.

Keywords: Remifentanil; Labour pain; Patient-controlled analgesia; Effect-site concentration; Pharmacokinetic modelling

Introduction

Numerous studies have shown a wide therapeutic range when intravenous remifentanil is used for patient-controlled analgesia (PCA) to treat labour pain. Many different regimens have been described; however, most publications have only reported the ranges or means of the PCA bolus doses, lock-out periods, background infusion rates, and remifentanil consumption.[1–7] Few studies have reported remifentanil concentrations taken from mothers during labour and from the umbilical cord after delivery.[6,8]

Recently, the use of target-controlled infusion (TCI) pumps has been reported, providing some insight into the hypothetical effect-site remifentanil concentration (ESRC) for labour analgesia.[9] Commercially available TCI pumps typically use Minto's three compartment pharmacokinetic/pharmacodynamic (PK/PD) model, established in non-pregnant volunteers.[10,11] This model has also been used for a simulation study on optimal PCA bolus timing.[12]

In our opinion, a better way to present remifentanil consumption and compare different dosing regimens is to report the time profile of ESRC during labour PCA. Furthermore, monitoring this parameter in real-time could be useful for improving remifentanil use. This approach has not been reported previously. The aim of this retrospective study was to explore hypothetical ESRC in PCA for labour. Our secondary goal was to analyse its value at childbirth and possible correlation with Apgar scores, and to analyse the association between pain and corresponding ESRC values before

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and after bolus administration, and their relative difference.

Methods

Approval for the study (77/01/14) was provided by the Republic of Slovenia National Medical Ethics Committee. We obtained written informed consent from the study participants for data processing. A historical cohort study was performed on data from our previous prospective single-blind randomised cross-over trial.[13] Healthy parturients with non-problematic singleton pregnancies were recruited between January 2010 and July 2010. We compared a 'modified' PCA bolus delivery regimen with a 'classical' one. The classical bolus delivery regimen used fixed remifentanil bolus doses (20–55 μg) whereas in the modified regimen the parturients were instructed to hold down the PCA button until the peak of each contraction and the dose depended on the duration of pressing (up to 60 μg). The remifentanil bolus infusion rate for the classical regimen was 1.2 μg/s throughout the bolus delivery, while the modified regimen started with 3 μg/s and decreased by 20% of the initial rate every 6 s in a stepwise fashion until the button was released. Both regimens included a low rate (50 μg/h) background remifentanil infusion and a lockout of 1 min. Participants were randomised to begin with one of the two regimens at the start of treatment. After a set of five successive contractions, the regimens were swapped. The evaluation period started with the first set and was terminated at the beginning of the active second stage; approximately 10 min before expected delivery. At least four sets had to be completed, and the highest even number of sets was considered for analysis. Apgar scores at 1 and 5 min were recorded.

For every uterine contraction, we assessed pain with a visual analogue scale (VAS) pain score with numeric values from 0 to 100. After every set, maternal parameters (non-invasive blood pressure, heart rate, arterial saturation, sedation) and fetal status (pulse, pulse variability) were assessed. We recorded side-effects, bolus adjustment interventions, and PCA bolus requests within the lockout period. A custom-made infusion pump was used which provided real-time calculation and display of hypothetical plasma and ESRC values (Appendix A).

In the present study, all cases from the previous clinical trial were included. The ESRC recordings were analysed from the beginning of the first set until the exact time of childbirth or until stopping the pump (e.g. transfer to the operation theatre for caesarean section). All available pain scores were used, including data from uncompleted sets.

Statistical analysis

To provide an overview of the values of ESRC throughout labour in our cases, we processed all recordings on a relative time scale, relative to the length of every recording, as defined earlier. We calculated the mean value and standard deviation (SD) of ESRC and looked for the maximums over relative time. In cases when labour ended with vaginal delivery, we performed a descriptive analysis of the ESRC at childbirth and of the corresponding Apgar scores. Kendall's Tau-b correlation coefficients were calculated. To demonstrate different presentations of remifentanil usage during PCA for labour, we compared the running 20-min and 60-min average consumption and the cumulative dose with ESRC in a real case. Possible association between pain, ESRC, and other confounders during labour progression was examined. We used successive bolus number instead of the time variable (real or relative), as pain was estimated immediately after every contraction (i.e. every bolus delivered during the evaluation period). For every bolus, we defined two points on the ESRC curve. The lowest ('residual') value appeared just seconds after starting the pump, following the demand for the new bolus (C_{low}). About 70 s after initiation of the bolus administration, ESRC reached its peak (C_{high}). The relative difference between them was C_{diff}. Fig. 1 demonstrates a 15 min section, showing infusion

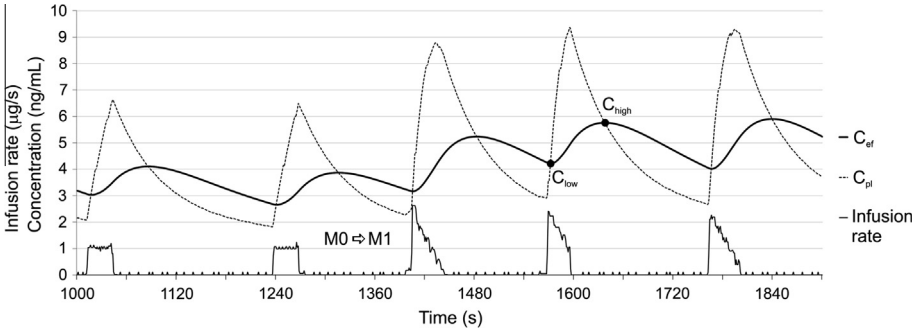

Fig. 1 Patient-controlled analgesia for labour. Time charts for infusion rate, calculated plasma (C_{pl}) and effect-site (C_{ef}) remifentanil concentrations are displayed in a 15 min section. C_{low} and C_{high} are marked for the fourth bolus only. Note the change in the mode of bolus delivery from the classical (M0) to the modified (M1) regimen between the second and the third bolus administration