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OBSTETRICS

Can remifentanil use in obstetrics be improved by optimal patient-controlled analgesia bolus timing?

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Editor's key points

- Patient-controlled remifentanil boluses may have a role in the management of labour pain.
- Ideally, peak levels of remifentanil should coincide with maximum uterine contractions.
- This study used quantifying contraction strength to improve modelling of remifentanil concentrations.
- It was not possible to coordinate peak remifentanil concentrations with contraction strength.
- Safe use of remifentanil boluses in obstetric pain management will still require careful clinical monitoring.

Background. The safety of patient-controlled i.v. analgesia (PCA) with remifentanil for obstetrical analgesia remains a matter of concern. The efficacy of remifentanil bolus application, that is, the coincidence between pain and remifentanil effect-site concentration, may be improved by forecasting contractions, but it is not known whether such a technique would also improve safety.

Methods. We recorded pain intensity during labour continuously using a handheld dynamometer in 43 parturients. Using these data, we compared different models in their ability to predict future contractions. In addition, we modelled remifentanil effect-site concentration using three simulated modes of bolus administration, with and without prediction of future contractions.

Results. The average duration of pain during contractions recorded by the dynamometer was 45 [14 standard deviation (SD)] s. The time interval between painful contractions was highly variable, with a mean of 151 (31 SD) s during the first and 154 (52 SD) s during the second recording. Using a simple algorithm (three-point moving average), the SD of the difference between predicted and observed inter-contraction intervals can be reduced from 0.95 to 0.79 min. However, the coincidence between remifentanil concentration and pain during contraction is not substantially improved when using these models to guide remifentanil bolus application.

Conclusions. Because of the large variability of inter-contraction intervals, the use of prediction models will not influence the mean remifentanil concentration in-between contractions. Using models predicting future contractions to improve the timing of remifentanil PCA bolus administration will not diminish the need of continuous clinical surveillance and other safety measures.

Keywords: analgesia, obstetrical; analgesia, patient-controlled; forecasting; pharmacokinetics; remifentanil; safety

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The use of remifentanil for analgesia during labour has become increasingly popular in recent years.[1–3] However, as documented by several case reports,[4–7] serious side-effects do exist, and therefore, studies looking at the optimization of the efficacy and safety of remifentanil patient-controlled analgesia (PCA) during labour are needed.

In theory, the efficacy of remifentanil application during labour will be determined by the effect-site concentration of remifentanil reached during a contraction. An optimal effect would be achieved if the remifentanil concentration is sufficiently high to be effectively analgesic during the total duration of pain during a contraction. On the contrary, the safety of remifentanil use during labour will be theoretically determined by the remifentanil effect-site concentration in-between two painful contractions, inducing respiratory depression. Thus, an optimal remifentanil application during labour would achieve high ('effective') remifentanil concentrations during each painful contraction and low ('safe') concentrations in between painful contractions.

With standard PCA systems, a bolus is demanded by the parturient at the beginning of the pain felt with a contraction. This way, peak remifentanil concentration will not be optimally

timed. At the beginning of the painful contraction, remifentanil concentration is still insufficient to alleviate the pain, whereas it will be still high after the end of the pain, inducing respiratory depression. Several attempts have already been made to improve the use of remifentanil during labour by modifying the bolus application[8 9] or forecasting future contractions.[10] The latter solution appears to be promising, since a remifentanil bolus may be delivered just before the beginning of a contraction, allowing peak remifentanil concentration to coincide with peak pain during the contraction.

To our knowledge, no study has until now attempted to compare the timing of pain during contractions and the remifentanil concentrations achieved with either standard bolus application at the beginning of the pain sensation or with optimized bolus delivery by prediction before the start of a contraction. Such a comparison would allow a better understanding of efficacy and safety of remifentanil use during labour.

Our study included an experimental part (clinical observation in the labour ward) and a mathematical modelling part. The study had three objectives. First, we aimed to record the timing and duration of pain during contractions using a new approach consisting of handgrip force measured by a handheld dynamometer (first part). In the second part of the study, we used these data to simulate time series of (painful) contractions and also remifentanil concentrations achieved with either standard bolus application at the beginning of the pain sensation or with optimized bolus delivery by prediction of the contractions. The objective of optimization is to find an optimum coincidence of remifentanil concentration and the intensity of pain during uterine contractions.

Finally, different models of prediction of future contractions were compared and the most parsimonious chosen for further evaluation of efficacy and safety of a hypothetical optimized remifentanil PCA application system during labour.

Methods

After institutional review board approval (Commission centrale d'éthique de la recherche sur l'être humain des HUG 12-077) and written informed consent, 43 parturients were included in the study. Parturients received information about the study on arrival in the delivery suite.

Experimental part of the study

After informed consent, the handling of the dynamometer was explained and reference values for handgrip force corresponding to subjective pain levels of moderate pain (5 on a scale of 0–10) and extreme pain (10 on a scale of 0–10) were obtained.

The dynamometer (Noraxon Biofeedback dynamometer, Velamed, Cologne, Germany) was connected via an analogue–digital interface to a portable computer. Handgrip force measured by the dynamometer was recorded continuously using Signal software (CED, Cambridge, UK) during periods of 20 min each. Women were instructed to compress the dynamometer with a force corresponding to their subjective pain level and hold it until the pain has subsided. In parallel, the external tocographic signal of uterine contractions and an abdominal wall electromyogram were recorded.

The first recording (20 min) of frequency and intensity of contractions was taken during the first stage of labour when women experienced regular painful contractions, not yet requiring analgesia except for physical relaxation techniques provided by the midwife.

A second recording of 20 min duration was obtained during more advanced labour at the time when women demanded epidural analgesia, but before epidural placement. There was no minimal cervical dilation for epidural analgesia and therefore, the time during labour for the second recording was variable, from early to late first stage of labour.

Analysis

The duration of the pain during contractions was measured as the time for which the dynamometer signal deviated from baseline, indicating pain. The interval between painful contractions was measured as the time between two starting points of the deviation from baseline on the dynamometer signal. These durations and intervals were compared with those recorded by external tocography.

Mathematical modelling

Modelling of contraction time series

Time series of duration and intervals of painful contractions obtained from the dynamometer signal were further analysed using the R statistical software.[11] Let δ_i be the contraction interval between contraction $i-1$ and i and knowing the first contraction interval, we are trying to forecast with an horizon of 1 the next contraction interval:

$$\delta_{i+1} = \Omega(\delta_0, \ldots, \delta_i)$$

The simplest way to forecast the next interval is to use the previous one ('naïve' forecasting):

$$\delta_{i+1} = \delta_i.$$

Another simple way of forecasting is to use a moving average of the last n contraction intervals. Here, we used $n=2-4$, because sample calculations with higher n did not improve forecasting.

More elaborate forecasting methods are exponential smoothing (ETS) and the autoregressive integrated moving average (ARIMA), both available as functions of the R forecast package.[11] The functions were used to provide automatic adaptation of all parameters and choice of an optimized model based on maximum likelihood estimation and Akaike's information criterion.[12] For each new contraction, a new optimal model was computed with both ETS and ARIMA and then used to forecast the next contraction interval.

To obtain longer time series to test the different prediction models, inter-contraction time interval data of at least 100 min duration derived from external tocography monitoring from an additional 25 parturients were used.

Modelling of remifentanil concentration

Remifentanil effect-site concentrations were modelled using STANPUMP (Steven Shafer, Stanford, available at www.