PCRC Proposal Cover Sheet

Title of Study or Project:	The prevalence of intravenous remifentanil use for labor analgesia in the Multicenter Perioperative Outcomes Group
Primary Institution:	Weill Cornell Medicine
Principal Investigator:	Robert S. White MD, MS
Co-Investigators:	Jaime Aaronson, MD, Sharon Abramovitz, MD, Virginia Tangel, MA, Anna Nachamie, BS
Type of Study:	Retrospective observational
IRB Number/Status:	The project has been approved by Weill Cornell Medicine's Institutional Review Board as non-human subjects research due to the de-identifiable data.
Hypothesis:	Our primary hypothesis is that the prevalence of remifentanil use for labor analgesia is low both in the number of hospitals using the analgesic and the number of patients within hospitals receiving it. Our secondary hypotheses are: • that remifentanil use is more prevalent in obstetric labor and delivery units that perform a larger number of neuraxial anesthesia for labor analgesia; • that remifentanil use is more prevalent in obstetric labor and delivery units that have greater availability of types systemic medication: fentanyl, morphine, meperidine, ketamine, sufentanil, nalbuphine, hydromorphone, and butorphanol; and • that the prevalence of inhalation nitrous oxide for labor analgesia will be low both in the number of hospitals using it and in the number of patients within hospitals receiving it.
Number of Patients/Participants:	All cases with a vaginal or Cesarean delivery listed on the record
Power Analysis:	None required
Proposed statistical test/analysis:	Frequentist approaches, including descriptive statistics and mixed-effects logistic regression
Resources (Brief summary of resources for data collection, personnel, financial):	The MPOG database will be queried for the specified concept IDs with programmatic support. Statistical analyses and operational oversight will be funded from the Center for Perioperative Outcomes in the Department of Anesthesiology at Weill Cornell Medicine.

Introduction

What is the significance of the clinical problem being addressed?

Remifentanil – a potent short-acting opioid analgesic – is most commonly offered to women when neuraxial labor analgesia is contraindicated. At the present time, there is no consensus regarding the optimal administration, dosing strategy, or requirements for maternal monitoring, which may pose a patient safety issue. Additionally, apart from our national study of academic obstetric units in the United States (conducted from 2014-2015), little is known about prevalence and practice habits of remifentanil utilization and/or adverse outcomes from its use.

For our initial survey, we contacted directors of 126 obstetric anesthesia units at academic medical centers in the United States. 84 completed our survey, resulting in a response rate of 67%. Our major findings were that IV remifentanil is used for labor analgesia in only one-third of the academic medical centers surveyed, mostly less than 5 times in the past year, and is administered in a variety of ways across centers. Respondents reported 14 serious complications associated with its use: 9 maternal and 5 neonatal adverse events. These numbers constitute a 4% to 13% morbidity rate associated with the use of IV remifentanil.

What current gaps exist in the understanding of this problem?

Several randomized clinical trials have evaluated the use of remifentanil for labor analgesia; however, they have resulted in mixed findings regarding its safety and efficacy in attenuating labor pain. Respiratory side effects, although of varying significance, are commonly reported, whereas analgesia is probably modest at best (1-7). In addition, although the use of remifentanil for labor analgesia has the potential to result in sedation, respiratory depression, and oxygen desaturation, clear recommendations for monitoring women receiving remifentanil in labor do not exist (8).

As stated above, apart from our conducted survey, no national study has investigated the prevalence of intravenous remifentanil use for labor analgesia. We acknowledge limitations to our survey. First, we only surveyed academic centers in the United States; therefore, our findings cannot reflect the current practice among nonacademic institutions across the country. Our questions about the characteristics of each center do not allow for reporting exact numbers. Second, we asked the obstetric anesthesia directors to report on the practice pattern of their center; their awareness and recall of adverse events, and their estimates of usage in their entire department may not be completely accurate. Third, we cannot describe the reported respiratory events precisely or whether any interventions were needed in the parturients or neonates. Although narrative comments were provided for all 9 maternal and 5 neonatal cases of adverse events associated with the use of remifentanil, the detail was insufficient for the purpose of comprehensive causal analysis. Last, we did not assess for nonresponse bias because the data were collected anonymously.

Our findings need to be confirmed and replicated in a large anesthesia registry (MPOG).

How will this project address this gap and advance clinical care and/or research knowledge?

At the present time, few, if any, effective alternatives to neuraxial labor analgesia exist. We previously conducted a study to evaluate the current practices regarding remifentanil use for labor analgesia at academic centers in the United States; the findings suggest that it is not used frequently at academic medical centers in the United States and, moreover, that complications associated with its use can be serious for both mother and neonate. Our survey also highlights the fact that there may be cases of maternal respiratory and/or cardiac arrest in the United States that have not been reported.

In light of the safety hazards revealed, it seems that developing a national consensus about the essential elements of a protocol for remifentanil administration may be one way to enhance its safe use as an alternative labor analgesic and could increase its availability to parturients who cannot have or do not want neuraxial labor analgesia. The use of MPOG data to study both the number and type of centers using remifentanil for labor analgesia will present the unique opportunity to better understand practice patterns, which in turn, would ideally lead to improvements in both clinical efficacy and patient safety. The specific aims of our projects are therefore to:

1. Investigate the national prevalence of intravenous remifentanil use of labor analgesia in the Multicenter Perioperative Outcomes Group (MPOG) electronic perioperative record database.
2. Explore characteristics of hospitals that utilize remifentanil with classical (frequentist) regression models.
3. Investigate the prevalence of complications/morbidity associated with the use of intravenous remifentanil use of labor analgesia.
4. Investigate the national prevalence of use of other medications used as an alternative to neuraxial labor analgesia.

Primary Outcome

Our primary outcome is the prevalence of remifentanil use for labor analgesia.

Secondary Outcomes

Our secondary outcomes include cardiovascular and pulmonary complications associated with remifentanil use for labor analgesia.

Exploratory Outcomes

Our exploratory outcomes are the prevalence of systemic medications (intravenous opioids, nitrous oxide) used for non-neuraxial labor analgesia.

Methods

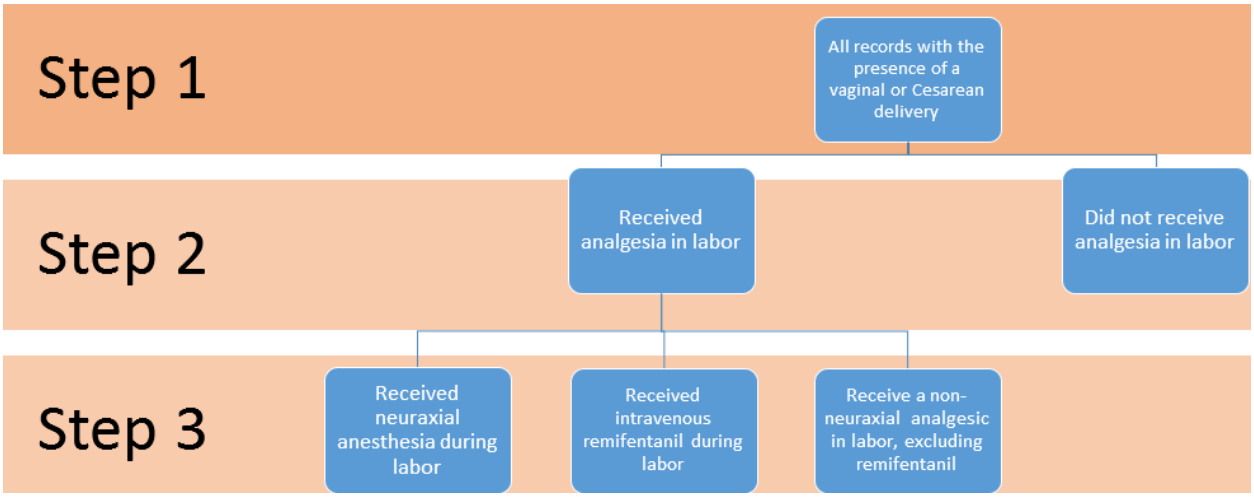
We will utilize data from the Multicenter Perioperative Outcomes Group (MPOG), a non-profit academic consortium of more than 100 investigators representing more than 8.2 million anesthetic cases integrated across 50 hospitals across 18 states and two countries. MPOG uses electronic health record

and administrative data to analyze relationships between patient comorbidities, surgical procedures, perioperative care, interventions, and postoperative outcomes.

Using an MPOG Public User File, we will conduct a retrospective cohort study to assess the prevalence of intravenous remifentanil use for labor analgesia in participating medical centers in the United States. To calculate total delivery volume by hospital, all cases with a listed vaginal (including operative vaginal) or Cesarean delivery from US institutions will be identified and included in the study population (Figure 1: Step 1). Within that population, all cases who received labor analgesia will be identified (Step 2). From that population, we will isolate three mutually exclusive study populations: cases that received intravenous remifentanil, cases that received neuraxial analgesia, and cases that received inhalational nitrous oxide or other intravenous opioids used for non-neuraxial labor analgesia (Step 3). If a case lists more than one labor analgesic used, the following coding hierarchy will be used: remifentanil cases > other non-neuraxial methods of labor analgesia > neuraxial anesthesia.

Exclusion criteria are the lack of a vaginal or Cesarean delivery on the record or records with a vaginal or Cesarean delivery but at a non-US institution.

Figure 1. Sample Selection



Our primary hypothesis that the prevalence of remifentanil use for labor analgesia is low both in the number of hospitals using the analgesic and the number of patients within hospitals receiving it. Our secondary hypotheses are: that remifentanil use is more prevalent in obstetric labor and delivery units that perform a larger number of neuraxial blocks for labor analgesia; that remifentanil use is more prevalent in obstetric labor and delivery units that have greater availability of types systemic medication: fentanyl, morphine, meperidine, ketamine, sufentanil, nalbuphine, hydromorphone, and butorphanol; that the prevalence of inhalation nitrous oxide for labor analgesia will be low both in the number of hospitals using it and in the number of patients within hospitals receiving it.

Variables and Preparation

We will use the following variables in our study: patient demographic characteristics (race, age), comorbidities as defined by Bateman (9) and identified using International Classification of Disease (ICD) codes, hospital and provider characteristics (institution type – academic vs. community, institution size, yearly delivery volume), indicators for delivery type (vaginal or Cesarean), case characteristics (ASA status, need for supplemental oxygen, oxygen saturation, blood pressure, pulse rate, end tidal carbon dioxide, medications used for labor analgesia), and cardiovascular and pulmonary complications defined by preexisting MPOG indicators or calculated based on intraoperative physiologic data (acute respiratory failure, respiratory arrest, respiratory insufficiency, cardiac arrest). A full list of variables, along with their associated MPOG concept identifiers, can be found in Table 1.

In multivariate fixed-effects logistic regression models, remifentanil will serve as our exposure of interest; a composite measure of complications (coded dichotomously), as well as individual complications (also coded dichotomously) will be outcomes. Other variables listed above will serve as covariates.

Statistical Analysis

Frequencies (percentages), means (95% confidence intervals), medians (interquartile ranges) will be used to characterize the data. The prevalence of remifentanil use will be calculated in three ways: as a measure of the number of cases in the entire database, as a measure of the number of hospitals with cases, and the number of cases within hospitals. Neuraxial and other analgesics used in labor will be calculated in the same way. All relevant pre- and intraoperative measures listed above will be compared by group: remifentanil use vs. no remifentanil use. These analyses will be conducted at the case level only. Categorical measures will be compared by the Pearson's chi-square test or ANOVA, as appropriate. Linear measures will be compared by the two-sided t-test. Equivalent non-parametric tests will be used in cases where the data is non-normally distributed.

Mixed-effects multivariate logistic regression models (with clustering by hospital) will be used to predict the likelihood of individual and composite complications.

All analyses will additionally be run separately by hospital type: academic or community.

IRB statement

The project has been approved by Weill Cornell Medicine's Institutional Review Board as non-human subjects research due to the de-identifiable data.

Study type

Retrospective observational (cross-sectional). The STROBE guidelines have been referenced and our proposal is in accordance with the checklist.

Variables to be collected

See detailed query specification.

Handling of missing data

Missing data will be diagnosed with appropriate techniques and addressed using multiple imputation, if necessary.

Areas for discussion/known limitations

- Institutions may not complete an anesthetic record when administrating intravenous remifentanil for labor analgesia
- Validity and accuracy of the primary data collection for labor and delivery records, use of neuraxial anesthesia, use of intravenous medications, use of nitrous oxide at participating institutions
- Missing data and resulting unknown selection bias
- MPOG population may differ from general labor and delivery population undergoing obstetric anesthesia in the US
- CPT/ICD code exclusions

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