Neonatal effect of remifentanil in cesarean section with general anesthesia
A protocol of systematic review and meta-analysis

Qi Zhang, MM, Hong-Li Kan, MM, Dong-Xin Wang, MM, Dong-Mei Fu, MM∗

Abstract
Background: Although several previous studies have reported the efficacy of remifentanil in cesarean section (CS) under general anesthesia, no study has specifically addressed its neonatal effect (NE) in CS under general anesthesia systematically. Thus, this study will systematically investigate the NE of remifentanil in CS under general anesthesia.

Methods: Electronic databases including MEDLINE, EMBASE, Cochrane Library, Web of Science, Chinese Biomedical Literature Database, and China National Knowledge Infrastructure will be systematically retrieved with the assistance of a specialist librarian to check randomized controlled trials reporting NE in CS under general anesthesia. We will retrieve all electronic databases from their initial time to March 20, 2020 without restrictions of language. All process of study selection, data extraction, and risk of bias evaluation will be carried out by 2 independent authors. We will invite another senior expert to solve the problems that arise between 2 authors. Data will be pooled and analyzed using RevMan V.5.3 software.

Results: Outcomes consist of assessment of neonatal adaptation, requirements for postoperative respiratory support of neonates, systolic and diastolic noninvasive blood pressure, mean blood pressure, heart rate, electrocardiography, umbilical cord blood gas analysis, and adverse events.

Conclusion: This study will present evidence of the NE of remifentanil in CS under general anesthesia. This information may inform benefits of intervention to guide the usage of remifentanil in CS under general anesthesia.

Study registration: INPLASY202040028.
Abbreviations: CS = cesarean section, NE = neonatal effect.
Keywords: cesarean section, neonatal effect, randomized controlled trials, remifentanil

1. Introduction

Cesarean section (CS) is one of the most common obstetric surgeries.1–4 It helps pregnant women deliver babies because of the dystocia or certain obstetric complications.5–7 Its prevalence increases annually due to the current increased marriage age and socioeconomic status.8–11 Participants with CS experience very strong pain intensity.12,13 Thus, finding a way to relieve pain and minimize complications, effective anesthesia drug choose is very important.14–17 A variety of studies found that remifentanil is good choice on neonatal effect (NE) in CS under general anesthesia.18–22 However, there is no systematic review that specifically assessed the NE in CS under general anesthesia. Therefore, this study will systematically evaluate the NE of remifentanil in CS under general anesthesia.

2. Methods

2.1. Study registration

This study has been registered on INPLASY202040028. It has been reported following the preferred reporting items for systematic review and meta-analysis protocols.23

2.2. Eligibility criteria

2.2.1. Type of participants. We will include pregnant women (more than 18 years old), who received remifentanil in CS under general anesthesia, irrespective race and educational background.

2.2.2. Type of interventions. We will include all participants who underwent remifentanil in CS under general anesthesia in the experimental group. However, in the control group, all participants can receive any anesthesia intervention except remifentanil.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

This study was supported by the Jilin Provincial Health Department Science and Technology Project (20170204050 SF), and Jilin Provincial Health Department Science and Technology Project (201601034JC). The supported funder was not allowed to involve any sections of this study.

Department of Anesthesiology, Jilin Cancer Hospital, Changchun, China.

∗Correspondence: Dong-Mei Fu, Department of Anesthesiology, Jilin Cancer Hospital, No. 1018 Huguang Road, Chaoyang District, Changchun, Jilin 130021, China (e-mail: dong001.medfu@aliyun.com).

Copyright © 2020 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Zhang Q, Kan HL, Wang DX, Fu DM. Neonatal effect of remifentanil in cesarean section with general anesthesia: a protocol of systematic review and meta-analysis. Medicine 2020;99:20(e20212).

Received: 7 April 2020 / Accepted: 10 April 2020
http://dx.doi.org/10.1097/MD.0000000000020212
2.2.3. **Type of studies.** We will consider all randomized controlled trials that exploring the NE of remifentanil in CS under general anesthesia for inclusion. However, we will not consider any other studies, except randomized controlled trials.

2.2.4. **Type of outcome measurements.** The primary outcome is the evaluation of neonatal adaptation, as measured using Apgar score or relevant tools. The secondary outcomes are requirements for postoperative respiratory support of neonates, systolic and diastolic noninvasive blood pressure, mean blood pressure, heart rate, electrocardiography, umbilical cord blood gas analysis (such as pulse oximetry, and base excess), and adverse events.

2.3. **Data sources and search strategy**

2.3.1. **Electronic searches.** In conjunction with a specialist librarian, following electronic databases will be searched from the beginning of each database to March 20, 2020: MEDLINE, EMBASE, Cochrane Library, Web of Science, Chinese Biomedical Literature Database, and China National Knowledge Infrastructure. We will not impose any language and publication status limitations. The example of search strategy for Cochrane Library is built in Table 1. We will also apply similar search strategies to the other electronic databases.

2.3.2. **Other resources.** In addition, we will also check conference proceedings and reference lists of all included studies.

2.4. **Data collection and analysis**

2.4.1. **Selection of studies.** Results from all literature citations will be imported into EndNote 7.0, and all duplicated citations will be excluded. Screening of titles and abstracts, and full-text records will be carried out by at least 2 independent authors. Any different views between 2 authors will be solved by consensus or discussion with the help of a third author if needed. The whole process of study selection will be demonstrated using a flowchart. The reasons of all excluded literatures will be recorded at each stage.

2.4.2. **Data collection process.** Data from all eligible studies will be extracted using a previous designed standardized data collection sheet. At least 2 authors will collect data independently. Any discrepancies between 2 authors will be resolved by another author through discussion to reach a final decision. The extracted information includes study information (such as time of publication, first author, and journal information), study characteristics (such as design, setting, location, and funding information), participant characteristics (such as race, age, sample size, and inclusion and exclusion criteria), intervention and control details (such as dosage, types, and duration), and outcomes (such as primary, secondary outcomes, and safety). If we identify any missing or insufficient, or unclear data, we will contact primary authors to request those data.

2.5. **Risk of bias assessment**

At least 2 independent authors will assess risk of bias for each included study using Cochrane risk of bias tool, respectively. Conflicts regarding the risk of bias between 2 authors will be verified and solved by a third author if needed. It will assess each study through 7 fields, and each one is classified as low, unclear, or high risk of bias.

2.6. **Statistical heterogeneity**

Statistical heterogeneity will be checked using $I^2$ statistic test, and it will be interpreted as follows: $I^2 \leq 50\%$ meaning low heterogeneity, and $I^2 > 50\%$ indicating high heterogeneity.

2.7. **Subgroup analysis**

If feasible from available data, we will carry out subgroup analysis to explore the possible reasons of high heterogeneity in according to the different interventions, comparators, and outcome measurements.

2.8. **Sensitivity analysis**

We will undertake sensitivity analysis to establish stability of outcome results by eliminating high risk of bias studies.

2.9. **Reporting bias**

If sufficient trials will be entered in this study, we will check reporting bias using funnel plots.[24]

2.10. **Statistical analysis**

We will undertake all statistical analysis using RevMan V.5.3 software. We will estimate continuous data as mean difference or

| Number | Search terms |
|--------|--------------|
| 1 | Mesh descriptor: ((caesarean section) explode all trees |
| 2 | ((caesarean section)  or (C-section)) or ((caesarean delivery) or (surgical delivery)) :ti, ab, kw |
| 4 | Mesh descriptor: (remifentanil) explode all trees |
| 5 | ((remifentanil) or (ultiva) or (general anesthesia) or (pain relief)) :ti, ab, kw |
| 6 | Or 4-5 |
| 7 | Mesh descriptor: (infant, newborn) explode all trees |
| 9 | Or 7-8 |
| 10 | Mesh descriptor: (randomized controlled trials) explode all trees |
| 12 | Or 10-11 |
| 13 | 3 and 6 and 9 and 12 |
standardized mean difference and 95% confidence intervals, and dichotomous data as risk ratio and 95% confidence intervals. Whenever there is low heterogeneity, a fixed-effects model will be applied, and meta-analysis will be conducted if sufficient studies focusing on the same treatments, comparators, and outcome measurements. Whenever there is high heterogeneity, a random-effects model will be used, and a subgroup analysis will be undertaken to investigate the reasons of high heterogeneity among included studies. Additionally, we will also report outcome results as narrative summary.

2.11. Ethics and dissemination

This study will not need any ethical documents, because no individual patient data will be used. The results of this study will be submitted to a peer-reviewed journal for publication.

3. Discussion

Although a variety of studies have addressed this issue, no systematic study on this topic has been done. Thus, this study aims to assess the NE of remifentanil in CS under general anesthesia systematically. The findings of this study will help to determine that NE of remifentanil in CS under general anesthesia is effective or not. It may also provide reference evidence for both patients and clinicians, and as it may inform clinical practice guidelines.

Author contributions

Conceptualization: Qi Zhang, Hong-Li Kan, Dong-Xin Wang, Dong-Mei Fu.

Data curation: Dong-Xin Wang, Dong-Mei Fu.

Formal analysis: Qi Zhang, Hong-Li Kan, Dong-Xin Wang.

Funding acquisition: Dong-Mei Fu.

Investigation: Dong-Mei Fu.

Methodology: Qi Zhang, Hong-Li Kan, Dong-Xin Wang.

Project administration: Dong-Mei Fu.

Resources: Qi Zhang, Hong-Li Kan, Dong-Xin Wang.

Software: Qi Zhang, Hong-Li Kan, Dong-Xin Wang.

Supervision: Dong-Mei Fu.

Validation: Hong-Li Kan, Dong-Mei Fu.

Visualization: Qi Zhang, Dong-Xin Wang, Dong-Mei Fu.

Writing – original draft: Qi Zhang, Dong-Xin Wang, Dong-Mei Fu.

Writing – review and editing: Qi Zhang, Dong-Xin Wang, Dong-Mei Fu.

References

[1] Poli-Neto OB, Campos Martins Chamochumbi C, Toscano P, et al. Electromyographic characterization of abdominal wall trigger points developed after caesarean section and response to local anaesthesia: an observational study. BJOG 2018;125:1313–8.

[2] Visconti F, Quaresima P, Ranzia E, et al. Difficult caesarean section: a literature review. Eur J Obstet Gynecol Reprod Biol 2020;246:72–8.

[3] Moradi F, Aryankhesal A, Heidari M, et al. Interventions in reducing caesarean section in the world: a systematic review. Malays J Med Sci 2019;26:21–37.

[4] Coates D, Homer C, Wilson A, et al. Indications for, and timing of, planned caesarean section: a systematic analysis of clinical guidelines. Women Birth 2020;33:22–34.

[5] Ymer H, Woldie H. Incidence and associated factors of chronic pain after caesarean section: a systematic review. J Obstet Gynaecol Can 2019;41:840–54.

[6] Sandall J, Tribe RM, Avery L, et al. Short-term and long-term effects of caesarean section on the health of women and children. Lancet 2018;392:1349–57.

[7] Salas Garcia MC, Yee AL, Gilbert JA, et al. Dysbiosis in children born by caesarean section. Ann Nutr Metab 2018;73(Suppl 3):24–32.

[8] Scioscia M, Vimercati A, Cito L, et al. Social determinants of the increasing caesarean section rate in Italy. Minerva Ginecol 2008;60:115–20.

[9] Miami C, Ludwig A, Breckenkamp J, et al. Socioeconomic and migration status as predictors of emergency caesarean section: a birth cohort study. BMC Pregnancy Childbirth 2020;20:32.

[10] Ishaq R, Baloch NS, Iqbal Q, et al. Frequency and evaluation of the perceptions towards caesarean section among pregnant women attending public hospitals in Pakistan and the implications. Hosp Pract (1995) 2017:45:104–10.

[11] Feng XL, Xu L, Guo Y, et al. Factors influencing rising caesarean section rates in China between 1988 and 2008. Bull World Health Organ 2012;90:30–9.

[12] Habibi A, Alipour A, Baradari AG, et al. The effect of adding lidocaine to patient controlled analgesia with morphine on pain intensity after caesarean section with spinal anaesthesia: a double-blind, randomized, clinical trial. Open Access Maced J Med Sci 2019;7:1946–50.

[13] Bjune K, Stubhaug A, Dodgson MS, et al. Additive analgesic effect of codeine and paracetamol can be detected in strong, but not moderate, pain after caesarean section. Baseline pain-intensity is a determinant of assay-sensitivity in a postoperative analgesic trial. Acta Anaesthesiol Scand 1996;40:399–407.

[14] Kourkouveli P, Leontiadis E, Kontomika M, et al. Reverse Takotsubo cardiomyopathy after caesarean section with epidural anesthesia: initial assessment and follow-up. J Cardiothorac Vasc Anesth 2020;34:756–8.

[15] Shi W, Zhang P. Effect of dexmedetomidine combined with lumbar anaesthesia on Th1/Th2 in maternal patients and neonates undergoing caesarean section. Exp Ther Med 2019;18:1426–32.

[16] Dennis AT, Mulligan SM. Analgesic requirements and pain experience after caesarean section under neuraxial anaesthesia in women with preeclampsia. Hypertens Pregnancy 2016;35:520–8.

[17] Devroe S, Van de Velde M, Rix S. General anesthesia for caesarean section. Curr Opin Anaesthesiol 2015;28:240–6.

[18] Van de Velde M. The use of remifentanil during general anesthesia for caesarean section. Curr Opin Anaesthesiol 2016;29:257–60.

[19] Noskova P, Blaha J, Bakhouche H, et al. Neonatal effect of remifentanil in general anaesthesia for caesarean section: a randomized trial. BMC Anesthesiol 2015;15:38.

[20] Mastaan M, Mokhberje S, Sirag A. Role of remifentanil for elective caesarean section in a morbidly obese, needle-phobic parturient. Int J Obstet Anesth 2006;15:177.

[21] Alexander R, Fardell S. Use of remifentanil for tracheal intubation for caesarean section in a patient with suxamethonium apnoea. Anaesthesia 2005;60:1036–8.

[22] Scott H, Bateman C, Price M. The use of remifentanil in general anaesthesia for caesarean section in a patient with mitral valve disease. Anaesthesia 1999;54:695–7.

[23] Shamsafer L, Moher D, Clarke M, et al. PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;349:g7647.

[24] Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol 2005;58:882–93.