Pain after Cesarean section- A Danish multicenter cohort study.

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Background

Worldwide, more than 20 million children are born by cesarean section each year (World Health Organization 2021), making it one of the most commonly performed surgical procedures. Postoperative pain is typically moderate to severe in intensity (Sun and Pan 2019) and inadequate pain relief significantly affects the new mother's ability to mobilize and care for herself and her baby (Ciechanowicz et al. 2019) . Pain may also impact recovery and negatively affect the early bonding between mother and child, as well as the establishment of breastfeeding (Roofthooft et al. 2021). Furthermore, there might be a correlation between inadequately treated acute pain and the development of chronic pain after cesarean section (Nikolajsen et al. 2004; Yimer and Woldie 2019). All these factors emphasize the necessity of effective pain management following cesarean section.

Only a few studies describe pain following cesarean section in a Danish population. Nikolajsen et al. (Nikolajsen et al. 2004) investigated the prevalence of chronic pain among 220 patients interviewed one year after cesarean section. A total of 46.8% recall to have experienced severe pain in the period shortly after the cesarean section. In a Danish randomized placebo-controlled trial involving 72 patients (Hansen et al. 2019) reported pain scores in patients allocated to either a Transmuscular Quadratus Lumborum block (TQL) or placebo TQL following a cesarean section. Both groups had access to intravenous morphine via patient-controlled analgesia. The patients scored their pain on a numeric rating scale (NRS), ranging from 0 to 10, where 0 is no pain and 10 is the most severe pain imaginable. After 6 hours, the TQL block group had an NRS (0-10) of 4 during movement, while the placebo group had an NRS of 5. At 12, 18 and 24 hours, both groups had similar NRS scores of 5, 4, and 3, respectively. The average 24-hour oral morphine equivalent consumption was 65 mg for the TQL block group, compared to 94 mg for the group given placebo.

That dosage is significantly higher than recently described in a Danish uni-center quality study of 100 patients (Duch 2023). Among these patients, 85 received the standard postoperative pain management for cesarean section, which aligns with the pain treatment protocols employed in most hospitals across the country: A fixed dose of paracetamol and NSAID, supplemented with oral morphine; nerve blocks or intrathecal morphine are not given routinely. The median 24-hour oral morphine equivalent dose given to the patients by request to the nurses was 30 mg (IQR: 20-50). The relatively lower opioid dose may suggest an existing underestimation and suboptimal treatment of the patients' pain. At 6, 12, 18 and 24 hours after the cesarean section the reported average NRS (0-10) pain scores during movement were 7,

6, 6, and 5 respectively, corresponding to moderate or severe pain, and further supports the possibility of underestimation and undertreatment of post-cesarean pain.

In a Danish multicenter survey conducted in 2020 to 2021 (Lindelof 2022), 861 cesarean section patients were asked 24-48 hours after surgery how much they agreed on having “experienced severe pain after the cesarean section” In this assessment, 45% scored >= 8 (NRS 0-10).

Overall, there is strong indications that currently a substantial number of women in Denmark experience severe pain in the first days after their cesarean section. To address this, we have established an obstetric-anesthesiologic research cluster as part of the national perioperative research network, CEPRA (Nørskov et al. 2023) with an aim to optimize pain treatment for the approximately 12,700 Danish patients who undergo cesarean section every year.

Objective

This study aims to map postoperative pain in Danish patients undergoing elective cesarean section. Specifically postoperative pain levels, impact on physical function, side effects from pain medication, and treatment approaches in the postoperative period.

Furthermore, we aim to test the feasibility of repeated SMS-based questionnaires sent to the patients in the postoperative period. Based on response rates and frequency of outcomes, data from this observational study will also be used to inform a randomized controlled multicenter trial aiming to test better postoperative pain interventions for cesarean section patients.

Method

Study design

Prospective Danish multicenter cohort study based on patient-reported outcomes (SMS-based questionnaires) and clinical data from electronic health records.

Inclusion criteria

Patients who undergo planned cesarean section under spinal anesthesia.
Patients who speak and read Danish and can provide informed consent to participate.
Patients who have a smartphone that can receive an SMS with a link to a questionnaire that can be accessed on an online website on the phone.

Exclusion criteria

Age < 18 years

Number of participants

Minimum 400 patients, included from minimum 9 centers representing all 5 regions in Denmark.

Outcomes

Outcomes have been selected to align with the outcomes in a subsequent randomized controlled multicenter trial, where we will investigate whether the addition of intrathecal morphine provides better postoperative pain control. Therefore, opioid side effects are given high priority in the outcome measures.

The following abbreviations are used in the section outcome measures:
Time intervals are specified as the time difference from the administration of the spinal anesthesia (t0), and outcomes are assessed either through patient questionnaires (P) or by reviewing medical records (J).

Outcome measures

Maternal outcomes

Primary outcomes

- Level of pain during the activity from lying to a seated position, after 24 hours. NRS 0-10 (P)

- Morphine associated adverse events within 24 hours after CS, assessed as a binary outcome including nausea, vomiting, dizziness, itching, or urine-retention (P). Vomiting and urine-retention, will be reported as yes/no. Nausea, dizziness and itching will be assessed as "none", "little", "moderate", or "severe", with patients reporting "moderate" or "severe" categorised as having a positive outcome.

Secondary outcomes

- Opioid consumption within the first 24 hours after caesarean section (oral morphine equivalents, mg) (J)
- Insufficient spinal anesthesia related adverse events during the caesarean section, as binary composite outcome of the proportion of patients in need of conversion to general anesthesia, intraoperative opioids, sevoflurane, or nitrous oxide for intraoperative pain, or repeated neuraxial procedure (spinal or epidural placement following failed spinal). (J)
- Level of pain during the activity from a lying to a seated position, after 6, 12, 18 hours. NRS 0-10 (P)
- The ability to mobilize independently at 24 hours after surgery. Yes/No (P)
- The ability to nurse infant independently at 24 hours after surgery. Yes/No (P)

Exploratory outcomes

- Level of pain at rest 6, 12, 18, 24, 48 hours, 7 days, and 30 days after surgery. NRS 0-10 (P)
- Use of analgesic medication (Paracetamol (PCM), Non-Steroidal Anti-Inflammatory Drug (NSAID) and opioid) 6, 12, 18, 24, 48 hours, 7 days, and 30 days postoperatively. Yes/No. (P)
- Level of pain during the activity from a lying to a seated position after 48 hours, 7 days and 30 days. NRS 0-10 (P)
- Localization of pain: Abdomen, shoulder, head, back, other. 6, 12, 18, 24, 48 hours. (P)

- Need for unplanned "rescue" ultrasound-guided truncal nerve block or epidural within 24 hours. Yes/No (J)
- Maternal satisfaction with pain-treatment during the first 24 hours. Assessed after 24 hours. Likert scale of 0-4. Very dissatisfied, dissatisfied, neither satisfied nor dissatisfied, satisfied, very satisfied. (P)
- Pain related self-efficacy and self-empowerment after surgery: The feeling of being in control during the first 24 hours, assessed after 24 hours, Likert scale (0-4). (P)
- Composite outcome of rare maternal adverse events (J):
    - Clinically significant maternal respiratory depression within 24 hours defined as the need for airway intervention; oxygen therapy >3 L/min; administration of an opioid antagonist to counteract depressed respiration; or an intervention beyond verbal stimulus to rouse the patient from sedation reported the first 24h after surgery *or*
    - Maternal hospital readmission within 7 days, *or*
    - Maternal re-attendance or unplanned out-patient visit within 7 days.
- The ability to handle own personal hygiene 24 hours after surgery. Yes/No (P)
- Itching after 6, 12, 18, 48 hours, 4-point scale: None, mild, moderate, severe (P)
- Dizziness after 6, 12, 18, 48 hours, 7 days, and 30 days, 4-point scale: None, mild, moderate, severe (P)
- Nausea after 6, 12, 18, 48 hours, 7 days, and 30 days, 4-point scale: None, mild, moderate, severe (P)
- The impact of pain on how often the patient has gotten out of bed in the last 6 hours. 6, 12, 18, 24, 48 hours. 4-point scale: None, a little, moderate, a lot (P).
- The impact of pain on how much the patient has breastfed or bottle-fed the infant in the last 6 hours? 6, 12, 18, 24, 48 hours. 4-point scale: None, a little, moderate, a lot (P).
- The impact of pain on the ability to resume regular daily activities. 7 and 30 days. 4-point scale: None, a little, moderate, a lot (P)
- Obstetric Quality of Recovery score using Obs-QoR-10 (Pervez Sultan et al. 2020; P Sultan et al. 2020)

  How much have you been bothered by this problem in the past 24 hours?

  1. Pain. 24 hours. None-worst imaginable 0-10. (P)
  2. Nausea or vomiting. 24 hours. None-worst imaginable 0-10. (P)
  3. Dizziness. 24 hours. None-worst imaginable 0-10. (P)
  4. Shivering. 24 hours. None-worst imaginable 0-10. (P)
  5. I have been comfortable. 24 hours. Not at all - all the time 0-10. (P)
  6. I am able to mobilize independently. 24 hours. Not at all - all the time 0-10. (P)
  7. I can hold my baby without assistance. 24 hours. Not at all - all the time 0-10. (P)
  8. I can feed/nurse my baby without assistance. 24 hours. Not at all - all the time 0-10. (P)
  9. I can look after my personal hygiene in the past 24 hours. 24 hours. Not at all - all the time 0-10. (P)
  10. I feel in control in the past 24 hours. 24 hours. Not at all - all the time 0-10. (P)

- Global Health Score (Euroqol 2023) 24 hours. Worst-best imaginable health state 0-100 (for validation of Obs-QoR-10) (P)
- Response rates for questionnaires after 6,12,18,24,48 hours plus 7 and 30 days after the cesarean section.
- Response time for questionnaires after 6,12,18,24,48 hours plus 7 and 30 days after the cesarean section.

Neonatal outcomes

Primary outcome

- Need for neonatal admission within 24 hours (yes/no). (J)

Secondary outcomes

- Infants in need of respiratory support within 48 hours (continuous positive airway pressure treatment, positive pressure ventilation, HNF (nasal high flow), intubation or oxygen therapy). Yes/No and time (J)
- Proportion with established breastfeeding at 30 days following delivery, if intended. (P)

Exploratory outcomes

- Apgar score at 5 minutes. (J)
- Apgar score at 10 minutes. (J)
- Proportion of infants with Apgar <7 at 5 minutes. (J)
- Readmission within 24 hours after discharge. Yes/No.
- Readmission within 7 days after discharge. Yes/No.

Development and validation of questions:

The questions were developed with inspiration from international consensus regarding obstetric recovery, including the incorporation of the Obs-QoR-10 score (Pervez Sultan et al. 2020; P Sultan et al. 2020) and the use of NRS scores for pain assessment (Eisenach et al. 2008; Hansen et al. 2019). Additionally, we have drawn on experience and knowledge gained from the pilot study by Duch et al. (Duch 2023) preceding this national study, which involved the participation of 100 patients. Patients, maternity staff, anesthetists, and obstetricians was consulted to determine the key areas of focus during the first postoperative days after a cesarean section. The questions were developed and validated by using standardized methods for designing and conducting surveys (Eysenbach 2004; Burns et al. 2008). Subsequently, the questionnaires were created in the database: Research Electronic Datacapture (REDCap) (“RedCap” n.d.)

Data collection

All data is entered directly into the closed and secure system, REDCap (Harris et al. 2009), which is approved by all the regions in Denmark. Questionnaires are sent to the patient after 6, 12, 18, 24, and 48 hours, as well as 7 and 30 days after spinal anesthesia for cesarean section (t0). The questionnaires are delivered to

the patient's smartphone as an SMS with a link to a questionnaire in REDCap. Data from journal entries are also entered into REDCap. At all hospitals, there is a data manager who has access to REDCap and can retrieve data for the patients included in the project. The primary investigator holds the overall responsibility.

Ethics and approvals

This study complies with the Helsinki declaration. The protocol will be made available on the website clinicaltrials.gov prior to inclusion of patients. Participation is completely voluntary, and consent can be withdrawn at all times.

Data Protection Authority

Approval for data collection, handling and storage has been granted by the data protection authority for the Capital Region (Region Hovedstaden) with case number P-2023-90. This includes approved data agreements between the Danish Regions, with a designated data manager from each participating hospital. (See Appendix 1)

Research Ethics Committee

The Research Ethics Committee (VEK) and the regional research ethics committee for the Capital Region of Denmark (Region Hovedstaden) have been presented with the project description and protocol and have waivered the need approval due to Danish legislation. Case number F-23004686. (See Appendix 1)

Informed consent

Verbal informed consent is obtained during the inclusion process with each patient. The patient must consent to receive questionnaires on the mobile phone and to the data manager accessing the medical records related to the cesarean section for the patient and the baby. The patient is informed that participation is voluntary and that their data will be securely stored. Written description of the consent is electronically sent to the patient, including a description of how to withdraw consent. This is approved by the data protection authority for the Capital Region of Denmark (Region Hovedstaden) with case number P-2023-90

Data Processing and statistics

All data will be handled in the secure REDCap database. Descriptive statistics will be used to analyze data. Continuous data will be summarized as median (interquartile range) or mean if the data is normally distributed. We plan to do a subgroup analysis on the groups where intrathecal morphine or TQL block has been administered. And categorical data as frequency (percentage). We will try to minimize missing data as much as possible, by sending questionnaires directly to the participants mobile phones. Number of missing data will be accounted for when describing data. Sample size is determined by convenience. The study is designed to be as large as possible, as all hospitals in Denmark, handling elective cesarean sections, will be invited to participate. Larger sites (>300 elective CS per year) commits to include 50 patients, medium scale sites (200-300 elective CS per year) commit to include 40 patients, and smaller sites (<200 elective CS per year) commits to include 30 patients.

Collaboration Agreement

A collaboration agreement has been established between project leaders and site coordinators, outlining mutual obligations and rules for data usage.

Inclusion Period

01.09.2023-31.12.2024, 1-6 months depending on the rate of inclusion at different sites.

Participating Departments

Maternity units from all 5 Danish regions. The following hospitals have agreed to participate:
Capital Region of Denmark (Region Hovedstaden): Hilleroed, Herlev, Hvidovre, Rigshospitalet
Region Zealand (Region Sjaelland): Roskilde
Region of Southern Denmark (Region Syd): Kolding, Odense
Central Denmark Region (Region Midt): Aarhus
North Denmark Region (Region Nord): Aalborg

The study is open for all Danish hospitals, where elective cesarean sections are performed. If any additional hospitals should wish to participate in the study within the specified time period, they will be included.

Data to be collected from the patient's medical record

Patient characteristics

- Pre-pregnancy BMI
- Parity
- Indication for cesarean section: Maternal request/Previous cesarean section as the only indication/Breech presentation/Maternal indication/Obstetric indication/Fetal indication/Other indication.
- Previous number of cesarean sections: 0, 1, 2, 3, or ≥4
- Previous abdominal surgeries: Yes/No. If yes: Laparoscopic or laparotomy
- Chronic pain patient (receiving regular opioid or other pain treatment besides NSAIDs and PCM) within 0-2 months prior to cesarean section: Yes/No
- Inflammatory bowel disease (Crohn's disease or ulcerative colitis): Yes/No
- Pregnancy-related illness? No/Gestational hypertensive disorder (Preeclampsia including HELLP, Gestational hypertension)/Gestational diabetes, Other.

Anesthesia information

- Spinal anesthesia: Bupivacaine, sufentanil, fentanyl, morphine. Mg and ml.
- Was the patient given an epidural-spinal? Yes/No
- Was general anesthesia administered as the initial preference for the patient? Yes/No
- Was the spinal anesthesia converted to epidural? Yes/No
- Was the spinal anesthesia converted to general anesthesia? Yes/No
- Was the spinal repeated following a failed spinal? Yes/No
- Was it necessary to supplement the spinal anesthesia with opioids, nitrous oxide, or similar due to breakthrough pain during the operation? Yes/No
- Did the patient have an epidural when going to the maternity ward after the recovery period? Yes/No. If yes: When was the epidural discontinued? Date and Time.

Operation information

- Operation time (minutes)
- Intraoperative bleeding. ml.
- Has the uterus been exteriorized during the operation? Yes/No/The information was not found in the medical record.
- Postoperative bleeding within the first 48 hours requiring blood transfusion. Yes/No
- Reoperation within the first 30 days: Yes/No. If yes: Abdominal bleeding/Vaginal bleeding/Suspected retained tissue or endometritis/Infection at the incision site/other reason

Pain management

- Nerve blockade within the first 24 hours after the cesarean section: Yes/No; Time; Block type, dose, medication, reason.
- Placement of an epidural within the first 24 hours after the cesarean section: Yes/No; Time, reason

- Opioid consumption within 0-24 hours, mg oral morphine equivalents
- Opioid consumption within 25-48 hours, mg oral morphine equivalents
- Administration of dexamethasone within the first 24 hours after cesarean section: Yes/No. Dose.
- Administration of antihistamine as itch relief within the first 24 hours: Yes/No
- Administration of naloxone as itch relief within the first 24 hours: Yes/No

Maternal hospitalization

- Duration of total hospital lengths of stay after cesarean section (number of days)
- Maternal readmission or unplanned outpatient consultation within 7 days. Yes/No
- Occurrence of clinically significant maternal respiratory depression within 24 hours, defined as the need for airway intervention; oxygen therapy >3 L/min; administration of an opioid antagonist to counteract depressed respiration; or an intervention beyond verbal stimulus to rouse the patient from sedation. Yes/No
- Ogilvie's syndrome/ileus, that requires surgery or neostigmine within the first 7 days after cesarean section: Yes/No

Infant

- Apgar score at 5 minutes
- Apgar score at 10 minutes
- Neonatal hospitalization within 24 hours: Yes/No
- Neonatal readmission within 24 hours: Yes/No
- Neonatal readmission within 7 days: Yes/No
- Neonatal need for respiratory support within 48 hours (CPAP, PPV, HNF, intubation, or oxygen supplementation): Yes/No; Time of initiation; Duration (hours < 24 or number of days > 1)

Appendix 1a-f

1a Project approval from the research lawyer at The Capital Region (Region Hovedstaden) Center for Data Notifications. Approval number P-2023-90.

1b Ethical approval assessment, journal number F-23004686.

1c-1f Data agreements for research projects between the regions.

Appendix 2: Collaboration agreement.

Appendix 3: Data extraction sheet for journal review.

Appendix 4: Overview of the questions that are set up as questionnaires in REDCap and sent to the patient via a link in SMS.

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