FACULTY OF MEDICINE AND HEALTH SCIENCES

Breakthrough pain during Caesarean Section: an observational study and literature overview

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List of abbreviations

CS: Caesarean section

ASO: Resident in Training (Dutch: Arts Specialist in Opleiding)

ASA: American Society of Anesthesiologists

SSS: Single Shot Spinal (Anaesthesia)

CSE: Combined Spinal and Epidural (Anaesthesia)

GA: General Anaesthesia

RSI: Rapid Sequence Induction

EVE: Epidural Volume Expansion

CSF: Cerebrospinal Fluid

BMI: Body Mass Index

VNRS: Verbal Numerical Rating Score

LAST: Local Anaesthetic Systemic Toxicity

PCEA: Patient Controlled Epidural Analgesia

Abstract

Background: Caesarean section (CS) is the most common surgical procedure performed worldwide. Neuraxial anaesthesia is the most commonly used anaesthetic technique to perform a CS. When neuraxial anaesthesia fails, the mother can experience breakthrough pain during surgery for which a change in anaesthetic technique may be required.

Objectives: The main purpose of this prospective, observational study was to determine the incidence of breakthrough pain during a CS defined as "pain requiring a change in anaesthetic technique or the administration of an additional anaesthetic in order to treat pain". In this trial also the risk factors of breakthrough pain during CS were determined.

Methods: The protocol of this observational, prospective study was approved by the hospital ethics committees UZ Leuven and ZNA Middelheim. Three hundred and ninety-three women who underwent a CS in UZ Leuven (206/393) and ZNA Middelheim Antwerp (187/393) were included in the study. All consecutive planned and unplanned CS performed under neuraxial anaesthesia during the study period were included in the observations. Anaesthetic care was the routine standard of care for the individual hospital and anaesthetist. The primary endpoint was the incidence of breakthrough pain. Possible risk factors were also evaluated. A p-value <0.05 was considered statistically significant. Subanalysis was made for planned (primary) and unplanned (conversion from labour to CS) operative deliveries.

Results: Sixty-five of the 393 cases reported breakthrough pain (16.5%). Of planned CS, 15.3% developed breakthrough pain, whilst 20.4% of unplanned CS reported breakthrough pain. Duration of surgery and epidural local anaesthetic drug used during CS were both significant risk factors of breakthrough pain. Most breakthrough pain episodes occurred at the end of surgery well after delivery of the baby. Level of anaesthetic experience as a risk factor for failure just did not reach statistical significance. No other factors were identified that were associated with an increased risk of breakthrough pain.

Conclusion: The incidence of breakthrough pain during CS is high (16.5%). Since breakthrough pain is extremely uncomfortable for the mother, a pro-active policy for its prevention is required. Our results demonstrate that strategies to reduce the incidence of breakthrough pain during CS include a reduction in duration of surgery and administration of a prophylactic epidural top-up in case of prolonged surgery.

Introduction and literature overview

1.Introduction

Caesarean section (CS) is one of the most common surgical procedures worldwide and the number of CS has almost doubled from the year 2000 till 2015 (1). Providing adequate anaesthesia during a surgical procedure such as a CS delivery remains a challenge for obstetric anaesthetists. Ideal intraoperative anaesthesia and pain relief should be tailored to the needs of the mother without interfering with the health of the baby. During the birth of the baby by CS, anaesthesia should be sufficient with a minimum of side effects. Neuraxial anaesthesia is the most commonly used anaesthetic technique to perform a CS, with various alternative options which will be discussed in this literature overview (2).
When this technique fails, the parturient can experience breakthrough pain for which a change in anaesthetic technique can be required.
The primary endpoint of this prospective, observational study was to determine the incidence of breakthrough pain during a CS performed under neuraxial anaesthesia. The secondary endpoint is to determine the associated risk factors for the occurrence of breakthrough pain during CS.
Breakthrough pain is defined as pain for which the patient requires a change in anaesthesia strategy or the administration of an additional anaesthetic in order to treat intraoperative pain. Prophylactic additional anaesthesia in order to prevent possible breakthrough pain is not included and is not seen as breakthrough pain treatment.

2.Literature overview

2.1 Caesarean Section

CS is probably the most common surgical procedure performed worldwide. On the basis of data from 169 countries, which includes 98.4% of the world's births, we estimate that 29.7 million births (21.1% of all births, 95% confidence interval 19.9–22.4%) occurred through CS in 2015, which was almost double the number of CS performed in 2000 (16.0 million [12.1%, 10.9–13.3] births). (1)
Since 1985, the World Health Organisation (WHO) has considered the ideal rate for CS to be between 10% and 15%. Since then, CS has become increasingly common in both developed and developing countries. Worldwide, the CS-rate continues to rise making a CS the method

of delivery in 28% of deliveries in 2017. (3) When medically justified, a CS can effectively prevent maternal and perinatal mortality and morbidity. However, there is no evidence showing the benefits of CS for women or infants who do not require the procedure. (2) On the contrary, CS may induce maternal and neonatal side-effects. Side-effects that may only become apparent in a next pregnancy (e.g. placental abnormalities or uterine rupture).

The indications to perform a CS can be maternal (e.g. preeclampsia), foetal (e.g. foetal distress) or obstetric (e.g. breech). The grade of urgency to perform a CS can be identified according to the internationally accepted Lucas Classification (see table 1). (4)

Lucas Classification	
1	Immediate threat to life of mother or fetus
2	Severe fetal of maternal compromise but not immediately life-threatening
3	Compromise which responds to therapy although underlying problem still exists and needs delivery
4	Elective

Table 1 : Lucas classification

The choice of anaesthesia is determined by the clinical condition of the patient, the urgency, available facilities and expertise of the anaesthetist.
The anaesthetic technique required to perform a Lucas grade 1 CS is often general anaesthesia due to the high grade of urgence and the lack of time to perform a regional technique. However, a regional technique is not contraindicated provided an experienced anaesthetist can perform the procedure without delay. For a grade 2 to 4 CS, neuraxial anaesthetic techniques are preferred since they result in less maternal morbidity. (5)

2.2 Anaesthesia for Caesarean Section

Anaesthesia for CS can be performed using one of two major anaesthetic techniques: Neuraxial anaesthesia or general anaesthesia (GA). Internationally, obstetric anaesthesia guidelines recommend spinal and epidural anaesthesia over GA for most CS. (6)
Neuraxial anaesthesia permits maternal participation in the birth process, limits potential for difficult airway or awareness under GA, avoids the depressant effects of systemic anaesthetic medication on the foetus and the uterine tone, and facilitates the provision of postoperative

analgesia. (7) Increased use of neuraxial techniques is responsible for a reduced incidence of anaesthetic induced maternal morbidity and mortality (2).
Prior to CS, every patient should undergo an evaluation by an anaesthetist to determine any co-morbidities that would impact the anaesthetic plan. (8)
Contra-indications for neuraxial anaesthesia techniques are: patient refusal, infection at the needle insertion site (risk of meningitis), significant coagulopathy (due to risk of epidural haematoma), hypovolemic shock, elevated intracranial pressure (primarily due to intracranial mass) and inadequate provider expertise. (9-10) When neuraxial techniques have failed or are contra-indicated, the anaesthetist can decide to go to GA to perform the CS. Hence, despite the clear preference for neuraxial anaesthesia, it is clear that a small group of patients will always require a GA. Neuraxial anaesthesia techniques can be divided into:

1. Single shot spinal anaesthesia (SSS)

2. De novo epidural anaesthesia

3. Combined Spinal Epidural anaesthesia (CSE)

4. Topping up a labour epidural catheter

2.2.1 Single Shot Spinal anaesthesia (SSS anaesthesia)

With SSS, a local anaesthetic solution is injected in the intrathecal space. The injection will usually be administered at the L3-L4 or L4-L5 lumbar interspace, to avoid the risk of spinal cord trauma. (8) Adding a lipid-soluble opioid (e.g., fentanyl, sufentanil) to a local anaesthetic solution enhances intraoperative anaesthesia by reducing the total dose of local anaesthetic, reducing hypotension, nausea and vomiting, and by improving the quality of anaesthesia. (11) The main adverse effect of SSS is hypotension. Maternal hypotension leads to uteroplacental hypoperfusion with foetal acidaemia and maternal nausea and vomiting. The risk of hypotension increases with higher doses of the local anaesthetic drug. (12)

A very important disadvantage of this technique is that it is a single shot technique. So an additional regional anaesthetic cannot be administered when breakthrough pain occurs or when surgery is prolonged.

Several strategies have been developed to prevent and treat spinal induced hypotension. Currently, the use of pure vasopressors such as phenylephrine are considered the cornerstone of prevention and treatment. Fluid co-loading and ephedrine are second line options. (13)

2.2.3. Epidural anaesthesia

Epidural anaesthesia is a very common anaesthetic technique. Using the loss of resistance technique, the epidural space is identified and a catheter is left behind to administer anaesthetic or analgesic drugs. The advantage of epidural anaesthesia is a gradual initiation of anaesthesia with better preservation of maternal haemodynamics and therefore its use is mainly in high risk patients in which haemodynamic instability after neuraxial anaesthesia should be avoided. Having an epidural catheter in situ gives the possibility to prolong anaesthesia whenever required. The main disadvantages of epidural anaesthesia are the slower speed of onset and the reduced quality of the block. The onset of epidural anaesthesia takes longer compared to spinal anaesthesia and breakthrough pain is much more frequent. (14) Additionally, much more local anaesthetic drugs are required to have a sufficient block for surgery, inducing the possibility of Local Anaesthetic Systemic Toxicity (LAST). (15)

The use of de novo epidural anaesthesia for CS, without prior use in labour, is almost non-existent in current obstetric anaesthesia practice.

2.2.2 Combined Spinal Epidural Anaesthesia (CSE)

The CSE technique is a combination of a single shot spinal technique and an epidural technique. It combines a single spinal shot of a local anaesthetic +/- opioïd with the placement of an epidural catheter. This is a very popular technique due the combination of the rapid onset and predictability of the spinal block, and the ability to modify and extend the block through an epidural catheter. (16)
The main advantage of the CSE technique is that the spinal dose can be lowered (resulting in less hypotension (12)) whilst there is an epidural catheter in place to prolong anaesthesia whenever surgery is unexpectedly prolonged or to manage insufficient anaesthesia. (17)

Low-Dose CSE

A CSE with a spinal dose less than 8 mg of hyperbaric bupivacaine is considered a low-dose CSE technique. (18)

Low-dose spinal anaesthesia for CS has been proven effective in preventing maternal hypotension and is a valuable method in improving maternal and neonatal outcome. From prospective trials, it is clear that lowering the spinal dose improves maternal

haemodynamic stability. Doses of intrathecal bupivacaine between 5 and 7 mg are sufficient to provide effective anaesthesia. Nevertheless, complete motor block is seldom achieved. (19)

Adequate anaesthesia is limited in time. If the uterus is not closed after 45 minutes, a prophylactic epidural top-up is given to prevent breakthrough pain. (20)

The epidural catheter can be used to extend anaesthesia. Once the spinal anaesthetic wears off, anaesthesia can be prolonged by epidural catheter drug administration. Careful block testing prior to surgery and prophylactic administration of epidural top-ups in the event of prolonged surgery allows the clinician to guarantee perfect anaesthetic conditions with minimal hypotension, which is easily treated.

2.2.4 Epidural Top-up

In the event of an unplanned CS, a well-functioning labour epidural catheter can be topped-up with a more potent anaesthetic solution. A recent retrospective cohort study with 1254 parturients showed that extending epidural analgesia using the well-functioning epidural catheter for epidural labour analgesia might be a reliable and effective anaesthetic method for intrapartum CS. (21) There are many local anaesthetic top-up solutions possible. A meta-analysis of 11 RCT's compared different lidocaine 2% solutions (with or without epinephrine or bicarbonate or fentanyl) and levobupivacaine 0.5%, bupivacaine 0.5% and ropivacaine 0.75%. Ropivacaine proved to produce the least breakthrough pain whilst lidocaine 2% solutions had the shortest onset time. (22)

A recent meta-analysis (23) analysed 24 RCT with 1280 women to compare the speed of onset of the six local anaesthetics most often used for anaesthesia for CS: lidocaine 2%, bupivacaine 0.5%, levobupivacaine 0.5%, 2-chloroprocaine 3%, lidocaine 2% + bicarbonate and ropivacaine 0.75%. This meta-analysis found that lidocaine 2% with bicarbonate had the fastest onset of surgical anaesthesia. 2-Chloroprocaine 3% had a similar onset time than lidocaine 2% without bicarbonate. However, when the time to add bicarbonate to the anaesthetic mixture was taken into consideration, 2-chloroprocaine was actually the fastest solution. This has the additional benefit that admixture errors cannot occur.

The rate of intra-operative hypotension was least after levobupivacaine 0.5% and highest after 2-chloroprocaine 3%. 2-chloroprocaine 3% has a short duration of action and therefore when surgery is prolonged additional epidural top-ups are required. Ropivacaïne 0.75%, levobupivacaine 0.5% and bupivacaine 0.5% were relatively slow in onset and may be

inappropriate for emergency delivery. The rate of intra-operative supplementation of anaesthesia was least after ropivacaine 0.75% (48 (19-118) per 1000) and highest after 2-chloroprocaine 3% (250 (112-569) per 1000). But the latter was due to inadequate prophylactic epidural top-ups when surgery was prolonged.

2.2.5 General Anaesthesia (GA)

GA for CS is used in emergency situations (Lucas classification 1), or when there is a failure of or a contraindication for neuraxial anaesthesia. (24) GA in pregnant woman is associated with many side effects and is an important cause of maternal and foetal morbidity and mortality. (25-26) Common side effects of GA are ventilation and intubation problems (difficult intubation and hypoxia), aspiration problems (pneumonia), neonatal sedation, relaxation of the uterus (increased risk of bleeding), nausea, intraoperative awareness, postoperative sedation, and increased maternal mortality. (26) The introduction of a rapid sequence technique of induction and the use of antacid aspiration prophylaxis have resulted in a reduced risk of complications. (26)

Rapid sequence induction (RSI) with cricoid pressure and endotracheal intubation remains the gold standard for all women having CS under GA. Because of the limited availability of thiopental and the noninferiority of propofol, the latter becomes increasingly popular for induction. The combination of rocuronium and sugammadex combines rapid onset and rapid reversal of neuromuscular blockade with a greater safety profile than succinylcholine, and provides very comfortable intubation conditions. Although maintenance with propofol seems to be beneficial with respect to the avoidance of uterine atony, sevoflurane is still widely considered the maintenance agent of choice in GA for CS. (24)

Remifentanil can be safely used at induction of GA, provided healthcare workers are available to manage short-lasting neonatal depression. Remifentanil seems to have short-lived respiratory depressant effects in approximately 50% of neonates, requiring short periods of mask ventilation or tactile stimulation of the neonate. Remifentanil produces excellent maternal haemodynamic stability avoiding tachycardia and hypertension, possibly reducing the risk of maternal awareness. (27)

Successful conversion from epidural analgesia to epidural anaesthesia is critical to avoid GA; emergency GA is linked to poor outcomes (postoperative pain and sedation, intraoperative awareness, postpartum hemorrhage, and morbidity and mortality from aspiration or failed tracheal intubation). The ability to successfully convert epidural analgesia to anaesthesia for

intrapartum CS has been proposed as a quality metric; in the United Kingdom, the National Institute for Health and Care Excellence (NICE) guidelines state that GA should be used in <1% of all elective CS and <5% of all emergency CS. (2)

2.3 Breakthrough pain during CS

2.3.1 Incidence

Breakthrough pain is defined as pain or a feeling of intense abdominal pressure that requires supplemental anaesthesia. Breakthrough pain is discomfortable for the mother but also increases the workload of anaesthetists in a busy operating theater. Breakthrough pain has important physical and emotional effects on the mother and can cause serious medicolegal consequences. Susanna Stanford, a patient experiencing pain during CS, described the experience vividly. (28)

David Bogod reported that the risks associated with obstetric GA, previously one of the top causes of maternal mortality, have been largely controlled. Pain during CS is now the most common successful negligence claim against anaesthetists in the UK. (29) Szypula et al. analyzed 841 anaesthetic claims reported by the National Health Service Litigation Authority in England. Of 366 claims related to regional anaesthesia, 186 (51%) were obstetric cases. The total cost of closed claims was 12,724,017 Pound Sterling. The total cost for obstetric closed claims was 5,433,920 Pound Sterling. Pain during CS was the most frequent cause for litigation (57 claims), followed by nerve damage and back pain. (30)

The incidence of breakthrough pain during CS varies in the literature between 1-20% according to the anaesthetic technique used.

Table 2: overview of studies that report failure of regional anaesthesia and failure rate / incidence of breakthrough pain (31-45)

Study & n	n	Type of RA	Definition of failure	Failure rate
Paech et al, 1998	4624	100% Epidural	Inadequate block for C-section	1.7%

Norris et al, 2000	1662	64% CSE 36% Epidural	Inadequate block at time of surgery	4% CSE 6% Epidural
Riley et al, 2002	246	83% Epidural 17% CSE	Need for another anesthetic technique	8% Epidural 7.5% CSE
Garry and Davies, 2002	2471	33% epidural top-up 67% spinal	Conversion to general anaesthesia	10.5% epidural 2.9% spinal
Tortosa et al, 2003	194	100% Epidural	Conversion to general anaesthesia	2.6 %
Pan et al 2004	4190	55% Spinal 41% Epidural 4% General (planned)	Inadequate analgesia or no sensory block after adequate dosing at any time after initial placement (requiring replacement of supplement technique)	7.1% epidural 2.8% spinal
Kan et al, 2004	2843	68.6% spinal 27.8% epidural top-up 3.6% CSE	Conversion to general anaesthesia	2.8% spinal 7.5% epidural top-up 3% CSE
Orbach-Zinger et al, 2006	101	100% Epidural	Conversion to general anaesthesia at any time after surgery started	19.8%
Kinsella et al, 2008	5080	63% Spinal 26% Epidural top-up 5% CSE 5% Primary general anaesthesia	Pre-operative conversion to another anaestetic or failure to achieve a satisfactory block. Or Intra-operative unsatisfactory anaesthesia requiring additional anaesthesia	6% Spinal 24% Epidural top-up 18% CSE

Halpern et al, 2009	501	100% Epidural	Primary outcome: conversion to general anaesthesia. Secondary: conversion to another form of replacement of epidural catheter	5.9%
Lee et al, 2009	1008	11% Epidural 89% CSE	Inadequate neuraxial blockade for cesarean delivery in the presence of adequate time of onset of epidural anaesthesia	6% epidural 1% CSE
Campbell and Tran, 2009	895	100% epidural	Inadequate epidural surgical anesthesia intrapartum	10.9%
Sng BL et al, 2009	800	100% Spinal	Conversion to general anesthesia (total failure) of the need for supplemental fentanyl and/or Entonox IV	0.5% total failure 4.6% partial failure
Bamgbade et al, 2009	1083	9% epidural top-up 91% Spinal	Inadequate block for C-section	2.9 % spinal 4.3 % Epidural
Adesope AO et al, 2016	5015	Spinal or CSE	-Repeat spinal to obtain adequate block height -Conversion to general anesthesia -Augmentation of initial block with epidural lidocaine before of within 30min of skin incision	5.5% overall failure rate

2.3.2 Risk factors of breakthrough pain

A systematic review and meta-analysis showed that the risk of failed conversion of labour epidural analgesia to epidural anaesthesia is increased with an increasing number of rescue boluses administered during labour, a more urgent type of CS (Lucas classification) and care being provided by non-obstetric anaesthetists. (46)

Some studies reported BMI as a factor possibly associated with failed epidural conversion, but only Orbach-Zinger et al.(38) reported a statistically significant association between weight and failed epidural anaesthesia.

Several studies (38,39,40,41,42,45,47) have identified factors associated with inadequate labour epidural analgesia and risk factors for failure to extend the epidural to anaesthesia in case of CS. Three types of failure are identified: anaesthetic, maternal and obstetric.
Anaesthetic risk factors include lack of a dedicated obstetric anaesthetist, inavailability of consultant back up for trainees, a conventional epidural technique for labour analgesia (as compared to a CSE technique for labour analgesia), drug regimens, history of opioid tolerance, inappropriate block assessment, previous failed epidural analgesia, inadequacy of pre-operative anaesthetic block, number of top-ups during labour, prolonged duration of epidural labour analgesia, incorrect primary epidural placement, secondary migration of the catheter, and suboptimal dosing of local anaesthetic drug.
Maternal factors associated with inadequate labour epidural analgesia and with failure of extension to epidural anaesthesia for CS include higher BMI, concomitant comorbidity, increased patient height and younger age.
Obstetric determinants related to higher failure rates are: high degree emergency for operative delivery, cervical dilatation >7cm, no previous CS, acute fetal distress as indication for CS, duration of surgery, higher gestational age and obstetric preference to GA. (47)

A meta-analysis of 2016 showed that the addition of a lipophilic opioid to the local anaesthetic improved intraoperative anaesthetic conditions as opposed to a local anaesthetic without an opioid. Women receiving the combination had less breakthrough pain, shorter sensory block onset time, and longer first analgesic request time. However, the addition of sufentanil to bupivacaine increased the incidence of pruritus. (48)

Reported factors associated with epidural conversion failure include the number of bolus doses for treatment of breakthrough pain during epidural labour analgesia, prolonged duration of analgesia, initiation of neuraxial analgesia using a traditional epidural technique compared with CSE labour analgesia, tall compared with short stature of the patient, epidural catheter placement by a non-specialist obstetric anaesthetist, and the urgency of CS. (49)

Table 3: An overview of risk factors to breakthrough pain during CS (38,39,40,41,42,45,49)

Risk factor	Study	Definition of Risk Factor	Findings
Age	Orbach-Zinger et al	Maternal age	Younger age = increased rate of failure (p=0.014)
Weight	Orbach-Zinger et al	BMI, weight at the end of pregnancy	Higher BMI and weight associated with failure p=0.0004
Breakthrough pain / number of boluses	Halpern et al	More than 1 clinical bolus in labor	OR (95% CI) of failure 1.6 (1.1-2.4)
	Lee et al	>2 episodes of breakthrough pain during labour	OR (95% CI) of failure 6.65 (2.5-17.9) =
	Orbach-Zinger et al	Number of boluses and VAS pain score in the 2h before C-section	OR (95% CI) of failure 4.39 (1.6-12.2)
	Campbell and Tran	One or more bolus	OR (95% CI) of failure 2.37 (1.6-3.5)
Duration of labour analgesia (h)	Lee et al	More than 12h since initiation of labour analgesia	OR (95% CI) of failure 1.06 (1.01-1.11)
Gestational age	Orbach-Zinger et al	Gestational age (weeks)	Greater gestational age associated with failure (P=0.008)
	Adesope OA et al		Failure rate higher in preterm than term patients (p=0.02)
Specialist Provider	Cambell and Tran et al.	Specialist manipulating the catheter and inducing GA (general anesthesia)	Obstetric anaesthesia specialists are more likely to manipulate an epidural catheter (85% vs 5.9%) and less likely to induce GA (1.2% vs 5.5%). OR (95% CI) of failure of generalist compared with specialist: 4.76 (1.5-15.6)
Epidural technique vs CSE	Lee et al.	Initiation of labour analgesia with stand-alone epidural compared with CSE	OR (95% CI) of failure 5.54 (2.1-14.9)

Urgency	Kinsella	LUCAS 1 (= threat to life of mother of fetus)	OR (95% CI) of failure 2.45 (1.4 – 4.4)

2.3.2 Treatment of breakthrough pain

When the parturient experiences breakthrough pain during a CS, drugs must be given in order to treat the pain and a change in anaesthetic strategy can be required. There are two options to treat breakthrough pain: the administration of an additional anaesthetic drug through the epidural catheter, or a change in anaesthetic technique by using IV drugs, inhalational anaesthesia or GA. Additional epidural local anaesthetic and/or opioid may be administered if a catheter is in place. In most cases, the additional local anaesthetic administered through the epidural catheter can be (levo)bupivacaine, ropivacaine, lidocaine or chloroprocaine-3%. The review in 2011 by Hillyard et al. (22) showed that lidocaine 2% has a significantly faster onset than bupivacaïne or levobupivacaine 0.5% or ropivacaine 0.75%. This solution of lidocaine 2% will be used in many cases of breakthrough pain because of its rapid and strong onset. However, in the review by Hillyard, chloroprocaine was not evaluated.

The recent meta-analysis of 2020 by Reschke et al. analysed 24 RCT with 1280 women to compare the speed of onset of the six local anaesthetics most often used for surgical anaesthesia for CS. This meta-analysis also found that lidocaine 2% with bicarbonate enabled the fastest onset of surgical anaesthesia. The rate of intra-operative supplementation of analgesia was least after addition of ropivacaine 0.75%. (23)

A change in anaesthetic technique

Small doses of systemic medication / conscious sedation may be effective for anxiolysis or treatment of visceral stimulation (ketamine 10 to 30 mg IV with midazolam pretreatment, nitrous oxide by mask, remifentanil 0.0.5-0.1 µg/kg/min). (50, 51) However, if the block is clearly inadequate, general anaesthesia should be induced and the airway secured, rather than administering multiple intravenous medications.

An experimental technique for a feeling of discomfort during manipulation of the uterus, in patients with an adequate sensory block, is the addition of an intraperitoneal local anaesthetic. The optimal volume and concentration of the local anaesthetic (LA) solution for intraperitoneal instillation and the risk of local anaesthetic toxicity have not been determined yet. In one case series of 32 patients who experienced pain during CS, 20 to 60 mL of 1% chloroprocaine (mean dose 11.8 mg/kg) was poured into the peritoneal cavity after delivery of

the fetus. One to five minutes later, excess LA solution was suctioned away. (52)

Kan et al. (51) already demonstrated that low IV doses of remifentanil (0.1 µg/kg/min) provide mild to moderate levels of sedation in patients undergoing CS under epidural anaesthesia. The foetal impact is minimal due to shortness of action of remifentanil.

A pro-active policy is absolutely necessary in order to prevent breakthrough pain or discomfort during surgery for CS. The neuraxial block should always be tested before surgery can start and a level of complete absence of cold sensation should be observed up to and including T4. Block to cold sensation is usually at a higher level than block to sharp pinprick. (53)
When low dose spinal anaesthesia is used and when surgery is prolonged beyond a certain time (40-50 min), a prophylactic epidural top-up should be given. (17)

The goal of the present investigation was to evaluate the incidence of breakthrough pain in consecutive CS and to describe the potential risk factors for breakthrough pain.

Methods

The study was performed at the anaesthetic departments of two Belgian hospitals: UZ Leuven and ZNA Middelheim Antwerp. The study protocol was approved by the ethic committees of both hospitals; in UZ Leuven by chairman Prof. Dr. Casteels M-R on 13th December 2017 with E.C. approval number 61018, in ZNA Middelheim Antwerp by chairman Prof. Dr. De Deyn on 10th of January 2018 with E.C. Approval number 5044.
The design of the study was an observational prospective study. During a 6-month study period, all consecutive women undergoing a planned or unplanned CS performed under any type of neuraxial anaesthesia were included and this at any possible time of day including weekends and after hours (24/24 7/7). There were no exclusion criteria.
All participants received normal standard of care, routine for the hospital and attending anaesthetist. Patients were treated either by a consultant or trainee. In principle and per routine care pathway, the effect of neuraxial anaesthesia had to be tested and an adequate block had to be established before surgery could start. An adequate block is defined as a block for cold to T4 with complete absence of cold sensation up to and including the T4 dermatome.
For data collection, a paper version of a case report form was used for each individual patient (*appendix 1)*. This form was completed by the anaesthetist during surgery. Only pain during

surgery was studied. Duration of surgery was defined as the time of completion of the spinal injection to wound closure or as the time of start of the epidural bolus to wound closure. Within 24 hours after each CS, a study collaborator collected the forms and checked them for accuracy and completion against the clinical records. Missing information was added by interviewing the attending anaesthetist.

At each participating centre, all relevant patient data were anonymously entered in an Excell database file. Only through the individual study identification number, it was possible to track back patients.

The primary endpoint of this study is the incidence of breakthrough pain. Breakthrough pain is defined as pain for which the patient requires a change in anaesthesia strategy or the administration of an additional anaesthetic in order to treat pain. Prophylactic additional local anaesthetic administration through the epidural catheter in order to prevent possible breakthrough pain was not seen as breakthrough pain or management of breakthrough pain.

The secondary recorded data were: the level of experience of the anaesthestist (trainee or staff member), expected difficult airway, labour epidural catheter, number of top-ups during labour + which drugs used during labour, epidural volume expansion (EVE) including time and volume, duration of analgesia during labour, number of PCEA boluses during labour, verbal numerical rating score (VNRS) before CS, VNRS score during CS, history of previous failed epidurals, chronic pain medication, deviation of the standard operating protocol, adequacy of the block before CS starts, ease of insertion of the catheter, the spinal drug, BMI of mother, maternal weight, maternal length, maternal age, maternal race, gestational age, repeat section, conversion from labor to CS, nulliparity, Lucas classification of urgency, breech, duration of surgery, Apgar score baby, weight of the baby at birth, umbilical blood gasses of the baby.

Statistical analysis was performed using SAS software version 9.4.

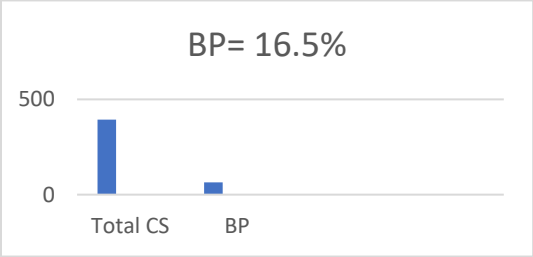
Univariate analysis of factors that might influence the origin of breakthrough pain was performed using a 2-sample t-test, or a Wilcoxon rank-sum test. All categorical variables were assessed using a chi-squared test. The univariate analysis was used to determine the factors that correlated with the origin of breakthrough pain. Factors that actually were associated with the origin of breakthrough pain in the univariate analysis, were put into a multiple logistic regression analysis to determine which factors are significant predictors for the outcome. Subanalyses were made for primary and secondary CS.

A post-hoc testing was used to compare all the drugs to each other, with Bonferroni correction for multiple testing.A p-value <0.05 defined statistical significance. All reported p-values are two-sided.

Results

A total of 393 patients were enrolled in the study over 6 months, 206 in UZ Leuven and 187 in ZNA Middelheim, 295 elective CS and 98 secondary CS. Of all 393 participants, 65 experienced breakthrough pain during the CS (16.5% - see figure 1), with a median (Q1; Q3) VNRS pain score of 6 (5; 7). In 39 of the 65 parturients (60%) who experienced breakthrough pain, the pain was described as a sharp, acute pain, while in 26 of the 65 participants (40%) the pain was described as an uncomfortable feeling.

Figure 1: Number of Caesarean sections (CS) and breakthrough pain (BP)



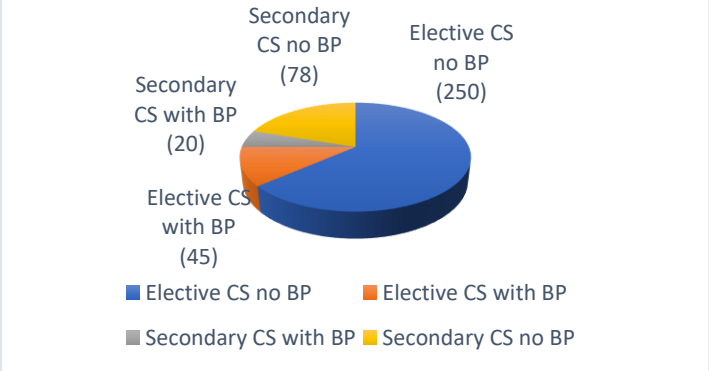
Both elective (n=295) and unplanned operative deliveries (n=98) were included in this audit. In elective CS 45 patients experienced breakthrough pain (15.3%), in unplanned, secondary CS 20 patients experienced breakthrough pain (20.4%). This difference was not statistically significant (p=0.234).

Table 4 : Difference in breakthrough pain in elective vs unplanned CS

Caesarean Section	No pain	Pain	Total	P-value
				0.234
Elective	250/295(87.7%)	45/295(15.3%)	295	
Unplanned	78/98 (79.6%)	20/98 (20.4%)	98	
Total	328 (83.5%)	65 (16.5%)	393	

Values are number n/N (%)

Figure 2: Number of elective and secondary Caesarean sections (CS) and breakthrough pain (BP)



The timing of occurrence of breakthrough pain was in 3% during skin incision, in 9% during peritoneal incision, in 20% between peritoneal incision and birth of the baby and in 68% after birth (near the end of the intervention). Breakthrough pain occurred with a median (Q1; Q3) time of 35 (22; 51) minutes after start of surgery. In most of the participants (58.7%), breakthrough pain was treated with an extra epidural bolus of an anaesthetic solution, other treatments of breakthrough pain were conversion to general anaesthesia (7.9%), a change in anaesthetic strategy (e.g. the addition of IV remifentanil or IV midazolam) (19.1%) and reassurance of the patient (12.7%). In 1.6% a combination of the above was used (see table 5).

Table 5 : Treatment of breakthrough pain

Treatment of breakthrough pain	**Antwerp**	**Leuven**	**Total N=65**
General anaesthesia	4/26(15.4%)	1/37 (2.7%)	5/63 (7.9%)
Change in Anaesthetic strategy	7/26(26.9%)	5/37(13.5%)	12/63(19.1%)
Extra Epidural Anaesthesia	7/26(26.9%)	30/37(81.1%)	37/63(58.7%)
Reassurance	7/26(26.9%)	1/37(2.7%)	8/63(12.7%)
Strategy change & extra epidural bolus	1/26(3.9%)	0/37(0%)	1/63(1.6%)
Missing data			2/65

Values are number n/N (%)

In elective CS, 16% of patients (n=49) were performed under SSS anaesthesia, 82% (n=241) with a CSE technique, 2% (n=5) were de novo epidurals because of failed spinal puncture or because the anaesthetist felt the need for perfect haemodynamic stability. Hyperbaric Bupivacaine 0.5% (doses between 6.6-8mg) was the most commonly used local anaesthetic, in 231 of CS (78.6 %). Prilocaine (50mg) was used in 11 patients (4%) and levobupivacaine (doses between 12.5-13.5mg) in 51 patients (17.4%). Breakthrough pain occurred in 45 patients. The incidence of breakthrough pain (n/N (%)- see table 6) was respectively 36/231 (15.6%) for Hyperbaric Bupivacaine 0.5%, 4/11 (36.4%) for Prilocaine and 4/51 (7.84%) for Levobupivacaine (p=0.049). After pairwise comparisons for multiple testing, there was no statistical difference between the 3 spinal local anaesthetics (see table 7). A larger sample size might be needed to show a significant difference.

Table 6: Spinal drug used and incidence of breakthrough pain

Spinal drug	Estimate	95% confidence interval	P-value
			0.049
Hyperbaric bupivacaine	15.6%	11.2%; 20.9%	
Prilocaine	36.4%	10.9%; 69.2%	
Levobupivacaine	7.8%	2.2%; 18.9%	

Values are number n/N (%)

Table 7: Pairwise comparison of spinal products used and the incidence of breakthrough pain

Spinal Drug	Adjusted P-Value (*)
Levobupivacaine vs Marcaine	0.48
Levobupivacaine vs Prilocaine	0.06
Marcaine vs Prilocaine	0.25

(*) Adjusted using Bonferroni correction

In patients who received a CSE as primary anaesthetic technique for elective CS (n=241), 41 patients experienced breakthrough pain (17%). Hyperbaric Bupivacaine 0.5% was the most common used local anaesthetic. 215 patients received Hyperbaric Bupivacaine as spinal drug (89.2%), eleven patients received Prilocaine (4.6%) and Levobupivaine 0.5% was used in 13 patients (5.4%). In 2 patients the spinal space could not be identified and no spinal anaesthetic solution was administered. The incidence of breakthrough pain (n/N (%) was respectively 34/215 (15.8%) for Hyperbaric Bupivacaine 0.5%, 4/11 (36.4%) for Prilocaine and 2/13 (15.4%) for Levobupivacaine.

In patients who received a SSS technique (49 patients), 3 patients experienced breakthrough pain. Twelve patients received Hyperbaric Bupivacaine 0.5% (24.5%), of which one patient experienced breakthrough pain. Of the 37 patients (75.5%) who received Levobupivacaine, 2 patients experienced breakthrough pain. There was no statistically significant difference between the type of spinal drug used and the incidence of breakthrough pain.

In elective CS, the primary anaesthetic technique on itself was not statistically significant for breakthrough pain (p= 0.053). The incidence for SSS technique was 6.12% for breakthrough pain (95% c.i. 1.28%; 16.9%), the incidence for CSE technique was 17% (95% c.i. 12.5%; 22.4%).

One hundred and three patients received an epidural drug as epidural top-up. Most patients received the epidural top-up because of conversion from labour analgesia to secondary CS

(n=93). Ten patients received the epidural top-up as part of a planned CS in which epidural local anaesthetic was given prior to start of surgery, because of a de novo epidural technique or because of a failed spinal in a CSE technique. There was a statistically significant difference between the type of epidural local anaesthetic drug used for CS and the occurrence of breakthrough pain (p= 0.003). Breakthrough pain occurred in 23 patients (22.3%), of which 4 (14.8%) received Ropivacaine 0.75%, 11 (22%) received 2-Chloroprocaine 3%, 1 (6.7%) received Lidocaine 2% and 7 (63.6%) received a combination of Ropivacaine + Lidocaine (see table 8). There was a higher chance of breakthrough pain when the combination of Ropivacaine+Lidocaine was used compared to the other local anaesthetics. These results were also confirmed in pairwise comparison of the different epidural drugs (see table 9). A pairwise comparison between the four epidural products used, demonstrated a statistical difference in incidence of breakthrough pain between lidocaine vs Ropivacaine+ Lidocaine (p=0.049) and Ropivacaine vs Ropivacaine+ Lidocaine (p=0.032). There was a higher chance of breakthrough pain when combined local anaesthetics (Ropivacaine+Lidocaine) were used compared to each of them as a single local anaesthetic.

Table 8 : Epidural drug and occurrence of breakthrough pain

Epidural drug	**Estimate probability of pain**	**95% CI**	**P-value**
			0.003
Ropivacaine	14.8%	(4.2% ; 33.7%)	
Chloroprocaine 3%	22.0%	(11.5% ; 36.0%)	
Lidocaine	6.7%	(0.17%; 31.9%)	
Ropivacaine+Lidocaine	63.6%	(30.8% ; 89.1%)	

Values are number n/N (%)

Table 9: Pairwise comparison of epidural local anaesthetics used and the incidence of breakthrough pain

Epidural Drug	**Adjusted P-Value (*)**
Chloroprocaine 3% vs Lidocaine	1.0
Chloroprocaine 3% vs Ropivacaine	1.0
Chloroprocaine 3% vs Ropivacaine+Lidocaine	0.06
Lidocaine vs Ropivacaine	1.0
Lidocaine vs Ropivacaine+Lidocaine	0.049
Ropivacaine vs Ropivacaine+Lidocaine	0.03

(*) Adjusted using Bonferroni correction

When we look at preventive top-ups to prevent breakthrough pain occurrence, in the CS performed under CSE (241 elective CS and 6 secondary sections of which 3 did not report on top-ups, n=244) preventive top-ups were given in 50 patients and no preventive top-up was given in 194 patients. Breakthrough pain occurred in 42 patients (17%). In patients with a preventive epidural top-up, 6 had breakthrough pain (12%). In patients without a preventive epidural top-up, 36 patients had breakthrough pain (19%) This difference was not statistically significant (p=0.274). In the secondary CS with an epidural top-up (93/98), preventive top-ups were given in 11 patients, no preventive top-up in 81 patients, and there was one patient with missing data. Breakthrough pain occurred in 18 patients, 2 patients with breakthrough pain did receive a preventive top-up, 16 did not receive a preventive top-up. This was also not statistically significant (p=0.90).

Duration of surgery was a significant risk factor for breakthrough pain during CS (P-value <0.001). The median (Q1;Q3) duration of surgery in patients who experienced pain was 49 (35; 60) minutes. The median (Q1;Q3) duration of surgery in patients who did not experience pain was 38 (28; 49) minutes.

In the present prospective study, maternal age, maternal BMI, maternal height, race, gestational age, conversion, repeat CS, experience of the anaesthetist (trainee vs staff member), Lucas classification of urgency, primary anaesthetic method, number of epidural (PCEA) boluses during labour, duration of labour before conversion, highest dermatome block, pain score at start of conversion, preventive topping-up the epidural catheter, difficult catheter insertion, chronic opioid use by the mother, and the weight of the baby were all no statistically significant risk factors in the incidence of breakthrough pain (see table 10). There were also no differences in neonatal outcome in patients with or without breakthrough pain (see table 11).

Table 10: Patient and baby characteristics by occurrence of breakthrough pain

Characteristics	**No breakthrough pain**	**Breakthrough pain**	**Total**	**P-value**
Maternal age [y]	[328]31(5)	[65]32(6)	[393] 32(5)	0.151
Maternal height [cm]	[326] 164 (7)	[65] 163 (7)	[391] 164 (7)	0.552
>167 cm	109/326 (33.4%)	17/65 (26.1%)	126/391 (32.2%)	0.25 1
BMI [kg/m²]	[326] 31 (5)	[65] 31 (5)	[391] 31 (5)	0.829
Race				0.580

Asian	20/328 (6.1%)	2/65 (3.1%)	22/393 (5.6%)	
Black	53/328 (16.2%)	9/65 (13.9%)	62/393 (15.8%)	
Hispanic	17/328 (5.2%)	6/65 (9.2%)	23/393 (5.9%)	
Caucasian	196/328 (59.8%)	41/65 (63.1%)	237/393(60.3%)	
Other	42/328 (12.8%)	7/65 (10.8%)	49/393 (12.5%)	
Gestational age [weeks]	[328] 38 (3)	[65] 38 (2)	[393] 38 (3)	0.731
Conversion	78/328 (23.8%)	20/65 (30.8%)	98/393 (24.5%)	0.234
Repeat CS	143/327 (43.7%)	30/65 (46.2%)	173/392(44.1%)	0.719
Lucas classification				0.936
Emergency				
Urgent	8/327 (2.5%)	2/65 (3.1%)	10/392 (2.5%)	
Scheduled	70/327 (21.4%)	14/65 (21.5%)	84/392 (21.4%)	
Elective	76/327 (23.2%)	17/65 (26.2%)	93/392 (23.7%)	
	173/327 (52.9%)	32/65 (49.2%)	205/392(52.3%)	
Primary anaesthetic method				0.163
Spinal	46/328 (14.0%)	3/65 (4.6%)	49/393 (12.5%)	
CSE	205/328 (62.5%)	42/65 (64.6%)	247/393(62.9%)	
Upload	74/328 (22.6%)	19/65 (29.2%)	93/393 (23.7%)	
New epidural	3/328 (0.9%)	1/65 (1.5%)	4/393 (1.0%)	
Experience provider(trainee)	224/328 (68.3%)	52/65 (80%)	276/393(70.2%)	0.059
Difficult catheter insertion	17/283 (6.0%)	6/62 (9.7%)	23/345 (6.7%)	0.294
N° PCEA boluses during labour	[39] 1 (0;4)	[13] 5 (1;7)	[52] 1 (0;6)	0.222
Duration of labour [min] before conversion	[70] 300 (180;540)	[18] 405 (300;720)	[88] 358 (205;555)	0.255
Highest dermatome block				0.212
C2	1/307 (0.33%)	0/61 (0%)	1/368 (0.27%)	
C4	2/307 (0.7%)	0/61 (0%)	2/368 (0.5%)	
C5	2/307 (0.7%)	1/61 (1.6%)	3/368 (0.8%)	
T1	8/307 (2.6%)	0/61 (0%)	8/368 (2.2%)	
T2	53/307 (17.3%)	10/61 (16.4%)	63/368 (17.1%)	

T3	91/307 (29.64%)	16/61 (26.3%)	107/368(29.1%)	
T4	111/307 (36.2%)	22/61 (36.1%)	133/368(36.1%)	
T5	25/307 (8.1%)	6/61 (9.9%)	31/368 (8.4%)	
T6	8/307 (2.6%)	3/61 (4.9%)	11/368 (3%)	
T7	1/307 (0.3%)	2/61 (3.3%)	3/368 (0.8%)	
T8	3/307 (1%)	0/61 (0%)	3/368 (0.8%)	
T9	2/307 (0.7%)	0/61 (0%)	2/368 (0.5%)	
T11	0/307 (0%)	1/61 (1.6%)	1/368 (0.3%)	
Pain score at start conversion	[66] 0 (0;1)	[18] 0 (0;7)	[84] 0 (0;2)	0.064
Preventive top-up	53/279 (19.0%)	8/61 (13.1%)	61/340 (17.9%)	0.278
Chronic opioid use in mother	1/326 (0.3%)	0/65 (0%)	1/391 (0.26%)	0.655

Values are number n/N (%), mean (SD) or median (Q1; Q3)

Table 11 : Neonatal Outcome parameters and occurrence of breakthrough pain

Neonatal Outcome Parameters	**No Pain**	**Pain**	**Total**	**P-value**
Weight (g)	[353] 3049 (795)	[69]2950 (809)	[422] 3032 (797)	0.346
Apgar after 1 minute				0.793
1	4/354 (1.1%)	1/69 (1.5%)	5/423 (1.2%)	
2	4/354 (1.1%)	0/69 (0%)	4/423 (1.0%)	
3	7/354 (2%)	1/69 (1.5%)	8/423 (1.9%)	
4	5/354 (1.4%)	0/69 (0%)	5/423 (1.2%)	
5	11/354 (3.1%)	3/69 (4.4%)	14/423(3.3%)	
6	9/354 (2.5%)	1/69 (1.5%)	10/423(2.4%)	
7	24/354 (6.8%)	7/69 (10.1%)	31/423(7.3%)	
8	44/354 (12.4%)	12/69 (17.4%)	56/423(13.2%)	
9	225/354 (63.6%)	42/69 (60.9%)	267/423(63.1%)	
10	21/354 (5.9%)	2/69 (2.9%)	23/423 (5.4%)	
pH				0.525
6	2/333 (0.6%)	0/67 (0%)	2/400 (0.5%)	
7	331/333 (99.4%)	67/67 (100%)	398/400(99.5%)	

Values are number n/N (%) or mean (SD)

Discussion

The goal of the present prospective audit of practice was to evaluate the incidence of breakthrough pain in CS and to describe the potential risk factors for breakthrough pain observed in this study and compare them to the literature. Of all 393 participants, 65 experienced breakthrough pain during CS, an incidence of 16.5% (see figure 1). So, our results are in line with reported incidences of breakthrough pain in literature (1–20%), despite the use of a low dose CSE technique in many cases and the use of the short acting local anaesthetic 2-Chloroprocaine for epidural top-up (18, 23). Additionally, it has to be acknowledged that our definition of breakthrough pain was broad. In literature sometimes (especially in the studies with lower incidences of breakthrough pain) the definition is rather strict and focused (e.g. conversion to GA required). Of note, the majority of procedures was performed by trainees, a factor that might also contribute to breakthrough pain according to many previous reports. (31, 40, 41, 42, 43)

In this observation, two significant risk factors for breakthrough pain during CS were observed: the duration of surgery ($p < 0.001$) and the used epidural drug ($p = 0.003$).

If surgery is prolonged, the reduced spinal local anaesthetic dose commonly used in both centers as well as the short acting local anaesthetic 2-chloroprocaine 3% can explain why despite good initial anaesthetic conditions, breakthrough pain occurs mostly at the end of surgery and this in two thirds of patients. Therefore, it would seem logical that a preventive top-up (an epidural top-up given prior to the occurrence of pain) would prevent breakthrough pain from occurring. However, we noted a reduced incidence of breakthrough pain with a top-up but breakthrough pain was not eliminated. In our audit we demonstrated that several epidural drugs are adequate to use for epidural top-up (ropivacaine 0.75%, Lidocaine 2% and 2-chloroprocaine 3%), however mixed local anaesthetics, usually a fast onset drug combined with a longer acting drug, increase the risk of breakthrough pain (see table 8 and 9) because they lose their potential when mixed together (the dose of the long acting local anaesthetic is too low).

All other potential factors that have been reported to be risk factors for breakthrough pain, were not confirmed in our cohort (see table 10). This might be due to a different anaesthetic approach or to a type-2 error. For instance, in both centers the dermatomal level that was required per protocol was full absence to cold sensation at T3. Since in most patients this level was achieved, this factor could not be identified as a risk factor in our cohort. Also, for some

risk factors we just did not include enough patients to identify the actual risk (eg. prilocaine spinally or e.g. number of PCEA boluses in labour).

Conclusion

Breakthrough pain during CS is extremely uncomfortable for the mother. In this observational study, the incidence of breakthrough pain during CS was 16.5%.
Duration of surgery and epidural drug used were both significant risk factors of breakthrough pain during CS in this audit. Although we could not show this in our results, a pro-active policy is required in order to prevent breakthrough pain or discomfort during CS. Early identification of problematic epidural catheters for labour analgesia, adequate level of anaesthetic block before surgery, and administration of a prophylactic epidural top-up if duration of surgery is prolonged as opposed to the choice of local anaesthetic used, could be essential in the prevention.

Further high-quality studies are needed to evaluate the many potential risk factors associated with breakthrough pain during CS.

Dutch translation

Een keizersnede is de meest uitgevoerde operatie wereldwijd. Deze ingreep wordt meestal (en preferentieel) uitgevoerd onder neuraxiale anesthesie, gezien enerzijds de potentiële risico's bij een keizersnede onder algemene anesthesie (o.a. gefaalde intubatie, aspiratierisico en het risico op awareness) en anderzijds de mogelijkheid tot participatie van de moeder aan het geboorteproces bij neuraxiale anesthesie. Wanneer deze neuraxiale anesthesie faalt, kan de moeder doorbraakpijn ervaren. Deze pijn zorgt voor een onaangename ervaring bij de moeder en kan zo ernstig zijn zodat een verandering in anesthetische strategie noodzakelijk wordt.

Het primaire eindpunt van deze prospectieve, observationele studie was het bepalen van de incidentie van doorbraakpijn tijdens keizersnede. Volgende definitie van doorbraakpijn werd gehanteerd: "pijn dewelke een verandering in anesthetische techniek of het toedienen van een extra anestheticum noodzakelijk maakt, met als doel de pijn te behandelen". Ook de potentiële risicofactoren voor deze doorbraakpijn, die reeds beschreven staan in de literatuur, werden onderzocht (=secundaire eindpunten). Een p-waarde < 0.05 werd als statistisch significant bevonden. Er werden tevens subanalyses gemaakt voor doorbraakpijn bij enerzijds geplande (=primaire) en anderzijds secundaire (= conversie van arbeid naar keizersnede) keizersneden.

Het protocol van deze observationele, prospectieve studie werd aanvaard door beide Ethische Comité's van de ziekenhuizen waar de studie werd uitgevoerd, namelijk UZ Leuven en ZNA Middelheim Antwerpen.
In totaal namen 393 patiënten deel aan deze observatie (206/393 in Leuven en 187/393 in Antwerpen). De inclusiecriteria waren: alle (zowel geplande als secundaire) keizersneden onder neuraxiale anesthesie gedurende een studieperiode van 6 maanden. Elke uitvoerende anesthesist had de vrije keuze welke neuraxiale techniek werd toegepast en welke spinale of epidurale producten gebruikt werden.

In deze studie rapporteerden 65 van de 393 patiënten doorbraakpijn (16.5%). In de literatuur is de incidentie van doorbraakpijn tussen 1-20%, wat overeenkomt met de incidentie gezien in deze observatie. Van alle electieve keizersneden ontwikkelde 15.3% van de patiënten doorbraakpijn, bij de secundaire keizersneden werd een incidentie doorbraakpijn van 20.4% gezien. Het verschil tussen beide was statistisch niet significant.
In deze studie weerhouden we 2 significante risicofactoren voor doorbraakpijn. Enerzijds was de duur van chirurgie een belangrijke risicofactor (p-waarde <0.001), met een duidelijke langere duur van chirurgie bij de patiënten die doorbraakpijn ervaarden. Mogelijks speelt het onvoldoende anticiperen op deze doorbraakpijn een belangrijke rol, zeker wanneer kortwerkende locale anesthetica gebruikt werden.
Een tweede significante risicofactor is het epidurale product/mengsel dat gebruikt werd (p-waarde 0.003). Hier werd beduidend meer doorbraakpijn gezien wanneer het mengsel Ropivacaine 0.75% + Lidocaine2% gebruikt werd in vergelijking met Ropivacaine 0.75%, Chloroprocaine 3% en Lidocaine 2% als soloproducten.
De meeste doorbraakpijn trad op tegen het einde van de ingreep (na de geboorte van de baby) en werd bij meer dan de helft (58.7%) van de patiënten behandeld met een extra epidurale bolus via de epidurale katheter. Bij 7.9% van de patiënten werd overgegaan tot algemene anesthesie, bij 19.1% werd er naar een andere anesthetische strategie overgegaan (vb conscious sedation met remifentanil, bolus midazolam), bij 12.7% was geruststelling van de patiënt een adequate behandeling voor doorbraakpijn en tot slot bij 1.6% werd een combinatie van bovenstaande behandelingen gebruikt.
Heel wat andere potentiële risicofactoren voor doorbraakpijn, weerhouden in de literatuur, werden eveneens geanalyseerd: maternele factoren zoals lengte, BMI en ras, de urgentiegraad van de keizersnede volgens Lucas classificatie, de primaire anesthetische methode (single spinal shot, CSE, de novo epidurale of epidurale top-up), het spinale product dat werd

gebruikt (in geval van single spinal shot of bij CSE), de ervaring van de uitvoeder (ASO vs staflid), het hoogste dermatoom dat pre-incisie volledig geblokkeerd was voor koude, moeilijke epidurale katheter plaatsing, het profylactisch toedienen van een epidurale top-up (in subgroep van CSE en de novo epidurale katheter), chronisch opiaten gebruik bij de moeder en het geboortegewicht van de baby. In geval van conversie van partus naar keizersnede werden ook de duur van de arbeid, het aantal PCEA boli tijdens arbeid en de pijnscore bij de start van de conversie onderzocht. Alle bovenstaande potentiële risicofactoren werden als niet significant bevonden in deze studie.

Doorbraakpijn tijdens een keizersnede is extreem oncomfortabel voor de moeder. Een pro-actief beleid is dan ook heel erg belangrijk om deze onprettige ervaring te voorkomen, onder andere door een vroege detectie van een falende epidurale katheter tijdens partus. Hoewel deze risicofactor in onze studie als niet-significant werd bevonden, is het volgens ons wel een belangrijke strategie om doorbraakpijn te voorkomen. Volgende belangrijke strategieën kunnen eveneens worden toegepast om de incidentie van doorbraakpijn tijdens een keizersnede te reduceren: beperken van de duur van chirurgie en het geven van een profylactische epidurale top-up bij een te lange chirurgische tijd, zeker wanneer kortwerkende locale anesthetica gebruikt werden.

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Appendix

Appendix 1 : Data collection form

worksheet

The origin of breakthrough pain during C-section: Incidence and risk factors

MVDV/ER112017

Chief Investigator: Prof. Dr. Marc Van De Velde

Name of site: UZLeuven, campus Gasthuisberg

CRF Version Number: 1, 05/12/2017

Adressogram Patient

Form completed by : …… Date ……

Study Number | | | |

Maternal factors

Maternal length (m):…….

Maternal weight (kg): ……

Maternal age (years):…….

Race (Choose one option):

- O Asian
- O Black
- O Hispanic
- O Caucasian
- O Other (specify): ……

C-section indication:

- O **Cephalopelvic disproportion**
- O **Breech**
- O **Fetal distress**
- O **Fetal condition**
- O **Maternal condition**
- O **Repeat C-section**
- O **Placenta/tumor previa**
- O **Maternal request**
- O **Other (specify): ……**

Obstetric factors

Gestational age (weeks): ……..

Repeat section:

- **No**
- **Yes**

How many repeats → ……

Conversion from labor to C-section :

- **No**
- **Yes**

Duration of labor (min) → ……

APG score:

- **A: ……..**
- **P: ……**
- **G: ……**

Lucas classification of urgency: ……..1 → Immediate threat to life of mother or fetus

2 → Severe fetal or maternal compromise but not immediately life-threatening

3 → Compromise which responds to therapy although underlying problem still exists and needs delivery

4 → Elective.

Duration of surgery (min):

- **Starting hour (First incision): .....u……..mi**

Anesthetic factors

Expertise of the anesthesiologist:

- **ASO (+ which year: …….)**
- **Staff member**

Which primary anesthetic method was used:

- **Single shot spinal anesthesia**
- **CSE**
- **Epidural top-up**
- **Epidural De Novo**

Expected difficult airway:

- **No**
- **Yes**

Epidural catheter depth (cm):

- **Distance from skin to epidural space:……**
- **Depth of the catheter into the epidural space:…….**

Drugs administered + dosage for:

- **Spinal component:……..**
- **Epidural component (in case of conversion from labor):…….**

Time of initial spinal injection: …….h…….min

Which drug was used to perform the top-up in case of conversion from labor:……..

Number of PCEA boluses during labor: ……

+ Dosage: ……

Duration of analgesia during labor (in case of conversion): ……

Adequacy of the block before the C-section starts (highest dermatome which is blocked):

After Installation on operating table:

- Highest completely blocked dermatome:…….
- Highest dermatome that is still fully unblocked: ……
- Not determined

After approximately 5 minutes:

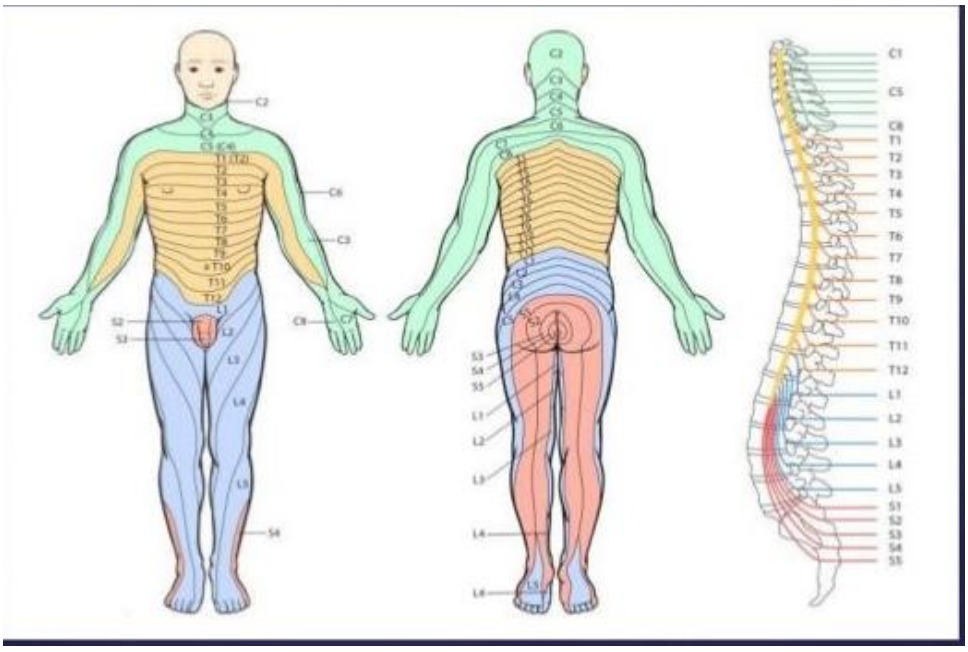
- Highest completely blocked dermatome:…….
- Highest dermatome that is still fully unblocked: ……
- Not determined

After surgical draping:

- Highest completely blocked dermatome:……..
- Highest dermatome that is still fully unblocked: ……
- Not determined

Just before the first incision:

- Highest completely blocked dermatome:……..
- Highest dermatome that is still fully unblocked: ……
- Not determined



Pain score in case of conversion from labor to C-section at the moment the decision is made to convert: ……/10

0 = No pain

10 = Worst pain imaginable

Highest pain score the patient experienced during the C-section (to ask after the last stitch): ……/10

Number of top-ups used in order to prevent breakthrough pain during C-section: ……

+ Dosage:…….

Which drug was used to perform the top-up:……..

- EVE (epidural extension volume) administered:
    - No
    - Yes: How long after initial spinal injection: ……

      Which volume was used: ……

- History of previous failed epidurals:
    - No
    - Yes, how many? → ……

- Chronic use of opioids:
    - No
    - Yes, which drug(s) → ……

- Deviation of the standard operating protocol:
    - No
    - Yes, which deviation → ……

- Ease of insertion of the catheter:
    - No problem
    - Difficult, why difficult → ……

- End of surgery (moment of last stitch) (min): .....u……..min

Breakthrough pain

Prophylactic anesthetic measurements in order to prevent possible breakthrough pain will NOT be seen as breakthrough pain.

- Breakthrough pain during the C-section:
  - No
  - Yes

- Pain score during the C-section when patient would request additional analgesia for breakthrough pain:

  ……./10

- Moment during the surgery that the patient indicates breakthrough pain:

  - At skin incision
  - At peritoneal incision
  - Prior to delivery of baby but after the peritoneal incision
  - After the delivery of the baby but before the last stitch
  - Other (specify): …….

- If there was breakthrough pain, how was it resolved:

  - Conversion to general anesthesia
  - Change in anesthetic strategy, specify: …….
  - Administration of an additional anesthetic, specify: …….
  - Other, specify: ……..

- Exact time that the breakthrough pain occurred: ……..h……..min

- How did the patient experienced the breakthrough pain episode:

  - A sharp “pain”
  - Uncomfortable feeling but not really “pain”

Baby factors

Apgar score after 1 minute: ……..

Apgar score after 5 minutes: ……..

Apgar score after 10 minutes: ……..

Umbilical artery blood gasses:

- pH: ……
- PCO_2: ……
- PO_2: ……..

Weight of the baby at birth (kg): ……