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Datum

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Voorwoord

Gedurende de opbouw van deze studie en de masterproef die hieruit voortvloeide, heb ik hulp gekregen van verschillende mensen en bij deze zou ik hen graag willen bedanken.

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1. Abstract

Objective: The primary goal of this study is to determine the median effective dose (ED_{50}) of chloroprocaine using an up-and-down sequential allocation method when chloroprocaine is administered spinally as part of a combined spinal-epidural analgesia regimen for parturients in labour.

Methods: Parturients (n=38) requesting epidural analgesia in labour were enrolled in this single centre, prospective trial. The patient received a standard combined spinal-epidural analgesia technique and received a given dose of chloroprocaine 1% intrathecally, using the technique of up-down sequential allocation. The initial dose of chloroprocaine was chosen to be 20mg and the testing interval was set at 2mg. Analgesic effectiveness was accepted if the visual analogue pain score decreased to 10mm or less on a 100mm scale within 15 minutes. An effective analgesia reduced the testing dose for the next patient while an ineffective analgesia caused an increase in the testing dose in the next patient. After the study period of 30 minutes parturients were offered a conventional patient-controlled epidural analgesia protocol containing levobupivacaine and sufentanil.

Results: Using the isotonic regression estimator method, the median effective dose (ED_{50}) of intrathecal chloroprocaine in the spinal component of a CSE for labour was calculated to be 12.0 (9.3 - 17.0) mg and the ED_{95} (95% CI) was estimated as 19.6 (16.0 - 20.0) mg.

Conclusion: To our knowledge, this is the first study suggesting a median effective dose of 12.0 mg for spinal chloroprocaine for labour analgesia.

2. Introduction

Parturients undergo one of women's most painful experiences in life and are therefore characterised by several physiological changes over numerous body systems. These changes are even more exaggerated during labour and can even induce maternal and fetal distress. For example the cardiovascular system is characterised by an increase in cardiac output that is 50% higher than the prelabour values and approximately 100% above nonpregnant measurements. This increase might not be well tolerated by parturients with valvular or coronary heart diseases. At the level of the respiratory system, the minute ventilation will increase with 50% and the oxygen consumption will increase with 60% above the nonpregnant values. In the first stage of labour and in absence of pain relief, these ventilatory parameters will be even more pronounced and the minute ventilation even can be tripled. This will lead to a severe hyperventilation with maternal $PaCO_2$ to values as low as 18 mmHg and will subsequently produce fetal acidosis because of diminished uteroplacental perfusion and initiating a shift of the maternal oxygen dissociation curve to the left (1).

To reduce the pain and the consequential noxious effects several strategies have been used to provide analgesia during labor pain. These include non-pharmacological approaches such as transcutaneous electrical nerve stimulation (TENS), hydrotherapy, hypnosis and pharmacological therapies such as the administration of nitrous oxide and parental opioids. Nevertheless it is found that the administration of neuraxial local anesthetics and opioids is superior and more reliable than the aforementioned methods (2). Trough history the administration of a combined spinal-epidural (CSE) analgesia for labour has become a widely accepted technique because of several advantages. Despite the widespread use of this technique and numerous published investigations, an optimal spinal drug regimen has not yet been defined (3).

Bupivacaine, ropivacaine or levobupivacaine are local anaesthetics that are routinely used for the spinal component of a CSE during labour. On the other hand, chloroprocaine has recently been reintroduced into clinical practice as "the new old drug" because of its beneficial pharmacological profile. It is an amino-ester local anaesthetic, known for a very quick onset of action and with high efficacy. It is rapidly hydrolysed by liver and plasma cholinesterases resulting in a short half-life in both mother and fetus (4). Considering these characteristics, it is found that chloroprocaine would be a suitable drug for CSE labour analgesia. Columb et al.

already determined the minimum local anesthetic concentration of epidural chloroprocaine in labour to be 0.42% w/v (5). As to the correct spinal dose of chloroprocaine in labour, no current information is available. Hereby we conducted a study, which has as primary goal to determine the median effective dose (ED_{50}) of spinal chloroprocaine 1% for CSE analgesia during labour, using an up-down sequential allocation method.

3. Methods

An initial literature search was performed using the databases Pubmed and Medline using the following keywords: labour analgesia, spinal, epidural, CSE, chloroprocaine, up-down sequential allocation method and isotonic regression estimator method. Relevant articles published from 1952 until 2016 were enrolled.

After a prospective and single center study protocol was conducted, the Ethical Committee of Ghent University Hospital provided the ethical approval. The inclusion criteria were age between 18-45 years, ASA physical status 1-2, a singleton fetus of 36-41 weeks and the parturient had to be in active labour requesting neuraxial analgesia. Women were not recruited if they had received opioid or sedative medication, had a cervical dilatation > 7 cm, preeclampsia, sensory or motor deficits in the lower body, fetal congenital abnormalities, or a known allergy to chloroprocaine. Parturients, participating in other clinical trials, were equally declined to contribute.

A written informed consent was obtained at the earliest opportunity after the parturient was admitted to the labour ward. After requesting regional analgesia, baseline heart rate, blood pressure and oxygen saturation were recorded and continuous monitoring of fetal heart rate and uterine contractions were established. After an intravenous infusion of Hartmann's solution was initiated, a CSE was performed with the women in the upright sitting position. After skin disinfection and local infiltration with 1% lidocaine, the epidural space was identified using a loss-of-resistance to saline technique at the L3-4 or L4-5 intervertebral space with an 18-G Tuohy needle. A 27-G, 127 mm Whitacre spinal needle was then introduced through the Tuohy needle until cerebrospinal fluid was obtained. The end of the spinal injection of a certain dose of chloroprocaine was defined as the start time of the study. Subsequently the spinal needle was withdrawn and an epidural dose of 7.5µg sufentanil with an additional epidural volume extension bolus of 5.5 ml saline was injected. An epidural catheter was inserted 4-5 cm into the epidural space, and after fixation of the epidural catheter the women were placed in a 45° head-up position with left uterine displacement. A patient-controlled epidural analgesia regimen, containing 112 ml levobupivacaine 1.1 mg/ml and 0.7 µg/ml sufentanil, was started 30 min after the spinal bolus of chloroprocaine.

As stated before, we did not find any guidelines for the dose of chloroprocaine for labour spinal analgesia in the literature. Low dose spinal anaesthesia for caesarean section is often performed

with 7.5 mg bupivacaine, although the ED_{95} of bupivacaine with 10 µg fentanyl is 13 mg [20], while the ED_{95} for spinal bupivacaine in labour analgesia is 3.3 mg (6). For ambulatory surgery, Lacasse et al. showed that 40 mg spinal chloroprocaine provides adequate duration and depth of surgical anaesthesia for short procedures (7). Therefore it was decided to start the sequential allocation with an arbitrarily chosen dose of 20 mg chloroprocaine 1%. For the subsequent parturients the dose of chloroprocaine was determined by the analgesic response of the previous patient. This resulted in the administration of either a higher dose of chloroprocaine in case of insufficient analgesia in the previous patient or a lower dose of chloroprocaine in case of a satisfying analgesia in the previous patient. For this up-down sequential allocation design a dose interval of 2 mg was used for the increments or decrements. The analgesic effectiveness was assessed using a 100 mm visual analogue pain score (VAPS), where 0 represented 'no pain' and 100 indicated 'worst pain possible'. The VAPS was measured at five-minute intervals during 30 minutes after spinal injection. Effective analgesia was defined as VAPS ≤ 10 mm at 15 minutes after the spinal injection. Women with a VAPS > 10mm after 15 minutes and thus an ineffective analgesia received 12 ml levobupivacaine 0.125% via the epidural catheter as a rescue dose to pursue an effective analgesia for every parturient as soon as possible.

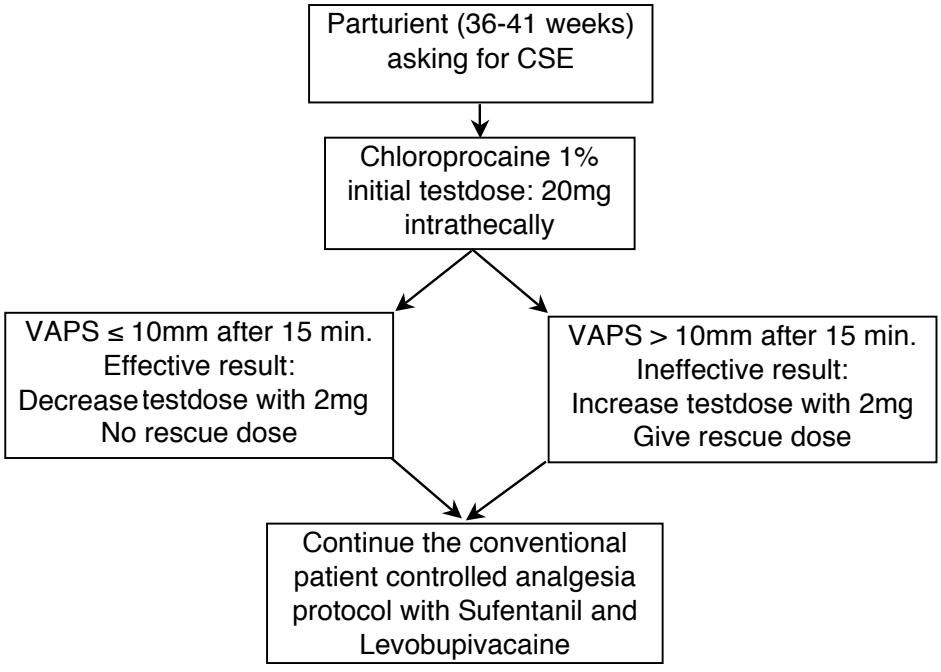

Figure 1. *Systematic flowchart of the study design.*

Further data collected at the five-minute intervals included sensory block levels and the degree of motor block. Sensory levels were determined by the loss of cold sensation to the application of ethyl chloride spray. Motor block was determined using a modified Bromage scale, where 1 = complete motor block with inability to move the legs; 2 = only possible to move the feet; 3 = possible to move knees; 4 = weak flexion of hips; and 5 = complete flexion of hips and knees. Additionally maternal heart rate, blood pressure and oxygen saturation, fetal heart rate and contraction frequency, were monitored during the next three hours.

The up-down sequences were analysed using the isotonic regression estimator method (8-10), from which we calculated ED_{50}, ED_{95} and 95% CI. Calculations were performed using R software (R 3.0.1. for Windows; R Foundation for Statistical Computing, Vienna, Austria). The biostatistics department of public health in Ghent university hospital performed these statistical analyses.

4. Results

In this chapter the exact data and results collected in the study will be reported. Also more extended information on CSE, the local anaesthetic chloroprocaine and the up-down sequential allocation method and the specific isotonic regression estimator method used in this study design will be provided.

4.1 Results and demographics

Of the 40 women enrolled, two were excluded. One woman received the wrong dose of chloroprocaine while another woman received a systemic opioid before the administration of the CSE, which is an exclusion criterion. In these two cases, the intended dose of chloroprocaine was used for the next parturient who was enrolled.

Finally a total of 38 parturients were considered in the analysis. The demographic and obstetric characteristics of the participants are shown in table 1. These data include age, height, gestational age, weight, cervical dilatation and parity. These data were collected from the medical file and by interview of the participants during the study.

***Table 1**. Demographic and obstetric characteristics of all 38 patients in the study. Values are mean (SD), median (IQR [total range]) or number (proportion%).*

Age, years	30.4 (5.0)
Height, cm	167.5 (6.3)
Gestational age, days	279.3 (8.4)
Weight, kg	72.5 (8.9)
Cervical dilation, cm	4 (3-5 [3-7])
Nulliparous	21 (55%)

A review of the cardiotocograms and the obstetric files showed no relevant abnormalities during the administration of the CSE and no clinical obstetric interventions were required in response to

fetal heart rate changes during the study period. Furthermore there was no recognition of any severe adverse effect after the administration of spinal chloroprocaine.

The sequences of effective and ineffective analgesia over all 38 parturients are demonstrated in figure 2. Using the isotonic regression estimator method, the ED_{50} (95% CI) was calculated to be 12.0 (9.3 - 17.0) mg, and the ED_{95} (95% CI) was estimated as 19.6 (16.0 - 20.0) mg.

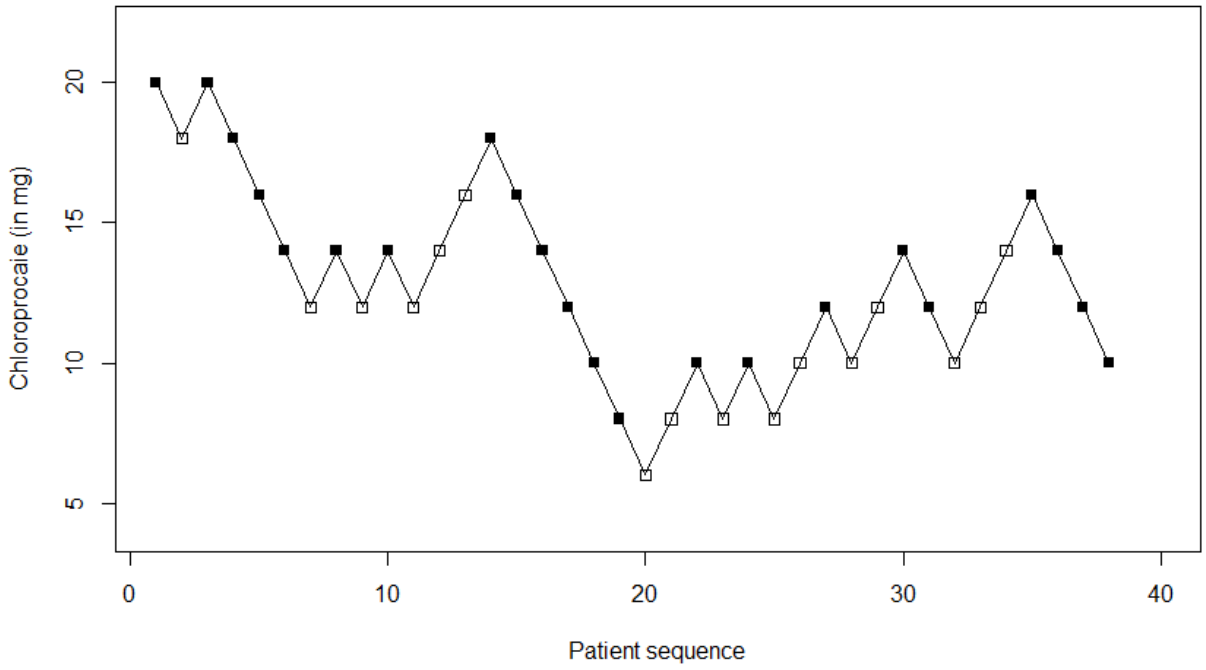

Figure 2. *Doses of chloroprocaine used in the up-down sequence. An effective dose (VAPS ≤ 10 mm at 15 min after spinal injection) is denoted by a filled square and an ineffective dose (VAPS >10 mm at 15 min after spinal injection) by an open square.*

4.2 Combined spinal epidural (CSE)

Throughout history, neuraxial labour analgesia has known a remarkable evolution starting with the epidural administration of a single high dose of local anaesthetic resulting in a distinctive motoric deficit resulting in an increase in instrumental deliveries. By lowering the concentration of local anaesthetics and by combining it with lipid-soluble opioids, the continuous neuraxial labour analgesia became more effective with less side effects. The introduction of patient-

controlled epidural analgesia even enhanced the satisfaction of the parturients (1). In the mid 1990s the introduction of a CSE gathered more followers and became a widespread accepted technique. The advantages include a fast onset of analgesia, reliable anaesthesia of the sacral roots, a lower need for oxytocin augmentation or instrumental vaginal delivery, and low maternal and fetal drug concentrations (3,11). The contra-indications, side effects and complications of CSE are comparable to the other neuraxial analgesia techniques used during labour. More specific, there are no differences in the incidence of caesarean section, fetal distress or length of the first or second stages of labour between CSE and a standard epidural analgesia (1). The only difference is a slight increase in the incidence of fetal bradycardia without any impact on obstetric or neonatal outcomes. The deposition of spinal opioids, resulting in an alteration in the circulating catecholamines with an increased uterine tonus, is held responsible for these fetal heart rate changes (11,12).

Concluding all this information, it was chosen to use a CSE in our study protocol in which only local anaesthetics were administered into the spinal space and a certain fixed dose of lipid-soluble sufentanil was instilled into the epidural space. The administration of sufentanil in the epidural space was preferred instead of a spinal deposition of opioids since the latter is held responsible for possible fetal heart rate changes and here specific the influencing of our study protocol.

Noteworthy is that also an additional volume bolus of saline was administered into the epidural space along with the opioid. This strategy is based on the principle of epidural volume extension that refers to the volume effect in the epidural space resulting in a spinal compression causing an upward displacement of the local anaesthetic in the spinal space. This is a technique that will achieve a higher sensory block level or that will allow us to lower the dose of the local anaesthetic instilled into the spinal space. Tyagi et al. concluded that a minimum effective volume of 7.4 ml saline into the epidural space provided a raise of the sensory block level by two or more dermatomal segments (13,14). In this study the epidural extension volume was 7.0 ml using the volume of 5.5ml of saline and 1.5ml of sufentanil. An additional effect of epidural volume extension is the venous compression caused by the increased epidural space pressure with a probably lowering risk for epidural venous punctures. This could be of considerable importance since the epidural venous plexus typically is engorged during pregnancy. There are yet no trials addressing these differences between pregnant and non-pregnant patients and further investigations on this topic are warranted (15).

4.3 Chloroprocaine

All local anaesthetics are made up of a similar molecular configuration consisting of a hydrophilic amine group and a lipophilic aromatic ring connected by a linking chain. This linking chain is used to classify the local anaesthetics in either amides or an ester group (16). Chloroprocaine can be classified as an amino-ester local anaesthetic and it is a direct descendent of procaine, which was the first synthetic local anaesthetic that allowed safe use of regional anaesthesia. Injectable chloroprocaine is chemically identified as 2-(diethylamino) ethyl 4-amino-2 chlorobenzoate monohydrochloride with the molecular formula of C13H19ClN2O2-HCl and the specific structural formula shown in figure 3.

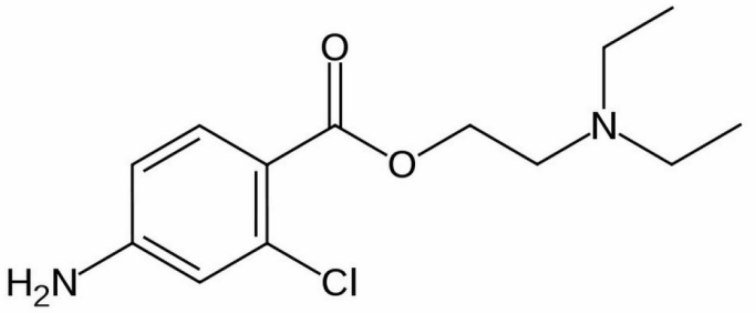

Figure 3. *Molecular formula of chloroprocaine.*

Each local anaesthetic features different physiochemical characteristics producing diversity in onset time, potency, duration and toxicity. The different physiochemical characteristics include the ionisation based on the dissociation constant (pKa), the lipid solubility based on the partition coefficient, the protein binding, the molecular weight and the stereochemistry. Chloroprocaine is characterized by a molecular weight of 270 g/mol, a pKa-value of 9.3 and a very low protein binding resulting in a rapid onset of action and an intermediate potency with a low risk for toxicity (16-17). Chloroprocaine is rapidly hydrolysed by both plasma and liver esterases with an in vitro plasma half-life in adults of 21 ± 2 seconds for males and 25 ± 1 seconds for females and the in vitro plasma half-life in neonates is 43 ± 2 seconds. However the spinal fluid contains practically no esterase and so anaesthesia will persists until the compound is absorbed into the blood. In the blood chloroprocaine is hydrolysed into the inactive metabolites 2-chloro-4-aminobenzoic acid (ACBA) and 2-diethyl-aminoethanol, which are excreted through the urinary

tract. These physiochemical and pharmacokinetic data conclude to a rapid onset time, a high efficacy, a rapid metabolism and a very short half-life in as well mother and fetus with a low risk for toxicity (17-19).

Historically it is known that chloroprocaine was first synthesized in 1946 as a direct descendent of procaine and it was first introduced into clinical practice in 1952. It was initially extensively used for epidural anaesthesia and peripheral blocks but also several successful reports of spinal anaesthesia were described. However, in the early 1980s some cases of transient neurological symptoms (TNS) associated with a possible accidental spinal injection of epidural chloroprocaine raised concerns regarding potential neurotoxicity (20). The TNS mostly resulted in pain or dysesthesia in the buttock region and in the lower extremities. A review of these reports suggested that the neurological injuries resulted from most likely a combination of very large volumes of chloroprocaine injected into the spinal space, the acidity of the solution and the relative toxicity of sodium bisulphite used as an antioxidant (21). The formulation of chloroprocaine has changed numerous times since its introduction in 1952 and since 1996 the drug was synthetized without additives. On the other hand, Taniguchi et al. reported a potential neuroprotective effect of sodium bisulphite if dosed correctly. To conclude all the conflicting data on this topic we can state that all local anaesthetics, even chloroprocaine can induce neurotoxic damage if administered at a sufficient dose or concentration (22).

Although chloroprocaine is not specifically indicated for spinal administration, the preservative- and antioxidant-free formulation has been extensively investigated for spinal anaesthesia in ambulatory surgical patients over a number of years (4,23). Large series of spinal anaesthesia with chloroprocaine without major perioperative neurological injury have been published (16). In fact, Casati et al. demonstrated a 33% incidence of TNS after the administration of spinal lidocaine compared with a zero incidence after the administration of spinal chloroprocaine (18). Because of several similar clinical studies and recently published volunteer studies, the spinal use of preservative-free chloroprocaine was approved in Europe (16,19,24). But even though the Federal Drug Administration (FDA) approves chloroprocaine as a local anaesthetic, it is not specifically approved for the use in spinal anaesthesia and therefore considered as off-label use (21).

In obstetric anaesthesia in the 1990s, chloroprocaine was primarily used for epidural analgesia during labour (25). It was Ackerman et al. that advised the use of chloroprocaine for its rapid

onset when topping-up an epidural for instrumental delivery (26). Chloroprocaine might be beneficial if the fetus is compromised, because of rapid hydrolysis in blood. Abboud et al. reported less late decelerations of fetal heart rate with epidural chloroprocaine versus bupivacaine (27). Considering this beneficial therapeutic profile, more recent studies have focused on spinal or epidural use of chloroprocaine in labour and at caesarean section. Columb et al. already determined the minimum local anesthetic concentration of epidural chloroprocaine in labour to be 0.42% w/v (5). But, like previously mentioned, there is no current information on the dosing profile of spinal chloroprocaine in labour analgesia and so this study and paper was conducted to fill this gap.

4.4 Up-down sequential allocation design and statistical analyses

Since the publication of the first up-down sequential allocation design in regional anaesthesia and the description of the minimum local analgesic concentration model in 1995, this design has been extensively enrolled and replicated with several adaptions to a variety of clinical and pharmacological research problems. Ideally a dose-response relationship is identified to define the median effective dose (ED_{50}) with the greatest precision. On the other hand this is a bulky and intensive approach while the up-down sequential allocation design is a very simple and efficient method for identifying the ED_{50}. The disadvantages of this approach include the fact that the ED_{50} always will remain an estimate and that potential errors at the extremes of the distribution can adversely bias the ED_{95} estimates (8, 28). As already clarified in the methodology, this design consist of the fact that the dose received by a subject is determined by the response of the previous subject using a fixed starting dose and a preliminary set testing interval. A positive result in the previous patient will cause a decrement in the testing dose of the next patient and contrariwise a negative result in the previous patient will cause an increment of the testing dose for the next patient. This approach will eventually middle around the final ED_{50}. Using this simple model it has been possible over the last decade to estimate the potencies of several local anaesthetics and the interactions with other analgesics or additives (28).

For the statistical analyses an isotonic regression estimator method was used because simulation studies have demonstrated that this estimator method has a smaller bias, a smaller mean square error and most importantly a narrower confidence interval. The isotonic regression estimator

method is perfectly capable to define the ED_{50} but the determination of the ED_{95} is only a rough estimation and therefore of a minor reliability (9). A study protocol using the biased coin design will produce a trustworthy result of the ED_{95}. The initial study design of a biased coin design is similar to the up-down sequential allocation method with an increase in testing dose in case of a negative result in the previous patient. But if a positive result is observed, the next patient is randomized with a probability of 0.05 to a lower testing dose and a probability of 0.95 to the same testing dose (10). Since only an up-down sequential allocation method was used in this study protocol it must be concluded that the ED_{95} has to be considered as a preliminary estimation and so this result should be applied cautiously when translated into clinical practice.

5. Discussion

This is the first study to determine the ED_{50} of spinal chloroprocaine in the first stage of labour as part of a CSE. We used an up-down sequential allocation method, which has greater precision and requires fewer subjects than traditional dose-response studies. The ED_{50} provides a value to compare the potency of chloroprocaine with other local anaesthetics currently used for labour analgesia. ED_{50} values estimated through an up-down sequential allocation method only represent a single point along the dose-response curve, but do not show the steepness of the curve. In clinical practice, the ED_{95} may be more important.

ED_{50} and ED_{95} values for spinal analgesia during labour for commonly used local anaesthetics have already been determined; these are median (95% CI%) 1.7 (1.4 - 1.9) mg and 3.3 (2.9 - 4.1) mg for bupivacaine, 2.2 (1.8 - 2.6) mg and 4.8 (4.0 - 6.7) mg for ropivacaine and 2.3 (2.0 - 2.7) mg and 5.0 (4.1 - 7.0) mg for levobupivacaine, respectively (7). We found that the ED_{50} of chloroprocaine 1% is 12.0 (9.3 - 17.0) mg, with a calculated ED_{95} of 19.6 (16.0 - 20.0) mg. However, as previously mentioned, a study using a biased coin design would be necessary to produce a more reliable result for ED_{95} and the result here obtained must be considered as a preliminary estimation (8,10).

There are some limitations to our study. A first problem with the up-down sequential allocation design is the possible confounding effect of obstetric factors. Capogna et al. found that factors determining the effectiveness of analgesia included initial VAPS, cervical dilation and induction of labour with prostaglandins (28, 29). In our study, only patients with a cervical dilation $\leq$ 7 cm were accepted for inclusion. However, we did not distinguish between spontaneous labour and prostaglandin induced labour, or nulliparous and multiparous women.

We also cannot exclude a possible influence of epidurally-administered sufentanil on our reported ED_{50} of spinal chloroprocaine. We routinely use epidural sufentanil immediately following spinal analgesia in our unit, in order to reduce the incidence of fetal heart rate abnormalities found with opioid given spinally (12), and we designed this study to reflect our clinical practice as much as possible. However, we suggest that, with the low dose of epidural sufentanil that we used, there would have been minimal effect at the 15-min assessment time (5).

Finally, there was no blinding of the investigator, who also performed the CSE. However, the parturient did not know what dose of chloroprocaine they received, and as a consequence their reporting of the analgesic effect was unbiased.

To conclude it can be stated that the beneficial pharmacokinetic profile of chloroprocaine explains the renewed interest in its use in obstetric anaesthesia. Rapid hydrolysis by plasma and liver cholinesterases guarantees a short half-life both in mother and fetus, with low risk of systemic side effects or toxicity. In this respect a further prospective study has been designed to determine the dosing profile of chloroprocaine given epidurally for caesarean section and more results are soon to be expected.

We have calculated an ED_{50} of median (95% CI) 12.0 (9.3-17.0) mg for spinal chloroprocaine spinally as part of CSE labour analgesia. It can be stated that further studies are necessary to determinate the full-dose response curve for spinal chloroprocaine and to determine a more trustworthy value for the ED_{95}.

There are no conflicts of interest and no external funding to the study can be declared.

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7. Nederlandstalige samenvatting

Inleiding: De arbeid van de zwangere vrouw wordt als een pijnlijke ervaring aanzien en wordt gekenmerkt door ernstige fysiologische veranderingen over de verschillende lichaamssystemen. Om deze fase te verlichten werden hiervoor doorheen de geschiedenis reeds verschillende pijnstillende technieken toegepast. De gecombineerde spinale-epidurale (CSE) pijnstilling wordt aanzien als de superieure vorm van pijnstilling wat betreft neuraxiale analgesie. De CSE-techniek is reeds een welgekende en goedgeoefende techniek die dagdagelijks wordt toegepast. Ondanks het veelvuldige gebruik van deze techniek zijn er echter geen wetenschappelijk gegronde doseringsprotocollen voor de toediening van de spinale lokale anesthetica beschikbaar. Hierbij zijn bupivacaine, ropivacaine en levobupivacaine courant gebruikte lokale anesthetica. Recent werd chloroprocaine echter opnieuw geïntroduceerd in de klinische praktijk. Dit is een lokaal anestheticum met als voornaamste voordelen een zeer korte inwerkingstijd en een snel metabolisme door plasma- en levercholinesterases. Dit resulteert in lage plasmaconcentraties met dus een nog lager toxiciteitsrisico voor zowel moeder als foetus. Gezien dit voordelige farmacologische profiel is er een toenemende interesse voor het gebruik van chloroprocaine als onderdeel van een CSE gedurende de arbeid. Tot zover gekend, werd er nog geen onderzoek verricht naar de spinale doseringsprofielen van chloroprocaine 1% bij zwangere vrouwen tijdens de arbeid.

Beschikkende over deze achtergrondinformatie werd een studie opgesteld met als primair doel de mediane effectieve dosis (ED_{50}) van chloroprocaine 1% te berekenen wanneer deze spinaal wordt toegediend als onderdeel van een CSE-techniek bij een zwangere vrouw gedurende de arbeid.

Methodologie: Een prospectief en single center gebaseerd studie protocol werd opgesteld waarbij 40 zwangere vrouwen gedurende de arbeid geïncludeerd werden. Inclusiecriteria omvatten een leeftijd tussen de 18 en 45jaar oud, een classificatie als ASA I en II patiënten en een zwangerschapsduur van 36 tot en met 41weken. Exclusiecriteria omvatten de toediening van opiaten of sedativa tijdens de arbeid, een cervicale dilatatie van > 7cm, de aanwezigheid van preeclampsie, identificatie van sensoriële of motorische defecten ter hoogte van de onderste lichaamshelft, gekende foetale afwijkingen of een gekende allergie aan chloroprocaine.

Een up-down sequential allocation methode werd toegepast waarbij de initiële testdosis van chloroprocaine werd ingesteld op 20mg en het doseringsinterval 2mg bedroeg. Bij iedere patiënte

werd een standaard CSE-procedure uitgevoerd waarbij er spinaal een testdosis van chloroprocaine 1% werd geïnjecteerd en epiduraal 7,5 µg sufentanil met 5,5ml fysiologisch werd toegediend waarna een epidurale katheter werd ingebracht. Het beëindigen van de injectie van chloroprocaine spinaal werd beschouwd als het startpunt van de studie. Gedurende de eerste 30 minuten van de studie werd de pijnstillende effectiviteit van chloroprocaine geëvalueerd aan de hand van een 100mm Visual Analogue Pain Score (VAPS). Een VAPS tot en met 10mm na 15 minuten werd als een effectief resultaat beschouwd met een aanvullende vermindering van de testdosis van chloroprocaine met 2mg voor de volgende patiënte in het onderzoek. Een VAPS van meer dan 10mm na 15minuten werd als een ineffectief resultaat aanschouwd met als gevolg een vermeerdering van de testdosis met 2mg. Om effectieve pijnstilling te garanderen werd er bij de patiënten met een ineffectief resultaat een aanvullende dosis van 12ml levobupivacaine 0,125% toegediend. Een PCEA-pomp op basis van chloroprocaine en sufentanil werd na 30 minuten na aanvang van de studie opgestart.

Als aanvullende data was er iedere 5 minuten evaluatie van het sensibel en motorisch blok met respectievelijke hulp van de applicatie van een ethylchloridespray en de toepassing van de aangepaste Bromage schaal. Ook werd op regelmatige basis de maternele hartslag, bloeddruk, saturatie en de foetale hartslag gemeten gedurende de eerste 3 uren van de studie.

Tot slot zal door middel van statistische analyses die gebruik maken van de isotonische regressie methode de ED_{50} berekend worden en een schatting naar de ED_{95} gemaakt worden.

Resultaten: Gebruik makende van de isotonische regressie methode wordt een ED_{50} (95% CI) van 12.0 (9.3 - 17.0) mg berekend. Deze methode is eigenlijk niet geschikt om de ED_{95} te bereken en dus moet de bekomen waarde van ED_{95} (95% CI) van 19.6 (16.0 - 20.0) mg aanzien worden als een schatting. Om deze tekortkoming weg te werken zou idealiter een biased coin design moeten worden toegepast.

Discussie: Dit is de eerste studie die de ED_{50} berekende van spinaal toegediende chloroprocaine 1% als onderdeel van een CSE bij zwangere vrouwen gedurende de arbeid. De beperkingen van deze studie zijn het feit dat er mogelijke confounding kan optreden door verscheidene obstetrische factoren. In deze studie werd wel een limiet bepaald voor de cervicale dilatatie maar er werd geen onderscheid gemaakt tussen een spontane of een geïnduceerde arbeid en een nulliparitеit ten opzichte van een multipariteit. Evenzeer kan een minimale beïnvloeding van de ED_{50} door de toediening van sufentanil epiduraal niet uitgesloten worden. Toch wordt een

epidurale toediening van opiaten verkozen boven de spinale toediening gezien een meer uitgesproken effect op het foetale hartritme bij spinale toediening. Tot slot kan er gesteld worden dat de onderzoeker niet geblindeerd was. De patiënte zelf had echter geen kennis over de exacte dosis chloroprocaine die zij toegediend kregen of over de voorafgaande resultaten.

Om te concluderen kan gesteld worden dat het voordelige farmacokinetische profiel van chloroprocaine de herintroductie in de obstretrische anesthesie kan verklaren. De snelle hydrolyse door plasma- en levercholinesterases verzekert lage plasmaconcentraties van chloroprocaine in zowel moeder als foetus. Deze studie concludeerde tot een berekende ED_{50} van 12.0 met een 95% CI van 9.3 - 17.0mg.