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Analgesia in obstetrics.
Influence of remifentanil patient-controlled analgesia vs. epidural analgesia on the second stage of labour, delivery type and neonatal outcome:
A retrospective comparative study

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I. Abbreviations

ASA	American Society of Anaesthesiologists
BE	Base excess
BMI	Body mass index
EA	Epidural analgesia
h	Hour
min	Minute
NICU	Newborn intensive care unit
PCA	Patient-controlled analgesia
PCEA	Patient-controlled epidural analgesia
PIEB	Programmed intermittent epidural bolus
s	Second
SD	Standard deviation

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III. Introduction

Analgesia in labour is a central issue in obstetrics and one of the most important matters for the parturient. Labour pain relief aims to provide relatively painless labour without interfering the birth process. That includes avoiding an inhibition of women´s participation in the birth experience or too much impact on physical mechanism regarding the mother like frequency and strength of contractions or oxygen supply. According to the commandment of the American College of Obstetricians and Gynaecologists, all women should receive pain relief on request [1]. The search for the ideal analgesic method has become a topic of major interest. Today several various strategies to provide pain relief during labour are available, including neuraxial analgesic methods and several systemic opioids, each associated with several benefits and risks.

Characteristics of labour pain

Labour is characterised by intermittent uterine contractions causing pain. These contractions gain frequency and intensity during delivery [2-4]. The start of regular, painful and progressive contractions defines the onset of labour. The phase from the onset of labour till complete cervical opening is termed as first stage or dilation stage. The first stage can be subdivided in an early dilation stage and an active dilation stage [5]. The early dilation stage is a latent phase, when cervical dilatation proceeds slowly until an opening of 4 to 6 cm is reached [5]. It is followed by the active dilation stage with a significantly increased cervical dilatation rate. At its beginning, contractions occur regularly approximately every 3 to 5 minutes [6]. The duration of the dilation stage is stated differently in literature, values range from 5.1 to 7.5 h for the early dilation stage in nulliparous and 2.2 to 5.7 h in multiparous women [7-9], and from 2.9 to 8.4 h for the active dilation stage in nulliparous and 2.2 to 4.7 h in multiparous women [8, 10-17]. The dilation stage ends at a complete opening (i.e. 10 cm) and effacement of the cervix. At this moment, the second stage of labour – also known as expulsion stage - begins [5]. The second stage of labour is defined as the period between full dilatation of the cervix and actual childbirth. It is marked by a change in the character of labour pain which then occurs in an average frequency of 3 to 5 contractions in 10 minutes [6]. The intensity of the contractions increases during the process of labour and shows peaks

of up to +30 mmHg in the first and +65 mmHg in the second stage [6]. The second stage begins with the passive expulsion (or expulsive) stage when complete opening of the cervix is reached but there is still no urge to push. The second phase of the expulsion stage is called active expulsion stage or pushing stage and is characterized by a reflexive urge to push with a completely effaced cervix and/or a visible infant or an actively pushing parturient [5]. The urge to push in the late expulsion stage is induced by the child´s head that enters slowly in the maternal pelvis. By pushing, the mother supports the uterine contractions. The intensity and processing of labour pain is individual, differs between each woman and can be affected by diverse psychological factors, such as prior experiences, anxiety or available emotional support [18]. Another key determinant that influences a woman´s pain perception by encouraging her self-confidence is feeling of control [19, 20]. Differences between nulliparous and multiparous women are documented, whereupon a stronger feeling of pain in nulliparous compared to multiparous is known. Not only the severity of pain differs nulliparas from multiparas, but also the phase of labour in which the pain is felt mostly. While multiparous women sense stronger pain in the pelvic phase of labour, when the pain is generated by the rapid descent of the neonate [21], nulliparous women experience a higher intensity of pain during early labour [22]. Basically, labour pain consists of visceral pain, which is caused by stretching and distension of the cervix and is significant in the early dilation stage of labour and during the expulsive stage, and somatic pain, due to distension, ischaemia and injury of the pelvic floor, vagina and perineum, shaping the late dilation stage and also appears in the expulsive stage. Labour pain is not only unpleasant for women giving birth to a child, but can also negatively affect her cardiovascular, respiratory and psychological health [23, 24]. Labour pain induces an increase in catecholamine levels, which leads to increased maternal cardiac output and peripheral vascular resistance, diminished uterine contractions and decreased uteroplacental perfusion [25]. Therefore, besides affecting the mother in physiological and psychological ways, labour pain may also endanger the child. Consequently, labour analgesia may also protect the foetus and reduce complications during labour. This must be taken into account when discussing pain relief to expectant mothers. Analgesia in labour is no longer luxury but has become a key issue in obstetrics.

Epidural analgesia

Among diverse options to provide pain relief throughout labour, epidural analgesia (EA)

remains the gold standard and is considered to be the most effective and most flexible method [26]. It mostly replaced the pudendal nerve block which was frequently used from the mid-1950s to the mid 1980s [27, 28]. For EA, initially, a local anaesthetic agent alone was commonly used, while later the addition of an opioid showed an improvement of pain relief [29]. A combination of opioid and local anaesthetic, most frequently fentanyl and bupivacaine, represents the current standard regimen [30].

EA is known to have fewer side effects on parturient and neonates compared to other analgesic methods [31]. Mild and often self-limiting side effects of EA on the mother, such as pruritus, nausea or vomiting are rather common [32]. Douma et al. also found an association of EA with maternal fewer [33]. In rare cases, severe symptoms like hypotension, somnolence, respiratory depression and urinary retention may occur [32]. Unlike the other named side effects, nausea, vomiting, somnolence and early respiratory depression are dose-related and therefore also user-dependent [32]. The publication of several cases of life-threatening respiratory depression after EA made respiratory depression the most concerning of all potential side effects for parturients [34, 35]. Nevertheless, according to the guidelines of the American Society of Anaesthesiologists (ASA) EA remains the least depressing to the central neuraxial system analgesic modality in obstetrics, and hence is recommended in labour [36]. In terms of effects on the foetus, current evidence is lacking due to very few and mostly non-randomised observational studies [37]. Many of the available studies deal with foetal heart rate abnormalities, one of the feared side effects of EA [38-40]. Some cases of emergency caesarean sections required after intrathecal fentanyl due to persistent foetal bradycardia in association with uterine hypertension are reported [41, 42]. An effect of EA on the initiation of breastfeeding is disputed [43-45] but could mean an impairment of the maternal-neonatal bonding and loss of the wide-ranging health benefits for the child as breastfeeding improves the cognitive development, prevents infection and might also protect from late-onset overweight and diabetes in adulthood [46]. However, there is still a lack of prospective randomized studies on this topic [43]. Due to its lipid solubility, fentanyl that diffuses freely from the epidural space into the maternal blood easily crosses the placenta [47, 48].

Neonate´s respiratory centre is immature and therefore prone to respiratory effects by opioids [49]. Some studies proved neonatal respiratory depression following EA [50-53]. In others, no significant effect on newborns´ respiration could be found [54-56]. Elder studies claim EA to weaken or even completely suppress the urge to push in the late expulsive stage and increase the incidence of prolongation of the expulsive stage and instrumented vaginal delivery [57-

61]. However, a higher rate of assisted vaginal births was also reported by Anim-Somuah et al. in a current systematic review [62]. Another important issue is women´s acceptance. Some women want to avoid invasive methods and thus decide against EA. If pain relief during labour is requested but EA is not welcomed by the pregnant, an alternative analgesic technique is required. An alternative is also needed when EA is contraindicated. For example, prophylactic anticoagulation [63] and coagulation disorders rank among the main contraindications for EA. Further contraindications that have to be considered are allergy to local anaesthesia, anatomical and physical conditions like spinal deformity or obesity, tattoos at the intended puncture site or infection close to it. Besides, there are cases were an epidural catheter is unable to be placed or only minor pain relief can be provided via EA. Pudendal nerve block can be applied as a supplement of EA or even as a replacement if EA is not appropriate. Though, pudendal nerve block is mainly effective in operative vaginal birth or in the late expulsion stage immediately before spontaneous vaginal delivery [64]. Furthermore, pudendal nerve block provides inferior pain relief for contractions [65] and can block the urge to push in the active expulsion stage when administered to early [64]. An effective and secure alternative when EA is not suitable seems to be still missing.

Systemic opioids

Intramuscular or intravenous opioids can provide a sufficient alternative to EA [66]. Their usage in labour pain is standard of care in many countries today. One of the most commonly used systemic opioids is pethidine [67]. Opioids readily cross the placenta, the period a newborn needs to eliminate the opioid and its metabolites differs between the substances. The half-lives of pethidine and the related metabolite norpethidine in neonates are highly prolonged [68]. Its elimination can take the neonate three to six days [69]. Pethidine is known to affect foetal heart rate variability, accelerations and decelerations during labour [70, 71] while it is said to be unable to provide sufficient pain relief [72]. Also in the neonate, distressing adverse effects are known, most relevantly low Apgar scores and respiratory acidosis [73]. However, studies on pethidine could also show that if doctors comply with a mean drug-to-delivery interval of 5.3 hours, compared to a placebo group, the number of 1-minute and 5-minute Apgar scores of less than 7, umbilical artery pH and admission to NICU was not significantly higher in the pethidine group [74]. Morphine is less frequently used in labour analgesia and more likely to cause respiratory depression in neonates than pethidine

[75]. An increasingly used opioid is meptazinol. Meptazinol is considered equivalent to pethidine concerning the analgesic potential which is rather low. Compared to morphine, the potency of meptazinol is about 0,1. However, meptazinol seems to have fewer side effects and less likely cause neonatal respiratory depression [76, 77]. Despite considerable effects on mother and child, long-acting opioids are still frequently applied in obstetrics. The ideal opioid that provides sufficient analgesia in labour without inducing maternal or neonatal respiratory depression, postural hypotension or decreased reflexes, seems to be still missing [78-81]. Neonatal respiratory depression and the need for resuscitation poses a main problem in opioid analgesia for labour pain. Here, the interval between drug administration and actual delivery seems to be pivotal. In the use of pethidine for example the highest rates of neonatal respiratory depression can be measured when given 3-5 hours prior to delivery [82, 83]. This dependency on timing counts for all systemic opioids and results in a gap of non-hazardous pain relief concerning the last period in labour when delivery is immanent and only minutes are left.

Patient-controlled analgesia

An alternative to standard parenteral opioid administration that might be able to close the gap of safe analgesia at the end of the second stage of labour is patient-controlled analgesia (PCA). Self-administered small boluses can provide titration and minimise side effects [84], but the safety depends on the used substance. PCA using fentanyl, for example, was associated with a 44 % incidence of neonatal respiratory depression in a retrospective study reported by Morley-Forster et al. [85]. The risk of severe neonatal respiratory depression is also given in alfentanil for PCA [86]. Both, fentanyl and alfentanil are doubt to be able to provide sufficient analgesia, while fentanyl seems to be slightly superior [84]. In conclusion, with or without PCA, common systemic opioids appear inappropriate as a secure and effective alternative to EA in labour analgesia.

Remifentanil

Remifentanil, which was first introduced to obstetrics practice in the 1980´s, is increasingly used for labour pain due to its unique pharmacokinetic and pharmacodynamic characteristics.

Remifentanil is an ultra-short-acting, selective opioid μ-receptor agonist with a fast onset and offset, independent of the duration of administration [87-89]. Its onset time accounts for 30 to 60 sec, it has a peak analgesic effect of 2.5 min, and with a context-sensitive half-life about 3 to 4 min a high metabolic rate [88, 90, 91]. A comparison of remifentanil and other opioids regarding half-life is given in figure 1. Remifentanil crosses the placenta with no difficulty [92-94]. Though, it can be rapidly degraded and redistributed by the foetus due to non-specific esterase activity [92, 94]. Studies of remifentanil in children of different ages showed, that pharmacokinetics are comparable to those in adults, especially half-life was found to be not age-related [95-98]. This accordance of pharmacodynamic characteristics among all age ranges also includes neonates [99]. The elimination of remifentanil is non-organ specific and independent of liver and kidney function [100, 101]. Therefore, there is no risk of accumulation even when remifentanil is used for a long period. For these special pharmacological features, remifentanil is a convenient opioid for labour pain. However, the side effects of remifentanil on mother and child are also in the focus of research. A reduced foetal heart rate variability is one of those discussed side effects [102, 103]. Some studies suggest, that remifentanil might also induce foetal and neonatal acidosis [33, 66, 92] as a result of reduced oxygen saturation and increased carbon dioxide levels as already seen in the use of systemic opioids [82]. Among distressing effects on the mother, the occurrence of maternal sedation, dizziness, nausea, vomiting and pruritus have been reported [66, 92, 104-109]. Also in the use of remifentanil, maternal respiratory depression is the most concerning risk. Studies are supporting the assumption of remifentanil having a significantly higher impact on maternal respiration in comparison to EA. So, Stocki et al. found in a randomised controlled study a significantly higher occurrence of apnoea in women with remifentanil PCA while giving birth than in those with EA (26 % vs. 0 %; n = 38) [110]. Douma et al. stated a significantly higher incidence of maternal respiratory depression (15 % vs. 48 %; n = 20) and also stronger sedation during analgesia with remifentanil PCA compared to an EA-group [33]. The respiratory depressant and sedative effect of remifentanil was also described by Volmanen et al. [103]. Remifentanil PCA causing respiratory arrest and/or cardiac arrest in labouring women has been described in several of case reports [111-113]. Some of these reports point out iatrogenic factors like previous opioid administration or erroneous drug dosing as risk factors for respiratory arrest. Compared to fentanyl and pethidine, remifentanil shows more potential in pain reduction measured by the visual analogue scale [66, 114]. It also provides better pain relief compared to nitrous oxide [25, 105, 115]. Regarding the proportion of epidural conversions, remifentanil PCA showed significantly better results

compared to intramuscular pethidine [116]. There are comparisons between remifentanil and EA reported in the literature that show, that there is no significant difference in pain reduction [110, 117-120]. Other studies report, the decrease was greater in the epidural group, while satisfaction was similar in both groups [33] or the analgesic efficacy of remifentanil was found less than that of EA [33, 108, 115, 120]. Evident is the sufficient analgesic effect of remifentanil in the dilation stage [103], while its power close to delivery is doubtful [104]. Remifentanil is known to provide better safety compared to other opioids administrated via PCA. For example, PCA with fentanyl showed in a report by Marwah et al. [121] a significantly higher number of neonates requiring resuscitation as compared to remifentanil PCA. However, in the same study, a greater oxygen desaturation in parturients receiving remifentanil for labour pain (13 %) than those receiving fentanyl (2 %) was found. Still, available literature supporting the use of remifentanil is limited and for the most part show a low quality level of evidence. This can for instance be read in a current review including 20 trials by Weibel et al. [122]. Thus, the fear of negative effects of PCA with remifentanil on the foetal outcome still restricts its usage.

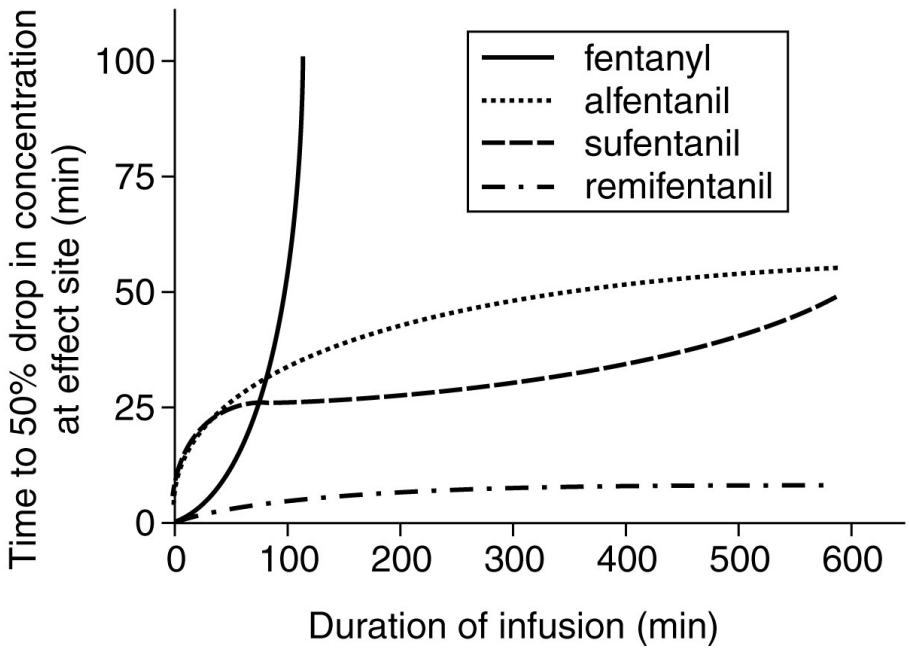

Figure 1: ***Half-life remifentanil and other opioids*** [123]

Foetal outcome

Apgar Score

The Apgar-score is a standardised tool to quickly assess the newborn´s clinical condition and its adaption to living outside the uterus immediately after birth. The score was developed and named by the US-American obstetrical anaesthesiologist Virginia Apgar in 1952. 5 simple criteria summarize the child´s health on a scale from 0 to 2. By summing the 5 values the Apgar-score is determined. To evaluate the mortality and the survival rate, respectively, the value 5 minutes after birth is known to be the most meaningful. While a 1-min Apgar score of 0 to 3 is not suitable to predict any individual infant´s outcome, a 5-min Apgar score of 0 to 3 can be correlated with neonatal mortality [124, 125]. However, the Apgar score is a mainly subjective valuation conducted by gynaecologists or paediatricians and can thereby vary depending on the examiner.

Umbilical cord arterial blood gas analysis

Umbilical cord arterial pH value and base excess (BE) is a commonly used objective measure of perinatal asphyxia as a predictor for the neonatal outcome. For cord arterial pH has been used as a primary marker of ischaemic injury for a long time, currently, the BE is suspected to be more useful than pH due to its resistance to respiratory acidosis and gestational age which make the BE suitable for the direct measurement of foetal metabolic acidosis and thereby to indicate the duration of insult [126]. -8.6 to -2.6 mmol/L is defined as normal arterial cord blood BE [127]. An arterial umbilical pH of less than 7.20 is defined as abnormal [128]. Moderate acidosis rates from 7.20 to 7.10, an arterial pH below 7.10 defines a severe umbilical acidosis. Serious consequences can follow respiratory acidosis in a newborn. Respiratory acidosis is known to depress cardiac function by decreasing the contractility of the heart muscle [129] causing pulmonary oedema and decreased blood pressure and pulse [130-132].

Apgar Score

Gestational age_____weeks

Sign	0	1	2	1 minute	5 minute	10 minute	15 minute	20 minute
Color	Blue or Pale	Acrocyanotic	Completely Pink					
Heart rate	Absent	<100 minute	>100 minute					
Reflex irritability	No Response	Grimace	Cry or Active Withdrawal					
Muscle tone	Limp	Some Flexion	Active Motion					
Respiration	Absent	Weak Cry; Hypoventilation	Good, Crying					
			Total					

Comments:

Resuscitation

Minutes	1	5	10	15	20
Oxygen					
PPV/NCPAP					
ETT					
Chest Compressions					
Epinephrine					

Figure 2: ***Apgar-score*** [133]

Aims and Scopes

EA, the gold standard in obstetric analgesia, provides efficient pain relieve for many labouring women. We searched for an alternative to this gold standard for cases in which EA is contraindicated, unable to be placed or not accepted by the parturient and so started the use of remifentanil PCA for the management of labour pain. The initial enthusiasm was inhibited by critical reactions of both medical staff and patients due to missing experience and lacking literature for remifentanil in terms of foetal safety. In general, very little information about the use and risks of remifentanil PCA for labour pain is available in literature.

Thus, it remains to be investigated, to what extent PCA with remifentanil interferes with the delivery process and affects the neonate.

The aim of this retrospective study presented here was to investigate the effect of remifentanil patient-controlled analgesia during labour on the process of delivery and the short-term foetal outcome in comparison to the gold standard EA.

We focused on the following questions to evaluate this effect of remifentanil PCA:

1. Does remifentanil PCA prolong the second stage of labour?
2. Is there an influence on the mode of delivery?
3. Is there a negative effect on the neonatal outcome concerning Apgar-score, arterial pH and BE?

4. Do parturients with remifentanil PCA need more additional opioids?
5. Is there an increase in the demand for oxytocin?
6. Does the starting time differ between remifentanil PCA and EA?

Answers to these questions may influence future standard regimes for analgesia in modern obstetrics.

IV. Participants and methods

Participants

Between 2012 and 2014, a total of 234 women, starting from the age of 18, labouring at the Klinikum rechts der Isar, University hospital of the Technical University Munich were included in this study. The women were both nulliparous and multiparous, gestation age at the time of delivery was more than 37 weeks in each case. Multiple pregnancies had been excluded. The parturients were subdivided into three groups according to the chosen analgesic method during delivery. Group division according to the analgesia was:
PCA-group (using remifentanil PCA), EA-group and non-opioid-group (no analgesia or analgesia including paracetamol and butylscopolamine) as a control group.

The study was performed in accordance with the Declaration of Helsinki. Approval from the local ethics committee was obtained prior to the investigation.

Data collection

For this retrospective study, data were obtained from the Bayerische Perinatalerhebung. Detailed delivery documentations of the Frauenklinik Klinikum rechts der Isar, University hospital of the Technical University Munich completed by the midwife in charge were evaluated.

Analgesic methods

Epidural analgesia regimen

Epidural analgesia (EA) was performed upon request of the parturient or according to other indications e.g. prolonged birth. In general, EA was applied when regular contractions leading to a cervical dilatation of about 3cm were present. Lumbar epidural catheters were placed and supervised by anaesthetists from the Department of Anaesthesia. Pre-interventional, a standard informed consent was obtained from the patient by the anaesthetist. During the placement of the epidural catheter, the pregnant woman was monitored by cardiotocography, electrocardiogram, pulse oximetry and blood pressure monitor. The patient was either placed in a seated position or left lateral position. Epidural catheters were placed at intervertebral space L 2/3, L3/4 or L4/5 at the discretion of the anaesthetist. Epidural space was identified with a Tuohy cannula by the "Loss of resistance" technique using saline and a catheter subsequently inserted. Epidural medication consisted of a solution containing 1 mg/ml ropivacaine and 0.75µg/ml sufentanil in a total of 100 ml administered via a CADD Solis® patient-controlled epidural analgesia (PCEA) pump with integrated programmed intermittent epidural bolus (PIEB). A fractioned first bolus of 2 times 5 ml was immediately administered via the "Physician-bolus"-mode to exclude an accidental intrathecal position of the catheter. The absence of any neurological changes confirmed the epidural location of the catheter. Additional boluses were given by the anaesthetist until maternal satisfaction was achieved. Following this, the parturient was able to give herself boluses of 8 ml every 60 min via the pump (PCEA). The PIEB was automatically injected if the parturient had not requested an additional bolus within the last 90 min.

Intravenous remifentanil analgesia regimen

Intravenous patient-controlled analgesia (i.v. PCA) with remifentanil was chosen on request of the patient or when EA was not possible due to contraindications including coagulation disorders, anticoagulation intake, allergy to local anaesthetics or diverse anatomical conditions. In cases of failure of placement or dislocation of the epidural catheter or unsatisfying analgesia via EA, i.v. PCA using remifentanil was offered as second line. I.v. PCA was also used when anaesthesia was required by the pregnant in an advanced stage of labour with not enough time left for the placement of an epidural catheter. For i.v. PCA, a separate intravenous cannula was placed for isolated injection of remifentanil. Remifentanil

was also administered with the CADD Solis® pump programmed to i.v. PCA. Boluses of 20 µg remifentanil could be administered every 4 minutes. To account for the onset time of remifentanil, parturients were instructed to activate the pump at the beginning of a contraction. During the whole course of i.v. PCA patients were monitored with pulse oximetry.

Non-opioid analgesia regimen

For opioid-free analgesia, 1 g paracetamol intravenous as a short infusion or butylscopolamine bromide 20 mg i.v was given.

Non-pharmacological methods to reduce labour pain were not recorded.

Examined parameters

Age

The parturient´s age, stated in completed years, was acquired from the patient documentation. As already lined out, an inclusion criterion was an age of at least 18.

Week of gestation

The week of gestation at the time of delivery was adopted from the German mother-and-child-pass, where the mentoring gynaecologist fills in the estimated delivery date. This date is calculated according to Naegele´s rule, i.e., the first day of the last menstrual period plus 9 months plus 7 days and corrected according to the foetal crown-rump length, respectively. Figures are stated in *weeks* + *days*. Parturients from 37+0 weeks of gestation were included in this study.

Body mass index

The body mass index (BMI) is defined as the body mass divided by the square of the body height, expressed in units of kg/m^2, resulting from mass in kilograms and height in metres.

Women´s height and weight before the beginning of pregnancy was obtained from the German mother-and-child-pass.

Mode of delivery

The documented birth methods were categorized into 4 groups:

- Spontaneous vaginal delivery: Vaginal delivery with or without induction of labour excluding assisted vaginal delivery
- Operative vaginal delivery: Vaginal delivery assisted by forceps or vacuum extractor
- Secondary caesarean section: Every unforeseen caesarean section that has not to be performed as an emergency within 20 minutes
- Emergency caesarean section: Secondary caesarean section that has to be carried out within 10 minutes to prevent mother and /or child from physical damage

Additionally, in the case of secondary caesarean section or emergency section the indication for the conversion was cited.

Parity

The women´s parity was received from the patient documentation. Nulliparous, as well as multiparous women, were included in the study.

Delivery type of preceding births

In the case of multiparas, the delivery methods of the previous deliveries were taken from the patient's medical history using the same classification as for the present delivery type.

Oxytocin

The administration of parenteral oxytocin while delivery was obtained from the delivery documentation. Oxytocin was used for labour augmentation after the indication of the obstetrician. In the present study, we differentiated between oxytocin administration before or after the application of EA and PCA, respectively.

Induction of labour

Cases, where labour was induced medically, have not been excluded from this study. The

following pharmaceuticals for induction of labour were applied: Dinoprostone (Minprostin® Vaginalgel), misoprostol (Misodel®), oxytocin i.v. and non-pharmaceutical induction by balloon catheter.

Comorbidity

The existence of previous diseases was obtained from the patient´s medical history.

Hypertension

The pre-existence of hypertension and pregnancy-induced hypertension was obtained from the medical history. The occurrence of preeclampsia, eclampsia and HELLP-syndrome was taken from the delivery documentation.

Additional opioids

As additional opioids pethidine 100 mg or meptazinol 100 mg in 250 ml NaCl 0.9 % at 300 ml were given in several cases of the EA- and PCA-group before the start of EA and PCA.

Cervical dilation

The cervical dilation in cm at the time of application of EA or PCA was obtained from the delivery documentation and compared between the two groups.

Second stage of labour

Among the different designations for the stages of labour, we chose the term `expulsive stage` for the first phase of the second stage and `pushing stage` as the late phase of the second stage for our study.

The duration of the two phases in minutes was taken from the delivery documentation.

Complications

Complications like looping of the umbilical cord or bleeding, requiring blood transfusion, were cited.

Birth weight and height

Birth weight and height were obtained from the delivery documentation and indicated in kg and cm, respectively as well as in percentiles.

Apgar-score

In our study, we gathered the Apgar-value after 1, 5 and 10 minutes. Apgar values less than 7 are stated to be abnormal [134]. Due to the short-acting character of remifentanil, we concentrated on the 1-minute Apgar-score for our analyses.

Umbilical cord arterial blood gas analysis

Umbilical artery was punctured immediately after cord clamping by skilled midwifes. Blood analysis was conducted using a radiometer. For our study, we stated a pH less than 7.10 as critical according to the standard classification [135]. As an asphyxial injury is not suspected to occur until foetal BE exceeds 12 mmol/l which means 2 SDs below the mean [126] we chose 12 mmol/l as a threshold value. This also meets the criteria to define an acute intrapartum hypoxic event described by MacLennan in an international consensus statement in 1999 [136].

Further influence factors

To ensure the aim of this investigation - the influence of the analgesic method on the maternal-foetal outcome - we also performed an analysis of possible influence by other parameters on our target parameters. In this uni- and multivariate analysis, we included age, BMI, birth weight of the newborn, delivery type of previous births and the administration of oxytocin.

Statistical analysis

To evaluate the influence of the different analgesic approaches on the target parameters named under *Examined parameters* we performed univariate and multivariate regression analysis as well as group comparisons carried out by Wilcoxon-Mann-Whitney-U-test and Fisher´s exact test. Statistical analysis was performed using the software package SPSS version 24 (SPSS Inc, Chicago, Illinois). All data were tested for normal distribution using the

Kolmogorov-Smirnov test. Unless otherwise stated, descriptive results were demonstrated as mean ± standard deviation (SD). Significance was set at $P < .05$ for all tests.

To exclude a possible influence of the additional intravenously given opioids to several women of the PCA- and EA-group on the investigated outcome parameter, a separate statistical analysis was performed. In this analysis, we examined the influence of the time interval between the last infusion of an additional intravenous opioid and the delivery on the delivery type, the duration of the second stage of labour, the Apgar-score 1 minute postnatal, and the umbilical arterial blood pH and BE. For this analysis, we used Wilcoxon-Mann-Whitney-U-test, Fisher´s exact-test as well as univariate and multivariate regression analysis.

V. Results

Participant Characteristics and Clinical Findings

In total, 234 labouring women were included in our study. 82 women were treated with i.v. PCA with remifentanil, 76 received analgesia via EA and 76 laboured without analgesia or with non-opioid analgesia. Mean maternal age was 32.1 ± 5.1 years, mean BMI 22.5 ± 4.7 and mean gestational age 39.1 ± 1.2. An overview of participant characteristics is given in Table 1. There was a significant difference in mean gestational age between multiparas of the PCA- and the EA-group (p = 0.001) as well as between multiparas of the PCA- and the non-opioid-group (p = 0.022). In both comparisons, multiparas of the PCA-group delivered in a higher week of pregnancy. Differences in maternal age, BMI and the occurrence of gestation diabetes never reached the level of significance. Pre-existent arterial hypertension as a risk factor for preeclampsia appeared in two cases of the PCA-group and one case of the EA-group. Other comorbidities were rare and therefore not considered as relevant and not cited here. One parturient of the EA-group suffered preeclampsia. HELLP-syndrome occurred in two cases, in one patient with non-opioid analgesia and in one patient who received PCA. Eclampsia did not occur in any cases. 11 neonates had to be transferred to the newborn intensive care unit (NICU). 7 of their mothers were included in the PCA-group, 4 in the EA- and one in the non-opioid-group. The indication for NICU admission was hyperbilirubinaemia in one case of the PCA-group and two cases of the EA-group, congenital cardiac defect in two cases of each group, underweight in two cases and adaption disorder and

amniotic infection syndrome in one case of the PCA-group. Looping of the umbilical cord was reported in 3 cases, two of the PCA- and one of the EA-group. One parturient of the PCA-group suffered bleeding during labour that required a blood transfusion.

Table 1: ***Patient´s characteristics***

	PCA		**EA**		***p*-value PCA vs. EA**		**Non-opioid**		***p*-value PCA vs. Non-opioid**	
	Para = 1	Para > 1	Para = 1	Para > 1	Para = 1	Para > 1	Para = 1	Para > 1	Para = 1	Para > 1
n	60	20	59	17			40	36		
Age	31.1 ± 5	33.5 ± 3.5	31.5 ± 5.3	35.1 ± 6.5	0.597	0.149	31.6 ± 4.9	33.2 ± 5.2	0.972	0.789
BMI	22.8 ± 6.8	22.4 ± 3.6	22.5 ± 3.5	23.6 ± 6.2	0.368	0.67	22.1 ± 2.8	22.1 ± 3.8	0.475	0.613
Gestational age	39.2 ± 1.2	39.6 ± 0.9	39.1 ± 1.1	38.5 ± 1	0.525	0.001	39.4 ± 1.4	38.7 ± 1.4	0.675	0.022
Gestation diabetes (%)	2 (3.4 %)*	1 (5 %)	4 (6.8 %)	3 (17.6 %)	0.671	0.303	2 (5 %)	4 (11.2 %)**	1	0.787

Table 1: Age (years), and gestational age (weeks) at the time of examination; BMI (kg/m2) before pregnancy; occurence of gestation diabetes until the time of examination; Age, BMI and week of gestation given in mean ± SD. In case of missing data, the number of patients with available data can be found under * and **, respectively.

* Data available in 58 of 60 cases

** Data available in 32 of 36 cases

Additional opioids

In the PCA-group, 47 (78.3 %) of the primiparous and 9 (45 %) of the multiparous women already received an intravenous opioid before they switched to the chosen analgesic method, i.e., EA or remifentanil PCA. In the EA-group that included 28 (47.5 %) primiparas and 9 (52.9 %) multiparas (Table 2). Comparing the two groups, significantly more primiparas of the PCA-group asked for additional opioids than primiparas of the EA-group ($p = 0.001$). There was no significant difference in the use of additional opioids between the multiparas. The time period between the last infusion of opioids and the delivery showed no correlation with the delivery type, duration of the expulsive stage or the pushing stage, the Apgar-score 1 minute postnatal and the umbilical arterial pH and BE. Thus, we assumed the administration of additional intravenous opioids in the PCA- und EA-group to be neglectable for the remaining analysis.

Labour induction and administration of oxytocin

In 13 (21.7 %) of primiparous and 7 (35 %) of multiparous women of the PCA-group labour was induced. In the EA-group, labour induction was used in 22 (37.3 %) primiparas and 3 (17.7 %) multiparas. In the non-opioid-group, labour was induced in 10 (25 %) cases of the primiparas and in 5 cases (13.9 %) of the multiparas. Comparing the PCA- and the EA-group, no significant difference in the number of patients receiving labour induction could be shown neither in primiparous nor in multiparous women. Though, in comparison of multiparas of the PCA- and the non-opioid-group, significantly fewer women of the non-opioid-group received labour induction ($p = 0.018$).

Oxytocin had to be used less frequently in primiparous women with PCA compared to those with EA ($p = 0.006$). Nulliparas treated with PCA were given oxytocin in 41 cases (68.3 %), 11 (18.3 %) before and 30 (50 %) after starting analgesic therapy via PCA. For the multiparous PCA-patients, oxytocin was used only after starting PCA and given in 7 cases (35 %). In the EA group, 45 (76.3 %) of the primiparas (2 (3.4 %) before and 43 (72.9 %) after the administration of EA) and 4 (23.5 %) of the multiparas (all after the administration of EA) received oxytocin. Comparing the PCA- and the EA-group concerning the time of the administration of oxytocin, i.e., before or after starting PCA and EA, respectively, a significant difference between primiparas of the two groups could be shown ($p = 0.005$).

While in the EA group 72.9 % of the primiparas received oxytocin after and only 3.4 % before EA, in the PCA group that was 50 vs. 18.3 %.

In the question of the usage of oxytocin, a comparison between primiparous and multiparous women of the PCA-group and those giving birth without opioid-analgesia presented a significant difference ($p < 0.0005$). In the non-opioid-group, 9 (22.5 %) of the primiparas and 2 (2.6 %) of the multiparas obtained intravenous oxytocin during labour.

Univariate and multivariate regression analysis showed that the administration of oxytocin has a significant effect on the duration of the second stage of labour ($p < 0.0005$). Influence on the delivery type, 1-min Apgar-score and arterial cord blood pH and BE could be disproved. Detailed results are also given in Table 2 and 9.

Table 2: ***Labour induction, oxytocin, cervix dilatation, additional opioids, birth weight and percentile***											
		PCA		**EA**		**Non-opioid**		***P value***			
								PCA vs. EA		**PCA vs. non-opioid**	
Para		1	>1	1	>1	1	>1	1	>1	1	>1
n		60	20	59	17	40	36				
Labour induction		13 (21.7 %)	7 (35 %)	22 (37.3 %)	3 (17.7 %)	10 (25 %)	5 (13.9 %)	0.200	0.327	0.777	0.018
Oxytocin	Total	41 (68.3 %)	7 (35 %)	45 (76.3 %)	4 (23.5 %)	9 (22.5 %)	2 (5.6 %)	0.006	0.715	< 0.0005	< 0.0005
	Before	11 (18.3 %)	0	2 (3.4 %)	0			0.005			
	After	30 (50 %)	7 (35 %)	43 (72.9 %)	4 (23.5 %)						
Cervix dilatation (cm)		8.8 ± 1.7	8 ± 1.8	5 ± 1.9	6.8 ± 2.3			< 0.0005	0.131		
Additional opioids		47 (78.3 %)	9 (45 %)	28 (47.5 %)	9 (52.9 %)			0.001	0.746		
Weight		3404 ± 450.4	3569.2 ± 349.9	3357.8 ± 370.7	3273.2 ± 336.4	33362 ± 364.4	3415 ± 364.7	0.732	0.022	0.665	0.388
Percentile (weight)		44.1 ± 28.3	48 ± 25.3	42.1 ± 24.8	37.9 ± 16	39 ± 26.3	46.3 ± 26.1	0.815	0.339	0.439	0.290

Table 2: Labour induction, administration of oxytocin in total, before and after administration of PCA and EA, respectively and use of addional opioids. Average cervix dilatation (cm) at time of PCA/EA, birth weight (g) and percentile of birth weight given in mean ± SD.

Cervix dilatation

In our study, we compared the mean cervical dilatation at the time of application of PCA and EA, respectively, and found, that in primiparous women PCA was started significantly later in the course of labour than EA. Primiparas had a mean cervix dilatation of 8.8 ± 1.7 cm when receiving PCA and 5 ± 1.9 cm when receiving EA ($p < 0.0005$). Multiparas received PCA when the cervix was dilated to a mean opening of 8 ± 1.8 cm and EA when dilated to 6.8 ± 2.3 cm ($p = 0.131$). Further details can be obtained from Table 2.

Birth weight and percentile

Neonate´s birth weight of multiparas was significantly lower in the EA-group compared to the PCA-group ($p = 0.022$). In primiparas, birth weight and depending percentile were rather evenly distributed among the three groups.
Details are provided in Table 2.

Second stage of labour

Regarding the duration of the second stage of labour, women who were treated with remifentanil PCA required significantly more time from full cervical dilatation to delivery than women with non-opioid analgesia. In cases of primiparas that was on average 105.3 ± 69.3 min for the expulsive stage and 33.3 ± 18.8 min for the pushing stage in opposition to 85.9 ± 141.1 min ($p = 0.009$) and 23.4 ± 11.6 min ($p = 0.041$). Concerning multiparous women, the expulsive stage had a mean duration of 61.4 ± 71 min and the pushing stage a mean duration of 19.4 ± 20.7 min in the PCA-group. In the non-opioid-group it was 20.1 ± 44.3 min ($p = 0.001$) for the expulsive and 7.5 ± 6.4 min ($p = 0.003$) for the pushing stage.
When comparing the PCA- with the EA-group, the second stage of labour showed similar durations with no significant difference. In the EA-group the mean duration of the expulsive stage accounted for 114.2 ± 67.9 min for primiparas and 52.6 ± 54.2 min for multiparas. The pushing stage lasted for 25.7 ± 11.4 and 22.8 ± 20.1 min, respectively. An overview is given in Table 3 and Figure 3 In multivariate regression analysis of multiparas, a significant

influence of the analgesic method on the duration of the pushing stage but not on the expulsive stage could be shown (p = 0.037).

Delivery type

In the PCA-group, 31 (51.7 %) of the primiparas and 17 (85 %) of the multiparas delivered spontaneously vaginally. Instrumental assistance for vaginal delivery was necessary in 10 (16.7 %) and 2 cases (10 %), respectively. 16 (26.7 %) of the primiparous women needed secondary caesarean section and 3 (5 %) even needed emergency section. Among multiparas, one (5 %) caesarean section and no emergency caesareans had to be conducted.

In the EA-group, spontaneous vaginal delivery made up 45.8 % (27 patients) in primiparas and 70.6 % (12 patients) in multiparas. Operative vaginal delivery accounted for 18.6 % (11 patients) and 23.5 % (4 patients), respectively. A secondary caesarean section became necessary for primiparas in 21 cases (35.6 %) and for multiparas in one case (5.9 %). No emergency caesarean section was documented in the EA-group.

In women who received only non-opioid analgesics during labour, the rate of spontaneous vaginal deliveries accounted for 27 (65 %) in primiparas and 27 (75 %) in multiparas. Three (7.5 %) of the primiparas but none of the multiparas required operative assisted vaginal delivery. Secondary caesarean section was performed in 11 (27.5 %) of the primiparas and 9 (25 %) of the multiparas. An emergency section was not performed in any case of the non-opioid-group.

Comparing the PCA- with the EA-group, no significant difference considering the delivery type could be proved. Multiparous women with non-opioid analgesia differed significantly from multiparas of the PCA-group in terms of delivery type (p = 0.019). While those from the non-opioid-group had a higher rate of secondary caesarean sections, operative assisted vaginal delivery was more frequent in multiparas from the PCA-group. Differences between primiparas of the non-opioid and the PCA-group never reached the level of significance.

In univariate regression analysis, no significant influence of the analgesic method on the delivery type could be proven. In multivariate regression analysis of multiparas (including the previous delivery type as an influencing factor) as well as of primiparas, a significant influence of the analgesic method on the delivery type concerning spontaneous versus secondary caesarean section could be shown (p = 0.042 and 0.015, respectively).

Table 4 and Figure 4 show an outline of the delivery method.

Apgar-score, pH and BE

As in our study population 5 as well as 10 min postnatal all neonates had an Apgar-score above 7, we focused on the 1-minute Apgar-score when comparing the different groups.
Overall, analysis of the foetal outcome defined by Apgar-score 1 min postnatal, umbilical arterial pH and BE yielded no significant differences when comparing the PCA-group neither to the EA-group nor to the non-opioid-group (Table 5). Also in univariate and multivariate regression analysis, no significant influence of the analgesic method on the foetal outcome could be proven (Table 10).
Four babies (6.7 %) of the babies from primiparous women in the PCA-group and one (1.7 %) of those in the EA-group had a 1-min Apgar-score of less than 7. All neonates of multiparous women treated with PCA or EA had a 1-min Apgar-score of 7 or more. In the non-opioid-group, the 1-min Apgar-score fell below 7 in one case (2.7 %) concerning newborns from multiparas and did not occur in any case concerning primiparas´ babies. All newborns had a 5-min Apgar-score as well as a 10-min Apgar-score of 7 or more. The Apgar-scores are listed in detail in table 6-8.
In the PCA-group, in 3 (5 %) of the primiparous and 2 (10 %) of the multiparous parturients, a pH of less than 7.10 could be determined in blood gas analysis of the arterial cord blood. That was also the case in one neonate of primiparas of the EA- (1.7 %) and in one of the non-opioid-group (2.6 %). Arterial cord blood analysis proved a pH with a minimum of 7.10 in all multiparous parturients of the EA- and the non-opioid-group.
Regarding the umbilical arterial BE, a value less than -12 mmol/L was found in 2 cases (3.3 %) of primiparous and in one (5 %) of multiparous women delivering with PCA and in one (1.7 %) of primiparas as well as in one (5.9 %) of multiparas who received EA. In primiparas of the non-opioid-group one neonate (2.6 %) had a BE of less than -12 mmol/L. In multiparas of the non-opioid-group, all analysis proved a BE with a minimum of -12 mmol/L.
Figure 5, 6 and 7 provide an overview of the foetal outcome.

Age, BMI and birth weight

Univariate and multivariate regression analysis confirmed, that the women´s age has no significant effect on the delivery type, the duration of the second stage of labour, the 1-min Apgar-score and the arterial cord blood pH and BE.

In terms of BMI, a significant influence on the pushing stage could be shown in univariate (p = 0.047) but not in multivariate analysis (p = 0.062). However, a higher BMI seems to prolong the pushing stage. Assessing the number of spontaneous vaginal deliveries in contrast to operative assisted vaginal deliveries, univariate regression proved a significant influence by the patient´s BMI (p = 0.021) that could not be shown in multivariate analysis. Thus, a higher BMI leads to a higher risk of instrumental assistance in vaginal delivery. On the need for secondary caesarean section instead of spontaneous vaginal delivery, BMI had no significant effect, just as on the neonate´s 1-min Apgar-score, pH and BE.

No significant impact of the neonate´s birth weight on the delivery method could be shown, neither in univariate nor in multivariate regression analysis. Though, the birth weight had a significant influence on the 1-minute Apgar-score in univariate (p = 0.010) and multivariate (p = 0.009) regression analysis, where a higher birth weight resulted in a lower occurrence of a 1-minute Apgar score below 7. Furthermore, the influence on the arterial cord blood pH was significant (p = 0.017 and 0.019). Concluding, a higher birth weight resulted in a lower risk for 1-minute Apgar < 7 and umbilical arterial pH < 7.10. Excluding neonates under the 10^{th} percentile with only 2 children under the 5^{th} percentile, similar results regarding this effect could be shown. Still, univariate regression analysis (n = 217) showed a significant influence of the birth weight on the 1-minute Apgar-score (p = 0.026) as well as on the pH of the umbilical artery (p = 0.010).

On the other end points, the duration of the second stage of labour and BE no significant effect could be found.

Statistical analysis proved the impact of the previous delivery type on the current one. This could be seen comparing spontaneous vaginal delivery with instrumental assisted vaginal delivery in univariate regression (p = 0.018) (but not in multivariate analysis) as well as in comparison to secondary caesarean section (p = 0.001 in univariate and 0.021 in multivariate regression). Moreover, in contrast to the pushing stage, the duration of the expulsive stage was significantly influenced (p = 0.003 in univariate regression). According to these findings, women who needed a caesarean section, emergency caesarean section or instrumental assisted birth in previous deliveries, had a prolonged expulsive stage. An effect on the newborn´s 1-min Apgar-score, arterial cord blood pH and BE could be disproved. Details are provided in Table 9.

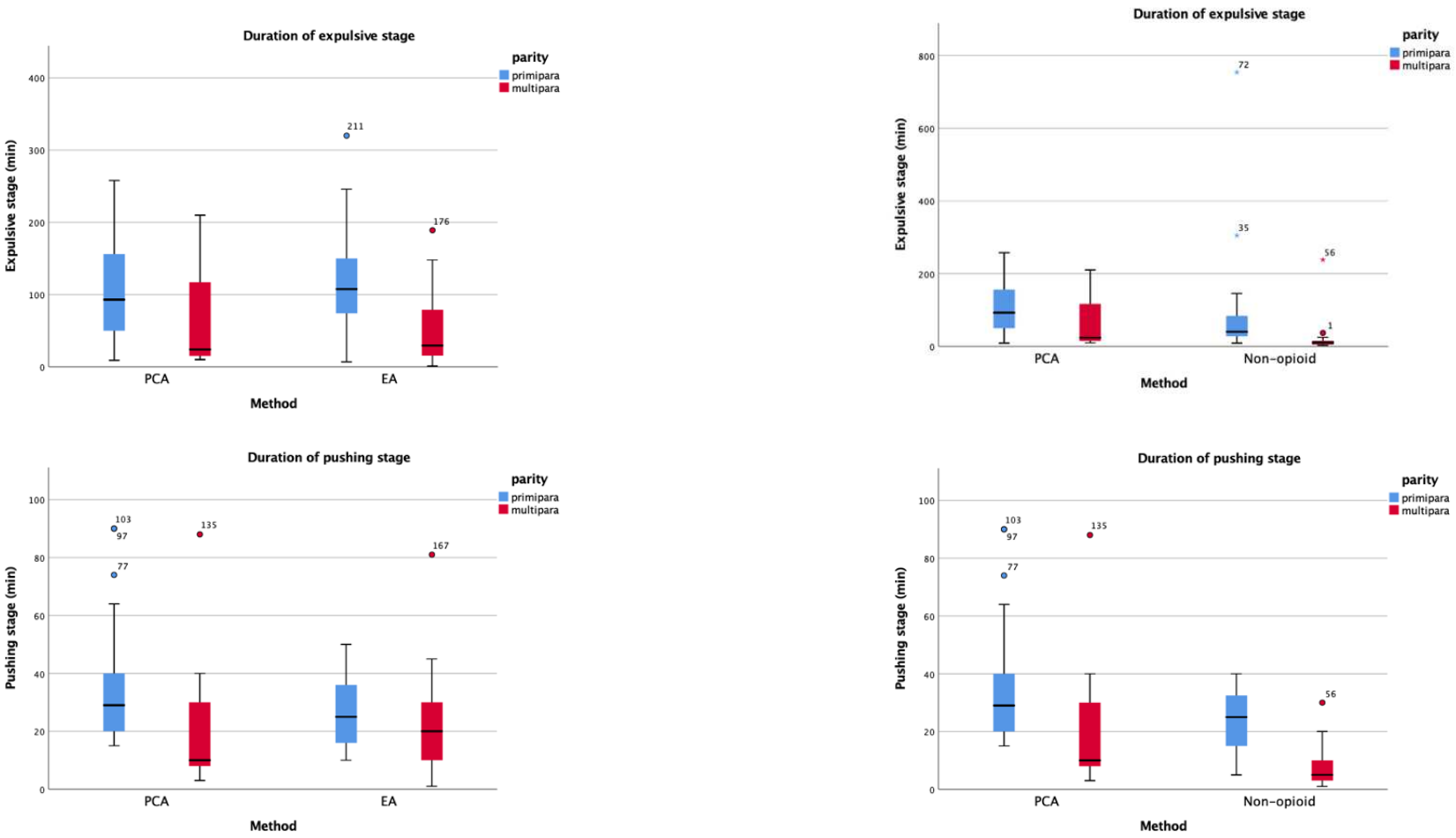

Figure 3: ***Duration of the second stage of labour***

Duration of the expulsive stage (min), PCA vs. EA and PCA vs. non-opioid and duration of the pushing stage (min), PCA vs. EA and PCA vs. non-opioid for primiparas and multiparas.

Table 3: ***Duration of the second stage of labour***

	PCA		EA		Non-opioid		*P* value			
							PCA vs. EA		PCA vs. non-opioid	
Para	1	>1	1	>1	1	>1	1	>1	1	>1
n	41	18	38	16	29	27				
Expulsive stage	105.3 ± 69.3	61.4 ± 71	114.2 ± 67.9	52.6 ± 54.2	85.9 ± 141.1	20.1 ± 44.3	0.459	0.917	0.009	0.001
Pushing stage	33.3 ± 18.8	19.4 ± 20.7	25.7 ± 11.4*	22.8 ± 20.1	23.4 ± 11.6**	7.5 ± 6.4	0.112	0.396	0.041	0.003

Table 3: Duration of the second stage of labour (min), subdivided in expulsive stage and pushing stage. Results given in mean ± SD.

* Data available in 35 of 38 cases

** Data available in 27 of 29 cases

Table 4: *Delivery type*

	PCA		EA		Non-opioid		*P* value			
							PCA vs. EA		PCA vs. non-opioid	
Para	1	>1	1	>1	1	>1	1	>1	1	>1
n	60	20	59	17	40	36				
Spontaneous vaginal	31 (51.7 %)	17 (85 %)	27 (45.8 %)	12 (70.6 %)	26 (65 %)	27 (75 %)				
Operative vaginal	10 (16.7 %)	2 (10 %)	11 (18.6 %)	4 (23.5 %)	3 (7.5 %)	0				
Secondary caesarian section	16 (26.7 %)	1 (5 %)	21 (35.6 %)	1 (5.9 %)	11 (27.5 %)	9 (25 %)				
Emergency caesarian section	3 (5 %)	0	0	0	0	0				
							0.305	0.683	0.279	0.019

Table 4: Delivery type.

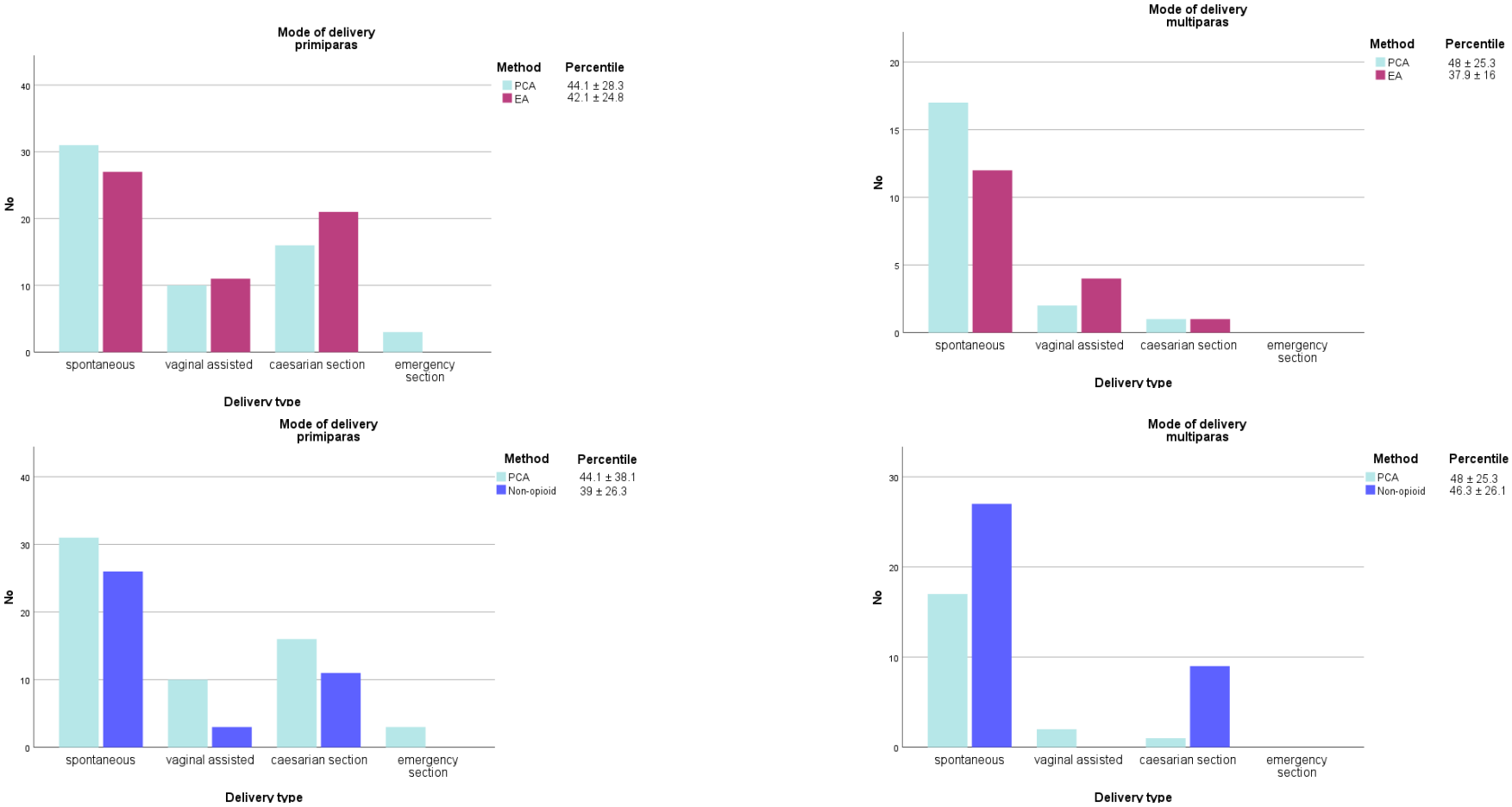

Figure 4: ***Birth mode***

Delivery type (spontaneous vaginal, instrumental assisted vaginal, secondary caesarean section and emergency caesarean section) given in absolute numbers. PCA vs. EA (primiparas, multiparas); PCA vs. non-opioid (primiparas, multiparas). Percentiles of birth weight are given in mean ± SD.

Table 5: *Pathological 1 min Apgar-score, pH and BE*

	PCA		EA		Non-opioid		*P* value			
							PCA vs. EA		PCA vs. non-opioid	
Para	1	>1	1	>1	1	>1	1	>1	1	>1
n	60	20	59	17	39	37				
Apgar 1 min < 7	4 (6.7 %)*	0	1 (1.7%)	0	0	1 (2.7 %)	0.364		0.149	1
pH < 7.10	3 (5 %)	2 (10 %)	1 (1.7%)	0	1 (2.6 %)	0	0.619	0.489	1	0.119
BE < -12 mmol/L	2 (3.3 %)**	1 (5 %)	1 (1.7%)***	1 (5.9%)	1 (2.6 %)****	0	1	1	1	0.351

Table 5: Occurence of Apgar-score 1 minute postnatal less than 7, arterial cord blood pH less than 7.10 and base escess (BE) less than -12 mmol/L. In case of missing data, the number of cases with available data can be found below.

* Data available in 59 of 60 cases

** Data available in 56 of 60 cases

*** Data available in 55 of 59 cases

**** Data available in 38 of 39 cases

Table 6: *1-min Apgar-score*

	PCA		EA		Non-opioid	
Para	1	>1	1	>1	1	>1
n	59	20	59	17	40	36
1-min Apgar						
10	1 (1 .7 %)	3 (15 %)	7 (11.9 %)	2 (11.8 %)	8 (20 %)	5 (13.9 %)
9	30 (50.8 %)	11 (55 %)	26 (44.1 %)	8 (47.1 %)	27 (67.5 %)	24 (66.7 %)
8	20 (33.9 %)	4 (20 %)	19 (32.2 %)	6 (35.3 %)	2 (5 %)	6 (16.7 %)
7	4 (6.8 %)	2 (10 %)	6 (10.2 %)	1 (5.9 %)	3 (7.5 %)	0
6	2 (3.4 %)	0	1 (1.7 %)	0	0	1 (2.8 %)
5	1 (1.7 %)	0	0	0	0	0
4	1 (1.7 %)	0	0	0	0	0

Table 5: Incidence of Apgar-values (4-10) 1 min postnatal.

Table 7: 5-*min Apgar-score*

	PCA		EA		Non-opioid	
Para	1	>1	1	>1	1	>1
n	59	20	59	17	40	36
Apgar 5 min						
10	25 (42.4 %)	10 (50 %)	31 (52.5 %)	10 (58.8 %)	29 (72.5 %)	26 (72.2 %)
9	28 (47.5 %)	8 (40 %)	17 (28.8 %)	6 (35.3 %)	9 (22.5 %)	9 (25 %)
8	4 (6.8 %)	2 (10 %)	10 (16.9 %)	1 (5.9 %)	2 (5 %)	0
7	2 (3.4 %)	0	1 (1.7 %)	0	0	1 (2.8 %)

Table 7: Incidence of Apgar-values (7-10) 5 min postnatal.

Table 8: *10-min Apgar-score*

	PCA		EA		Non-opioid	
Para	1	>1	1	>1	1	>1
n	59	20	59	17	40	36
Apgar 10 min						
10	37 (62.7 %)	18 (90 %)	43 (72.9 %)	15 (88.2 %)	38 (95 %)	30 (83.3 %)
9	20 (33.9 %)	2 (10 %)	15 (25.4 %)	2 (11.8 %)	2 (5 %)	5 (13.9 %)
8	2 (3.4 %)	0	1 (1.7 %)	0	0	1 (2.8 %)

Table 8: Incidence of Apgar-values (8-10) 10 min postnatal.

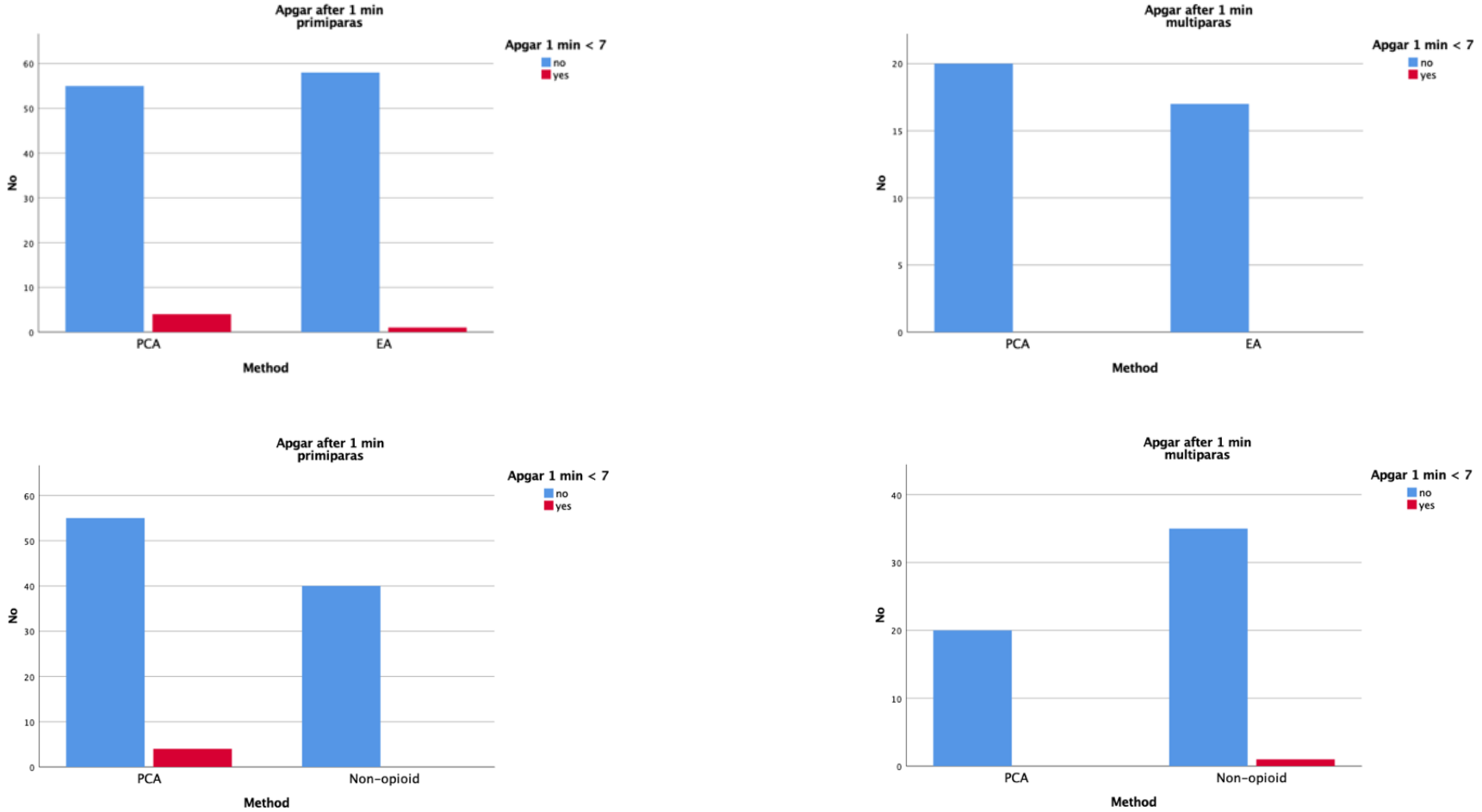

Figure 5: ***Pathological 1-min Apgar***

1-minute-Apgar < 7 given in absolute numbers. PCA vs. EA (primiparas, multiparas); PCA vs. non-opioid (primiparas, multiparas).

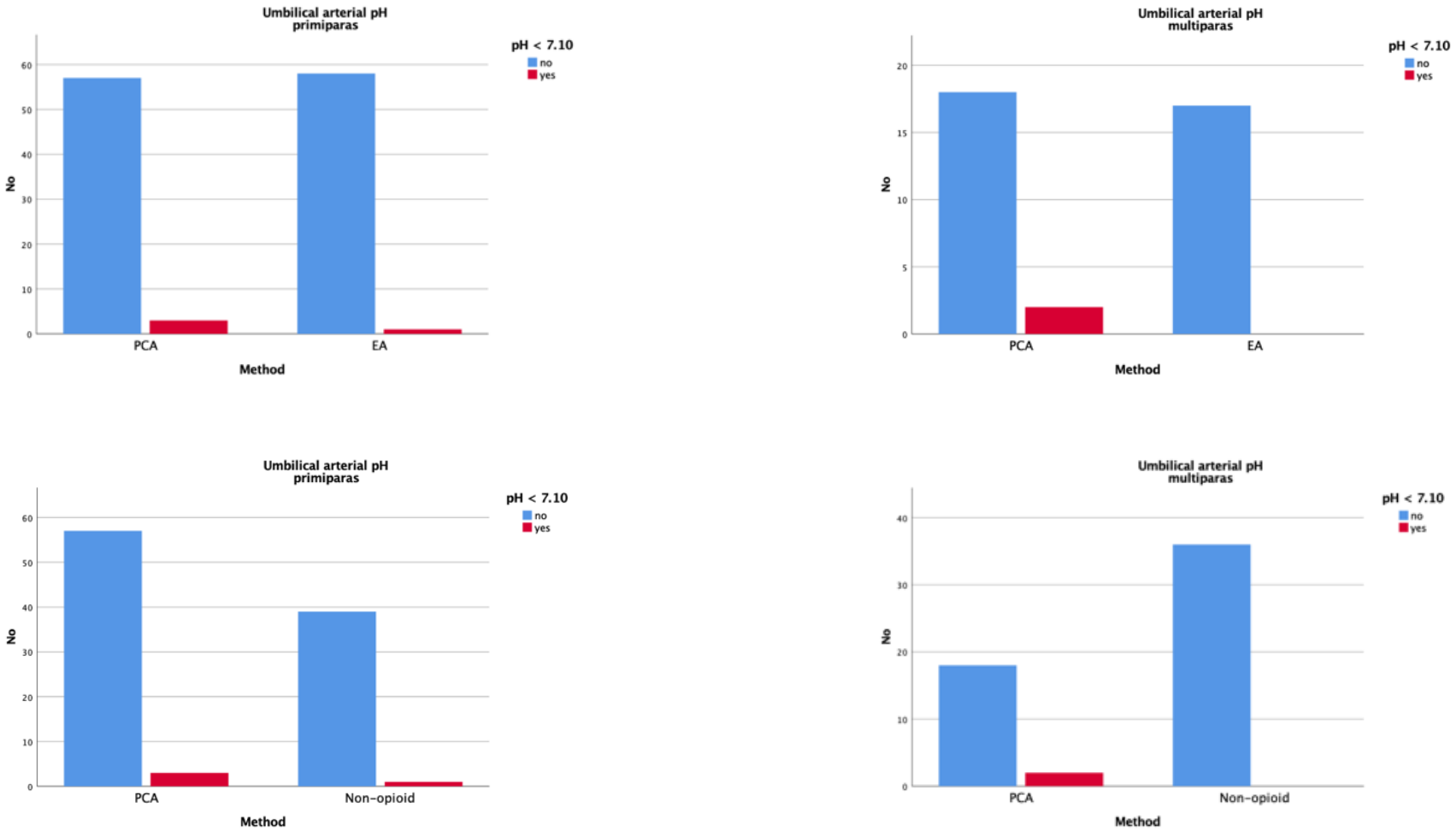

Figure 6: ***Umbilical arterial pH***

Umbilical arterial pH < 7.10 given in absolute numbers. PCA vs. EA (primiparas, multiparas); PCA vs. non-opioid (primiparas, multiparas).

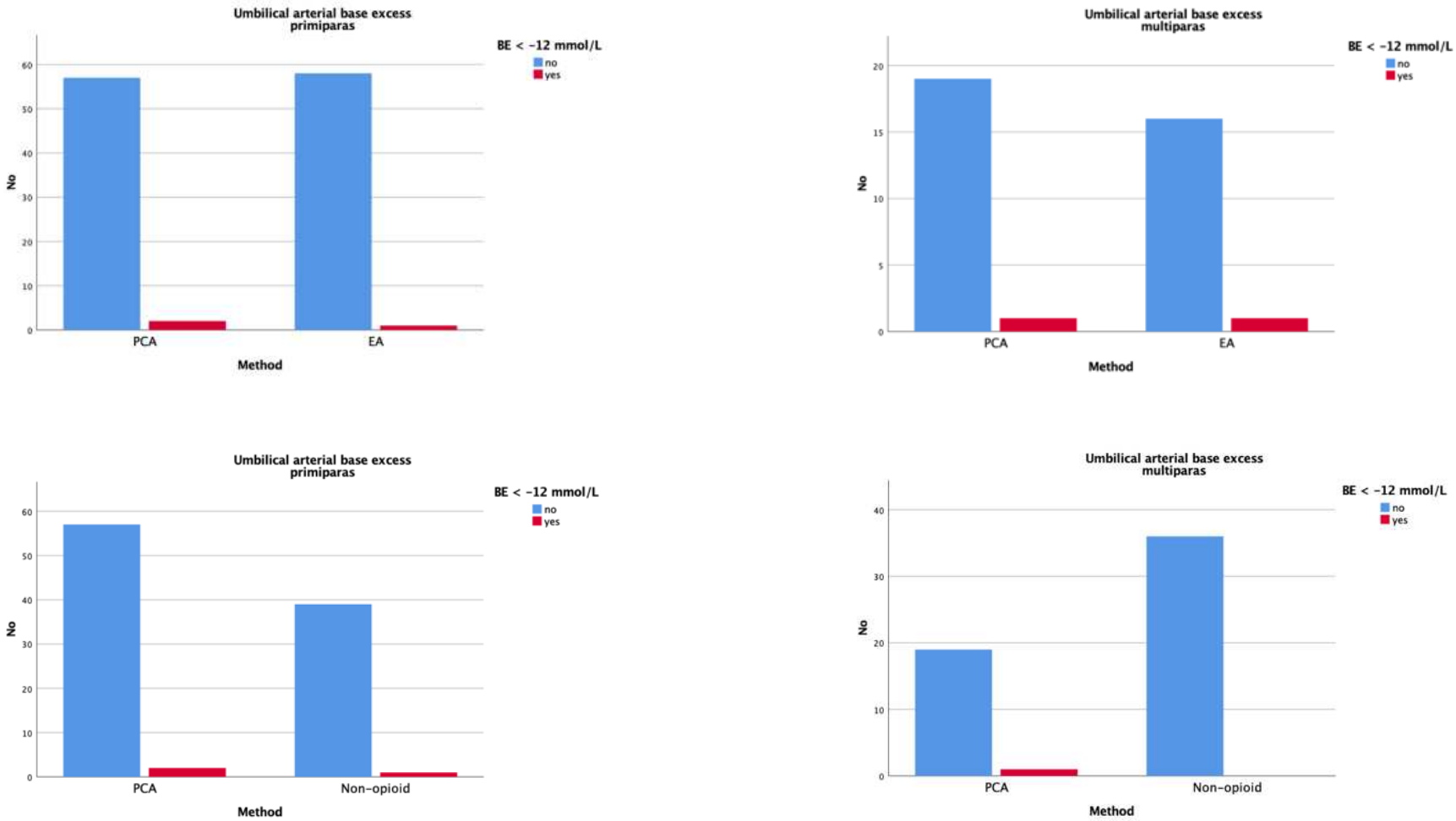

Figure 7: ***Umbilical arterial base excess***

Umbilical arterial BE< -12 mmol/L given in absolute numbers. PCA vs. EA (primiparas, multiparas); PCA vs. non-opioid (primiparas, multiparas).

Table 9: ***Influence of age, BMI, birth weight, previous delivery type and oxytocin on the course of labour and foetal outcome***

		Age		**BMI**		**Birth weight**		**Previous delivery type**		**Oxytocin**	
		Uni	Multi	Uni	Multi	Uni	Multi	Uni	Multi	Uni	Multi
Delivery type	Spontaneous vs. operative vaginal	0.770 0.989 0.919 to 1.064	0.469 1.033* 0.946 to 1.129**	0.021 1.102* 1.015 to 1.196**	0.024 1.108* 1.014 to 1.211**	0.112 0.999* 0.998 to 1**	0.234 0.999* 0.998 to 1**	0.018 2.129* 1.138 to 3.984**	0.111 2.464* 0.814 to 7.459**	0.097 1.960* 0.885 to 4.342**	0.091 2.531* 0.863 to 7.42**
	Spontaneous vs. caesarean section	0.335 1.03 0.97 to 1.095	0.277 1.037* 0.971 to 1.107**	0.135 1.066* 0.98 to 1.16**	0.152 1.067* 0.976 to 1.165**	0.807 1* 0.999 to 1.001**	0.475 1* 0.999 to 1.001**	0.001 2.294* 1.379 to 3.817**	0.021 11.866* 1.45 to 97.142**	0.717 0.894* 0.489 to 1.636**	0.556 0.805* 0.391 to 1.657**
Expulsive stage		0.854 -0.238* -2.796 to 2.319**	0.392 1.146 -1.49 to 3.783	0.309 1.498 -1.399 to 4.395	0.419 1.137 -1.636 to 3.909	0.080 0.031 -0.004 to 0.066	0.064 0.033 -0.002 to 0.067	0.003 16.941 6.189 to 27.693	0.037 14.357 0.913 to 27.802	0.000 53.651 27.951 to 79.351	0.000 57.258 27.581 to 86.935
Pushing stage		0.961 -0.13* -0.529 to 0.504**	0.238 0.308 -0.206 to 0.821	0.047 0.564 0.007 to 1.121	0.062 0.511 -0.026 to 1.047	0.311 0.004 -0.003 to 0.011	0.335 0.003 -0.003 to 0.01	0.009 4.555 1.177 to 7.932	0.224 2.889 -1.831 to 7.608	0.000 10.026 4.767 to 15.285	0.000 10.413 4.652 to 16.174
Apgar 1-min < 7		0.382 0.936* 0.807 to 1.085**	0.238 0.893* 0.739 to 1.078**	0.4 0.87* 0.629 to 1.203**	0.134 0.777* 0.558 to 1.081**	0.01 1.003* 1.001 to 1.005**	0.009 1.004* 1.001 to 1.007**	0.997 0.000 * 0.000 to 0.000**	0.983 0.000* 0.000**	0.316 2.408* 0.432 to 13.411**	0.423 2.298* 0.300 to 17.634**

pH < 7.10	0.836 0.985* 0.852 to 1.139**	0.810 0.98* 0.828 to 1.159**	0.761 0.969* 0.793 to 1.185**	0.540 0.928* 0.730 to 1.179**	0.017 1.002* 1 to 1.004**	0.019 1.003* 1 to 1.005**	0.952 1.032* 0.367 to 2.902**	1 0.045* 0.000**	0.557 1.577* 0.345 to 7.207**	0.756. 1.321* 0.228 to 7.646**
BE < -12 mmol/L	0.498 1.061* 0.894 to 1.260**	0.386 1.087* 0.9 to 1.311**	0.655 1.03* 0.904 to 1.175**	0.527 1.042* 0.917 to 1.185**	0.678 1* 0.997 to 1.002**	0.704 1* 0.997 to 1.002**	0.287 1.634* 0.662 to 4.035**	0.972 34.579	0.316 2.408* 0.432 to 13.411**	0.3 2.963* 0.379 to 23.140**

Univariate (Uni) and multivariate (Multi) ANOVA. Influence of age, BMI, newborn´s birth weight, previous delivery type and administration of oxytocin on delivery type, duration of the expulsive and pushing stage, Apgar-score 1 minute postnatal, umbilical arterial pH and BE. Analgesic method, preexistant hypertension and occurence of preeclampsia, eclampsia and HELLP-syndrome have been included in multivariate regression alaysis additionally. Results given in *P* value, B and 95% CI of B.

* expB

** 95% of expB

Table 10: *Regression analysis of analgesic method*							
		PCA vs. EA		**PCA vs. non-opioid**		**Multi**	
Para		1	>1	1	>1	1	>1
Delivery type	Spontaneous vs. operativ vaginal	0.998 -18.868	0.270 2.833 * 0.445 to 18.042**	0.148 2.796* 0.695 to 11.241**	0.998 19.063	0.223 1.642* 0.74 to 3.645**	0.221 3.384* 0.481 to 23.788**
	Spontaneous vs. caesarean section	0.333 1.507* 0.657 to 3.457**	0.812 0.348* 0.08 to 24.951**	0.675 1.22* 0.482 to 3.085**	exp0.114 0.176 0.02 to 1.52	0.015 2.077* 1.156 to 3.732**	0.042 0.015* 0 to 0.857**
	Spontaneous vs. emergency caesarean section	0.998 -18.868		0.998 18.868		0.589 0.568 * 0.073 to 4.412**	
Expulsive stage		0.566 8.916 -21.863 to 39.695	0.689 -8.826 -53.372 to 35.719	0.450 19.372 -31.463 to 70.206	0.020 41.315 6.718 to 75.912	0.497 9.467 -18.106 to 37.039	0.901 1.147 -17.403 to 19.698
Pushing stage		0.041 -7.603 -14.881 to -0.325	0.635 3.368 -10.933 to 17.669	0.018 9.873 1.773 to 17.972	0.007 11.926 3.358 to 20.494	0.575 -1.271 -5.757 to 3.215	0.037 6.932 0.421 to 13.444
Apgar 1 min < 7		0.204 0.237* 0.026 to 2.187**		0.998 18.582	0.998 -17.648	0.837 1.175* 0.254 to 5.433**	0.849 -2577.132

pH < 7.10		0.34 -1.116* 0.033 to 3.243**	0.998 -19.006	0.54. 2.053* 0.206 to 20.464**	0.998 19.006	0.9533 0.647* 0.165 to 2.545**	0.991 149.283
BE < -12 mmol/L		0.566 0.491* 0.043 to 5.571**	0.906 1.187* 0.069 to 20.539**	0.801 1.368* 0.12 to 15.618**	0.998 18.258	0.950 0.954* 0.218 to 4.177**	0.973 118.753

Univariate and multivariate (Multi)regression analysis. PCA vs. EA and PCA vs. non-opioid. Age, BMI, Birth weight, previous delivery type, administration of oxytocin and preexistant hypertension, occurence of preeclampsia, eclampsia or HELLP-syndrome were included in multivariate regression analysis. Results given in *P* value, B and 95% CI of B.

* expB

** 95% CI of expB

VI. Discussion

The focus on pain relief in labour has increased in the past decades and analgesia as a supportive tool while giving birth has become more accepted and more wanted by parturients [12, 137]. Based on these developments, a selection of sufficient and secure methods is elementary. For this providing, it is of great importance to examine alternatives to the gold standard, i.e., epidural analgesia. In the study presented here, intravenous PCA with remifentanil as a relatively new technique was compared to the most commonly used method, EA. To rule out diverse other influence factors, we included a control group consisting of women without analgesia or with non-opioid analgesia.

In our investigations, we verified the equivalence of remifentanil PCA in terms of the effect on the duration of the second stage of labour compared to EA. The parturients of both groups had similar duration times of both the expulsive and pushing stage. These findings have already been reported by Ismail et al., who neither found a difference in the duration of the second stage of labour in labouring women treated with remifentanil PCA compared to EA [119]. On the other hand, Freeman et al. discovered in a trial including 1414 women a shorter expulsive stage in primiparous women with remifentanil PCA compared to the EA-group [138]. In the latter study, parturients were advised to discontinue self-administration of the PCA during the second stage of labour to avoid neonatal side effects.
Several more or less recent publications describe a prolongation of the second stage of labour by EA in general [12, 59, 139-142]. Also, Cheng et al. reported in their retrospective cohort study including 42268 women, who delivered vaginally with normal neonatal outcomes, a significantly longer second stage in women with EA than in women without EA [143]. Controversially, Anim-Somuah et al disproved in their meta-analysis (including 897 women) a difference in the duration of the second stage of labour as well as of the first stage between EA and no analgesia [62].

Considering the higher utilization of i.v. oxytocin in the EA-group of our study, a prolonged second stage of labour in comparison to the PCA-group could be veiled by the effect of oxytocin on the duration of the expulsive stage. This accelerating effect of oxytocin on the

second stage of labour has also been proved in our study by univariate and multivariate regression analysis.
On the other hand, PCA was applied later in the course of labour than EA. Premature analgesia slows labour, a longer duration of analgesia might cause a corresponding longer duration of the second stage of labour. However, a longer duration of the second stage of labour in the PCA-group was not found in our study and thence, the first question drafted in the *aims and scopes* section can be answered with no – remifentanil does not prolong the second stage of labour.

Compared to the non-opioid-group, we found a prolonged expulsive stage in women treated with PCA. Studies comparing remifentanil with non-opioid analgesia in labour concerning the duration of the second stage of labour are currently not available in the literature. Long-acting opioids are suspected to prolong labour. Zondag et al. conducted a trial including 2074 nulliparous women where a difference in the duration of the second stage of labour between women with non-opioid and women with opioid analgesia during labour could not be found [144]. However, in both groups mean duration was significantly shorter than in parturients who received EA.
The basis of the differences between the non-opioid-group and the PCA-group in study concerning the duration of the second stage of labour remains to be investigated.

When evaluating the second question regarding the mode of delivery, no significant impact of the analgesic method could be proven in our study. Although multiple regression analysis of multiparas showed a significant influence of the type of analgesia on the rate of secondary caesarean section in contrast to spontaneous vaginal delivery, multiple regression including primiparas as well as univariate regression analysis did not bear this influence out. At this point, differences in gestational age, birth age and induction of labour among multiparas, that will be discussed in detail later, have to be considered as well.
Furthermore, we found only a significantly higher rate of secondary caesarean sections in multiparas of the non-opioid-group compared to those of the PCA-group. Apart from this finding, there was no significant difference in the rate of vaginal instrumental deliveries, secondary caesarean sections or emergency caesarean sections neither between the PCA- and the EA-group nor between the PCA- and the non-opioid-group.
Considering the rate of secondary caesarean sections of women with remifentanil PCA and EA, respectively, our results are consistent with those obtained by several authors (in total

1578 women in 9 trials) who reported no difference in the risk for a caesarean section when comparing the two techniques [33, 108, 110, 117-119, 145-147]. In contrast, Lin et al. conducted a trial including 370 primiparas in which they could prove a significantly higher conversion rate of caesarean section in women who received EA in comparison to those with remifentanil PCA [148]. The inclusion of both primiparous and multiparous women might be an explanation for the discrepancy between these findings and our results.
In terms of instrumentally assisted birth, diverse publications (in total 1550 women included in 8 trials) showed, in accordance with our results, neither advantage nor disadvantage of remifentanil PCA in the risk of assisted vaginal delivery compared to EA [33, 108, 110, 117, 145-147].

Referring to the neonatal outcome, our analysis could refute suspicions of remifentanil to have negative effects. Thus, also the third question can be answered with no - there is no negative effect on the neonatal outcome. A significant influence of the analgesic method on Apgar-score after 1 min, umbilical arterial pH and BE was not given in our analysis. There were no Apgar values < 7 after 5 and 10 min. For umbilical arterial pH, previous studies (1245 women in 5 trials) showed lower mean values under remifentanil PCA compared to EA [33, 110, 117, 119, 145]. Though, this was assessed as without clinical relevance for mean values did not drop below 7.10. Moreover, except for the clinical trial of Douma et al., in which the mean was 7.13 [33], mean umbilical arterial pH values varied within the normal range. Further studies confirmed the assumption of remifentanil not affecting umbilical arterial pH [92, 104, 149, 150].
In our analysis, we didn´t find a significant difference in neonate´s 1-minute Apgar score or pH and BE of the umbilical artery when comparing the PCA with the EA and non-opioid-group Respecting umbilical arterial BE, in the literature (75 women in 3 trials), compared to EA a larger mean base deficit under remifentanil PCA is reported [33, 110, 117]. Similar to the results of arterial pH, Douma et al. was the only author of the named trials who described a mean BE under both methods out of normal range (-11.1 under PCA and -8.8 mmol/L under EA) [33]. Consequently, a valid effect of remifentanil PCA on newborn´s BE could not be proven. Other studies shared this view due to the results of their analysis, in which no effect of remifentanil on umbilical arterial BE was given [92, 104, 149, 150].
Lin et al. also investigated Apgar-scores after 1 and 5 min in primiparas, where a significant difference between the remifentanil PCA- and the EA-group could not be determined [148]. Equally, in a randomised trial (including 45 women) by Volmanen et al. comparing

remifentanil PCA to EA, in both groups similar mean values of Apgar after 1 min were found [108]. In total, only one newborn, which was delivered under remifentanil, had a 1-min Apgar-score of 6, the remaining stayed above 8. Balcioglu and colleagues conducted a trial including 60 women receiving different doses of remifentanil during labour [151]. All neonates had Apgar-scores from 8 to 10 after 1, 5 and 10 min.
Concluding, our results of the neonatal outcome conform to those reported in the literature.

Our third question focused on the use of additional opioids. In primiparas of our study population a higher request of additional opioids was documented in those treated with remifentanil PCA than in those with EA. Therefore, the third question has to be answered with yes – parturients with remifentanil PCA do need more additional opioids
However, we did not differ between the time of opioid administration - before or after EA, while in the PCA group all additional opioids where given before the initiation of PCA. In our trial remifentanil PCA was administered significantly later in the course of labour than EA. This could explain the higher rate of additional opioids in the PCA-group.
We performed analysis to ensure that the use of additional opioids does not affect our main outcome parameters. In this analysis, no influence of additional opioids neither on the duration of the second stage of labour nor on the neonatal outcome was given. Furthermore, there was no significant difference concerning the named factors between women who were given additional opioids and those who weren´t, neither in the PCA- nor in the EA-group. This represents another point, why neglect of the higher usage of additional opioids in our PCA-group seems to be acceptable.

The demand for oxytocin was the issue of the sixth question that can´t be answered that easy. Analysis of the augmentation of labour by oxytocin showed in primiparas a significantly lower use in the PCA-group compared to the EA-group. In both groups, oxytocin was given more frequently after the administration of PCA or EA than prior to it. In the EA-group, this difference was significantly larger than in the PCA-group. The latter result might be related to the later application of PCA in primiparas compared to EA. Another explanation might be the contraction-inhibiting effect of remifentanil. An animal study by Nacitarhan et al. could prove a significant decrease in the contractility of myometrial stripes caused by remifentanil in pregnant rats [152].
In contrast to our results, Ismail et al. reported no difference in the use of oxytocin after analgesia between women treated with remifentanil, EA or combined spinal-epidural

analgesia [119]. Concluding results in the literature (1379 women in 6 trials), no evidence for remifentanil PCA to lower the rate of augmented labour by the use of oxytocin in comparison to EA [33, 108, 110, 117, 119, 146] was proven. Moreover, even when considering the fact, that in our study only a difference in primiparas was shown, opposite outcomes in the literature can be found. Thus, Lin et al. published, as an achievement of their clinical trial including 370 primiparas, no difference in the use of oxytocin between remifentanil PCA and EA [148]. The discrepancy between these conclusions and our results concerning primiparas might result from differences in the study populations, e.g. ethnicities.
In contrast to the comparison with EA, compared to women labouring without or only with non-opioid analgesia, in our study, primiparas and multiparas of the PCA-group received significantly more often oxytocin during labour. We relate this to the general extension of labour by opioids [153] and therefore resulting need for augmentation.

Our last question - *does the starting time differ between remifentanil PCA and EA* - can be answered with yes. Primiparas of our study population had a significantly larger cervix opening at the time of administration of PCA than primiparas at the time of administration of EA. As our study design was retrospective and women were not randomised, a possible reason for this difference might be the lack of time for application of EA. PCA needs less time to be applied and started, women who requested analgesia in a further proceeded course of labour were rather recommended PCA.
Freeman et al. determined, that significantly more women randomised to remifentanil PCA in their clinical trial (including 1414 women) requested and received analgesia compared to those randomized to EA [138]. This might be due to the patient´s perception of PCA being less invasive and easily available. However, in the named study, PCA was not applied by anaesthetists. In our hospital, PCA is applied by anaesthetists and hardly less time consuming compared to EA.
As already discussed above, the different time points of the start of analgesia among the two groups are expected to affect the duration of the second stage of labour.

Supplementary, our analysis led to diverse perceptions as secondary outcomes.
Among those, the effect of women´s BMI on the duration of the second stage of labour, though this effect couldn´t be confirmed in multivariate analysis. Moreover, a significant influence of the BMI on the rate of vaginal assisted births instead of spontaneous vaginal delivery was shown. In opposite of our results, Robinson et al. could disprove in a multicentre

trial including 5341 nulliparas an association between maternal BMI and the length of the second stage of labour [154]. However, they also didn´t find an increased risk for caesarean section in primiparous women with a higher BMI. The latter finding conforms to our outcome but not to what has been reported in more recent studies where the risk of caesarean section increases with maternal weight [155-158].
As expected, the impact of neonate´s birth weight on the Apgar after 1 min and the umbilical arterial pH was proven. A lower birth weight was correlated with a higher incidence of 1-minute Apgar < 7 and umbilical arterial pH < 7.10. A higher risk for a 5-minute Apgar < 7 correlating with a low birth weight has already been described by Temerinac et al. in a retrospective analysis of 5177 singleton deliveries [159]. Thus, they did not find a correlation between the birth weight and neonate´s umbilical arterial pH or BE.
Concerning the delivery type of preceding birth in multiparas, a significant influence on the current birth mode as well as on the duration of the expulsive but not on the pushing stage was determined. These findings have also been expected.

In our study population, no case of severe maternal apnoea was documented. However, we did not compare the mean maternal oxygen saturation between different groups. The higher number of apnoea in parturients with remifentanil PCA in the randomised study conducted by Stocki et al. might be a result of the chosen PCA regime. While our boluses contained 20 µg remifentanil with a lockout time of 4 min, Stocki et al used boluses of 20-60 µg up to every 2 min [110].

The study presented here offers some limitations.
First of all, the study was designed retrospectively without randomisation which leads to a vulnerability of selection bias. Besides, the group size was limited by the PCA-group, for the utilization of remifentanil PCA was just at its beginning in the university hospital that was used for data collection.
Severe differences in patient´s characteristics among multiparas of the three groups imply weaknesses of the reported study. Thus, considering multiparas, the mean gestational age was significantly higher in the PCA-group when compared to both other groups. Also, the newborn´s birth weight of multiparas was significantly higher in the PCA-group than in the EA-group. This must be taken into account, as birth weight affects neonatal outcome. Even if in our population unconfirmed, the baby´s birth weight also affects the duration of the second stage of labour [160].

The rate of women requiring induction of labour also differed among multiparas of the PCA- and the non-opioid-group and was significantly lower in the latter. There are studies that prove a higher request for pharmacological pain relief after induction of labour [161-163].

As we obtained data from a metropolitan university hospital with a comparatively high rate of high-risk pregnancies, our results might be distorted and not suitable for broad generalisation.

Furthermore, some aspects have not been considered in our analysis.
We did not perform an objective evaluation of women´s acceptance of PCA. Though, other studies investigated women´s satisfaction with pain relief using remifentanil PCA compared to EA [164].
Another point is the practicability and the expenditure of time. A second vein catheter has to be placed by the anaesthesist and in many hospitals, the PCA can´t be used whole day.
Also, the comparably complex safety measurements requested by PCA may play a role – especially in smaller clinics. These include the continuous presence of a midwife in the delivery room during the whole labour. A continuous pulse oximetry and a capnography are requested as well.
These points should be considered in further investigations.

VII. Conclusion

The results presented here approve remifentanil patient-controlled analgesia to be a valuable and, most importantly, secure alternative to epidural analgesia during labour. No negative effect could be shown, neither on the mode of delivery nor on the neonatal outcome when compared to EA. A prolongation of the second stage of labour was disproved as well.
These findings might facilitate the management of labour pain and contribute to clearing confusion in the literature.
When EA is contraindicated or not welcomed by the parturient, remifentanil PCA can provide sufficient and safe analgesia.
Larger, prospective and randomised studies are needed to confirm our data.

VIII. References

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