Programmed Intermittent Epidural Bolus (PIEB) versus Patient Controlled Epidural Analgesia (PCEA) for maintenance of labour analgesia:

A two-centre, double-blind, randomized study.

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Running head: PIEB for labour analgesia.

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Conflicts of interest:

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Summary

After initiation of labour analgesia using either a CSE or an epidural-based technique, labour analgesia must be maintained throughout the entire duration of labour. A novel technique for maintenance is Programmed Intermittent Epidural Bolus (PIEB). Recent meta-analyses have demonstrated superiority regarding pain relief, motor block and patient satisfaction in comparison to continuous infusion techniques with or without PCEA. However, many institutions worldwide still use PCEA only (without a background infusion). A comparative study between PCEA only and PIEB is not yet performed as far as we know. A prospective, 2-center, randomized, double-blind, controlled trial was designed to compare PIEB+PCEA with PCEA alone without background infusion. The primary outcome parameter was breakthrough pain. The secondary outcome parameters were incidence of motor blockade, pain scores, patient satisfaction, local anesthetic consumption and obstetric and neonatal outcomes. Hundred and thirty nulliparous women were randomized either to the PCEA group or to the PIEB group. The patients in the PCEA group had significantly more breakthrough pain compared to the PIEB group (63% vs 11%). There was also a significant difference in motor block between both groups, 12% in the PCEA group vs 2% in the PIEB group. There were no differences in patient satisfaction scores or obstetric or neonatal outcomes. The PIEB group also had a statistically significant increase in local anaesthetic consumption with fewer PCEA boluses. If we compare PIEB to PCEA in nulliparous women for maintenance of analgesia during labour, PIEB decreases breakthrough pain and motor block without affecting patient satisfaction and obstetric or neonatal outcome. Therefore, we suggest PIEB should be the preferred technique of choice for maintenance of labour analgesia.

Introduction

Neuraxial labour analgesia is increasingly used worldwide at the expense of parenteral opioid analgesia, despite the latter still being popular. [1] Following initiation of analgesia using either combined spinal epidural (CSE) or conventional epidural analgesia, maintenance of analgesia must be provided until delivery. Typically, maintenance can be achieved by manual intermittent boluses, continuous epidural analgesia (CEI), patient controlled epidural analgesia (PCEA) or a combination of those techniques. [2] Intermittent boluses and PCEA have been shown to reduce local anaesthetic consumption, reduce breakthrough pain (and anaesthetist interventions) and reduce motor block when compared to CEI. [3] In recent years programmed intermittent epidural bolus (PIEB) analgesia has been introduced in clinical practice for analgesia maintenance during labour. [4]

Since the first publication of PIEB, several studies have compared PIEB with CEI (with or without PCEA). [4,5,6] When compared to CEI, PIEB seems to be a promising technique for labour analgesia with better or equal pain relief with less local anaesthetic consumption, less and later PCEA boluses, less motor block, lower incidence of instrumental vaginal delivery, better maternal satisfaction scores and less anaesthetist interventions. [4,7] In many institutions, however, PCEA with no or a very small background infusion is used to maintain adequate analgesia. [8-10] Currently no study has been published which compares PIEB with conventional PCEA without a background infusion.

In this prospective, randomized, double-blind, controlled study, pain scores, satisfaction and motor block were compared in women who received PIEB or PCEA only for maintenance of labor analgesia. The primary outcome variable was breakthrough pain. Secondary outcome variables include incidence of motor blockade, local anaesthetic consumption, requested and received PCEA boluses, patient satisfaction, occurrence of complications, obstetric outcome and fetal and neonatal outcome. Our hypothesis was that PIEB would result in less breakthrough pain requiring less anaesthetist interventions.

Methods

The present study was registered at the Belgian federal agency for medicines and health products and registered with number EudraCT 2015-004600-30 (21 Jan 2016). Ethical committee approval was requested in both participating institutions and received at xxxx (ZNA) and 16 Jan 2016 (UZLeuven).

Between February 1st 2016 and February 28th 2017, ASA I and II, nulliparous, term women with singleton pregnancies in active labour with cervical dilatation <7cm were screened to participate in the study. Patients were excluded from study participation if they were ASA III or IV, had known allergies to the administered drugs, had a contraindication to neuraxial anaesthesia, were <18 years old and did not understand Dutch. If patients requested neuraxial pain relief and if the baseline visual analogue scale (VAS, 0 = no pain and 100 = worst imaginable pain) score for pain was >30 mm, parturients were approached to participate in the study. Following oral and written information, patients were included in the study provided written informed consent was obtained.

Before labour analgesia was initiated, an IV line was placed and 500 mL Ringer's lactate was administered. Labour analgesia was established using a single interspace CSE technique at the L3-L4 or L4-L5 lumbar interspace. To identify the epidural space, an 18G Tuohy needle was inserted and a loss of resistance to saline technique was used. Upon identification of the epidural space, a 27G pencil point spinal needle was inserted through the Tuohy needle to perforate the dura. All parturients received intrathecally 4mL of ropivacaine 0.120% and sufentanil 0.75 mcg/mL. The spinal needle was removed and a multi-orifice epidural catheter was inserted 4 cm into the epidural space.

Parturients were randomized to two study groups using a computer-generated list and sealed envelloppes which were opened by an anaesthetist not involved in data collection. In the PCEA only group analgesia was maintained using PCEA without a background infusion set at 5 mL bolus with a lock-out of 12 minutes. In the PIEB group analgesia was maintained using an hourly programmed bolus of 10 mL supplemented by PCEA boluses of 5 mL with a lock-out of 20'. The hourly bolus was administered for the first time 30' after initiation of the PIEB pump. In both groups, the pump was initiated 15' after the intrathecal injection was completed and if VAS scores were <20 mm. If VAS scores were >20 mm patients were excluded from the study. The total epidural hourly maintenance volume that could be given was 25 mL in both groups. Patients and study investigators were blinded to group allocation by covering the PCEA pump. The pump was programmed by an anaesthetist not involved in data collection.

The primary outcome parameter was the occurrence of breakthrough pain. Breakthrough pain was defined as a VAS score >30 mm for which the parturient requested additional analgesia after at least 1 PCEA bolus was administered. If breakthrough pain occurred the VAS score was noted and an additional epidural top up of 8 mL of the same local anaesthetic solution was administered. The VAS score was recorded 20 minutes later and if the VAS score remained >30 mm an additional top-up was given. If 20' later the VAS score was still >30 mm, patients were excluded from the study and the epidural catheter was considered to be failing and a new epidural catheter was sited. VAS scores were recorded every 5' for 30' and then every 15' for a further 30' and then every hour until delivery of the baby. The modified Bromage score (6-point scale) was recorded every hour as well as maternal heart rate and non-invasive blood pressure. A straight leg test was performed at full cervical dilatation: parturients had to stretch their both legs separately for 45" with the eyes closed and lift them to 45 degrees. Parturients also had to perform a knee bend at full cervical dilation in which they had to perform an unassisted bed through the knees. Side effects, occurring during labour and after delivery, were recorded.

Baseline demographic data and obstetric data were recorded as well as fetal, neonatal and obstetric outcome. Duration of labour, duration of second stage labour, mode of delivery, Apgar scores, umbilical artery blood gasses and neonatal weight were noted. Maternal satisfaction was recorded 1 hour and 24 hours after delivery using a VAS score for satisfaction (0 = completely unsatisfied and 100 = extremely satisfied).

Power analysis and Statistics.

Power calculation is based on the primary outcome variable breakthrough pain. Based on the available literature, breakthrough pain is expected in the PCEA only group in at least 25% of parturients. [11] With PIEB, it was expected that breakthrough pain would be reduced to approximately 5% or less. [12] To guarantee a power of 80% with statistical significance set at a level of 0.05, 58 patients were required in each group. To account for drop-outs 65 patients per group were randomized.

A binary logistic regression with a logit link function was used for the analysis of the primary outcome. In a univariable logistic regression, the indicator variable for breakthrough pain is regressed on the treatment conditions. In addition, a multivariable model is tested where the indicator variable for breakthrough pain is regressed on the treatment conditions, after controlling for the neonatal weight. This to ensure that the found effect is not due to differences in neonatal weight.

A Fisher's Exact test was used for the variables were the proportion of patients was compared between the PIEB and PCEA group (e.g., Mode of delivery). Next to the observed frequencies, the difference in proportion and its corresponding confidence interval (CI) based on a normal approximation is given. A Mann-Whitney U test was used for the variables that were measured on the ordinal or ratio level (e.g., dose, time to delivery). The Area under the Curve (AUC) with its corresponding 95% confidence interval is used as a measure of effect size.

Bromage score has theoretically 6 levels, but in the data most patients fell in category 4, 5 or 6. A binary variable was created where patients received a 1 when they had Bromage score of 4 or lower, and 0 if a patient had a Bromage score of 5 or higher. A logistic regression model for repeated measures was used to evaluate the binary Bromage score. This model contained the main effect of group (PIEB vs. PCEA) and a random patient intercept.

A linear model for repeated measures is used to the compare the evolution over time for VAS pain. Only the measurement moments for the first 7 hours are used. After 7 hours, the number of patients is too low in order to have meaningful parameter estimates. The mean difference (with 95% CI) between both conditions and across all measurement moments is estimated. Further, the interaction between measurement moment and condition is tested to verify if the evolution over time differs between both groups.

All analyses were performed using R version 3.3.3 (2017-03-06) in R studio.

Results.

The study started on February 1st 2016 and was finalized on February 27th 2017. In figure 1 a CONSORT overview of recruitment and patient inclusion is provided. A total of 149 patients were screened. Thirteen patients did not meet the inclusion criteria and 6 patients refused participation. The 130 included parturients were randomized to two groups with 65 patients in each group. In the PCEA group, 4 patients were excluded because of epidural catheter failure or protocol violation. In the PIEB group, 1 patient was excluded due to a failed epidural catheter.

No differences in patient demographics were identified between the groups and baseline obstetric data were similar between the PIEB and PCEA groups (TABLE 1). Breakthrough pain was significantly more frequent in the PCEA group (11% in the PIEB versus 62% in the PCEA group, $p < 0.001$) (Table 2, FIGURE 2). Pain scores at request of epidural analgesia were similar between the two groups (PIEB 7.95 ± 1.25 versus PCEA 8.97 ± 2.05). During the first two hours of analgesia, pain scores were similar in both groups. From 2 hours after the initial spinal injection, VAS pain scores were consistently lower ($p < 0.001$) in the PIEB group (FIGURE 3). Parturients in the PIEB-group requested and received less PCEA top-ups then parturients in the PCEA-group (Table 2). Patient satisfaction was similar between the two groups 1 and 24 hours after delivery (Table 2).

Significantly more motor block developed in the PCEA-group. In the PCEA-group 8 women developed a Bromage score of 4 or less (13%) at least once throughout labour and delivery versus only 1 woman in the PIEB-group (2%) ($p=0.033$) (Table 2). Although motor block was more frequent in the PCEA-group, local anaesthetic consumption was significantly lower in the PCEA-group (41.6+-24.5 mL in the PCEA-group versus 63.0+-26.9 mL in the PIEB-group, $p<0.001$) (Table 2).

Obstetric outcome and neonatal outcomes were similar between the two groups (Table 3).

Discussion.

Many different strategies to maintain analgesia during the entire duration of labour exist: physician or midwifery administered manual intermittent top-ups, continuous epidural infusions (with or without PCEA) and PCEA with or without a background infusion. Several studies and meta-analysis have clearly established that PCEA is superior to continuous epidural infusions to maintain analgesia. [3] Less motor block, less local anesthetic consumption and higher patient satisfaction with less breakthrough pain have been reported with PCEA. [3]

For more then a decade, PIEB has been introduced into clinical practice. [5] After initiation of analgesia by a CSE or epidural technique, a programmed bolus is given automatically through the epidural catheter following preset intervals by the epidural pump. Patient initiated epidural boluses (PCEA) can supplement the automated bolus. PIEB has been compared with CEI with or without PCEA in several well-designed prospective trials. [4-7] In the PIEB treatment groups, patient satisfaction and quality of analgesia was superior and the incidence of motor block lower compared to continuous infusions supplemented with PCEA or to PCEA supplemented with a background infusion (REF).

In many institutions, however, PCEA is used without a background infusion or with a very low volume continuous background infusion. [8-10] The present trial is, to our knowledge, the first study comparing directly PCEA *without* a background infusion to PIEB. The results of the present study demonstrate that PIEB analgesia is superior to conventional PCEA without a background epidural infusion. Under the conditions of the present study, PIEB produced less breakthrough pain, lower pain scores and less motor block without an increase in side-effects. Although motor block was reduced with PIEB, local anesthetic consumption was increased. The overall patient satisfaction was similar.

PCEA alone is not the standard modality of maintenance of labour analgesia in many institutions. Internationally there is no consensus that PCEA alone should be the modality of choice. Halpern and Carvalho compared 7 randomized clinical trials on PCEA with and without background infusions. [10] Although lower consumption of local anesthetic was reported in women who received PCEA alone, none of the other outcomes (maternal analgesia, maternal satisfaction, clinician workload, unscheduled clinician interventions, motor block) were significantly better in subjects who received PCEA without the basal infusion.

Despite the lack of consensus, PCEA alone is indeed a modality that is used in a significant number of institutions. Heesen et al. performed a meta-analysis and concluded that PCEA alone and PCEA with a background infusion

resulted in similar outcomes. [8] Haydon et al. concluded superiority from PCEA alone. [13] Matsoka et al. concluded that PCEA alone resulted in more breakthrough pain but less local anesthetic consumption. [14]

Many experts avoid a high background infusion because they realistically fear that this will increase side-effects such as motor block, especially in prolonged labours. Therefore, because PIEB shows a clear benefit regarding motor block, but always compared to studies with CEI [7] , we wanted to investigate if PIEB can demonstrate the same accountable difference in motor block when compared to PCEA alone without a background infusion which is a major contributing factor of peripartum motor block. Because motor block is more pronounced in long labours and most likely more problematic in nulliparous women, only nulliparous parturients were included in the study.

We indeed could show a reduced incidence of motor block in PIEB treated women as compared to PCEA treated parturients, despite higher local anesthetic consumption. With PIEB a higher injection pressure is generated when a bolus is administered and this results in better and more uniform spread as compared to continuous infusions. Capogna et al. have shown that PIEB results in a more uniform diffusion and a greater spread of the analgesic solution within the epidural space compared to continuous infusion, which contributes to a better quality of the neuraxial block. [7] With a continuous infusion, the local anaesthetic is continuously infused around a very small group of nerves and gradually over time the LA will penetrate the entire nerve also blocking the larger and deeper located motor fibers. With the more uniform spread with PIEB, a large volume spreads in the epidural space over many more dermatomes, blocking the nerves over several dermatomes, but there is gradual decrease in LA concentrations around the nerves before a new bolus is given. Hence, it is possible to only block the sensory fibers depending on the actual dose and concentration used. This explains why with PIEB less motor block appears compared to CEI. We hypothesize that this mechanism is also present in our study: the small, repetitive boluses in the PCEA group gradually increase the local anaesthetic concentration in the nerves of a small number of dermatomes eventually blocking motor fibers, especially when repetitive PCVEA boluses are administered. In contrast, in the PIEB group due to the above described mechanism, high neural concentration around motor fibers are never reached.

Currently, an ongoing discussion is what the effect is of high injection pressures. Klumpner et al. demonstrated in a laboratory, in vitro study that higher injection speed creates larger injection pressures. [15] Mowat et al. demonstrated in a porcine model that higher injection pressures give better spread of epidurally administered dye [16] This was confirmed in a very small porcine cadaveric study by Oliver et al. [17] PIEB boluses can vary in their

injection speed. There are different pumps on the market with different injection speeds. The injection speed of a PIEB bolus is clearly bigger than a continuous infusion and could be bigger than the speed of a PCEA bolus as well. In our study the speed of injection of the PIEB bolus was 500 mL/hour far exceeding that of the injection speed of a PCEA bolus. A recent study by Lange et al. in 2018 could not confirm the findings that high injection pressure are essential in PIEB. [18] These authors compared different injection speeds of local anaesthetics and could not find any difference in analgesia or intermittent top-ups.

PIEB produces better analgesia most likely because of the improved local anesthetic spread in the epidural space as a result of the automated high-volume hourly bolus. In several studies, it has been shown that more dermatomes are blocked and that especially the sacral dermatomes can be blocked, resulting in superior analgesia, especially during second stage labour. [19] Most PCEA regimens usually have lower bolus volumes than current-in-practice PIEB volumes. Based on current literature the optimal PIEB volume seems to be a minimal volume of 10mL to guarantee optimal spread. [20]

In both study groups a similar maximal hourly local anesthetic consumption could be delivered. Even though the patients had the possibility of having the same amount of LA, significantly less LA was used in the PCEA group. (table 2) We hypothesize this is due to the fact that in the PCEA group, women tend to wait to press the PCEA button until contractions become painful, whereas in the PIEB group, LA is given at pre-fixed intervals. Hence, actually in the PIEB group women receive supratherapeutic LA doses. This might explain the higher satisfaction scores often reported with PIEB as well as the reduced incidence of breakthrough pain. After initial relieve of labour pain, women can relax and even fall asleep. The settings of PIEB will prevent breakthrough pain from occurring, whereas with PCEA women will always have to maintain their LA themselves. It gives them more selfcontrol, but when they don't use the PCEA button early when contractions become painful again, real breakthrough will occur. And when real breakthrough pain occurs, it usually takes some time before women become pain-free again.

The present study can be criticized because of the very high incidence of breakthrough pain in the control group. The definition of breakthrough pain is much more strict in the present study (VAS of 3 or more) as opposed to 4 or higher reported in many studies. A second explanation for the high incidence of breakthrough pain is that we on an hourly basis actively asked if women had breakthrough pain, whilst this is often not actively questioned in many other studies.

So many women, although not requesting spontaneously an epidural top-up, when questioned and with a VAS of 3 or more some women requested a bolus. The latter was categorized as breakthrough pain. An additional explanation is of course that analgesia with PCEA might be inferior because of reduced epidural spread and less sacral spread.

In our study, despite significantly more breakthrough pain scores in the PCEA group, maternal satisfaction is similar in both groups. This is due to the fact that when breakthrough pain occurred, this was immediately treated accordingly the protocol, t.i. the administration of a PCEA bolus or a manual top-up if PCEA was insufficient of the same local anaesthetic solution. Although we could keep the women satisfied, there was a significant difference in workload by the anaesthesiologist who did the follow-up between the two groups. In the PCEA group there was a much higher anaesthetist intervention rate than in the PÌEB group.

A major limitation of the present study is that large volume PIEB (ie 10 mL) is compared to conventional volume PCEA (5 mL). We did this because we wanted to compare currently in practice PIEB to currently in practice PCEA. We tried to compensate this by setting the hourly possible consumption the same in both groups. Still we see that in the PCEA group the consumption of LA is much lower than in the PIEB group. Although we think that PIEB gives better pain relieve because of better spread and preemptive analgesia, the fact that the volume of PCEA was lower, could also contribute to lower spread and therefore higher pain scores. Therefore a study that compares high volume PCEA to high volume PIEB could maybe give an answer to this question.

Recently, efforts are made to refine the optimal settings for PIEB bolus volume, time intervals and frequency of boluses as well as optimal concentration of the local anaesthetic solution used, with the hope to further improve safety, efficacy and patient satisfaction in the future. [20,21] In our study we used Ropivacaine 0,12% with sufentanil, because at that time this seemed a good solution. Recent studies however have shown that the optimal concentration could be lower, t.i. 0,1%, and this could reduce motor block even further.

Conclusion.

Under the conditions of the present trial, PIEB+PCEA is superior to PCEA alone (without background infusion). It improves the quality of analgesia and produces less motor block despite an increased local anaesthetic consumption.

Further study is required comparing PCEA alone and PIEB+PCEA in which the PIEB bolus is of a similar volume as the PCEA bolus.

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TABLES.

Table 1: Demographic and baseline obstetric data in parturients in the PIEB- and PCEA-groups. Data are presented as a mean (standard deviation). $P < 0.05$ is statistically significant. NS: Not Significant.

	PIEB	**PCEA**	**Significance**
Age (y)	28.4 (3.6)	27.9 (4.3)	NS
Weight (kg)	81.2 (14.3)	81.6 (14.3)	NS
Height (cm)	165.6 (6.8)	165.0 (6.0)	NS
Gestational Age (weeks)	39.2 (1.6)	39.2 (1.2)	NS
Cervical Dilation (cm)	4.0 (1.1)	4.1 (1.3)	NS

Table 2: Incidence of breakthrough pain, requested and received PCEA top-ups, patient satisfaction at 24 hours, local anesthetic consumption and motor block in parturients in the PIEB- and PCEA-groups. Data are presented as a mean (standard deviation) or % of group total. $P < 0.05$ is statistically significant. NS: Not Significant.

	PIEB	**PCEA**	**Significance**
Breakthrough pain (%)	11	62	< 0.001
Requested PCEA bolus	4.7 (6.5)	11.8 (11.7)	< 0.001
Received PCEA bolus	1.6 (1.7)	7.2 (4.8)	< 0.001

VAS Patient Satisfaction at 24 hours (mm)	95.6 (0.7)	94.2 (1.3)	NS
Incidence of Bromage 4 or less (%)	2	13	O.033
Total Local anesthetic consumption (mL)	63.0 (26.9)	41.6 (24.5)	< 0.001

Table 3: Obstetric outcome and neonatal outcome in the PIEB- and PCEA-groups. Data are presented as a mean (standard deviation) or % of group total. $P < 0.05$ is statistically significant. NS: Not significant.

	PIEB	**PCEA**	**Significance**
Duration of labor (minutes)	334 (141)	328 (161)	NS
Cesarean delivery (%)	25	18	NS
Neonatal weight (g)	3493 (491)	3318 (348)	NS
Apgar <7 at 1 minutes (%)	8	2	NS
Apgar <7 at 5 minutes (%)	8	2	NS
Apgar <7 at 10 minutes (%)	0	0	NS
Umbilical artery pH	7.23 (0.07)	7.25 (0.07)	NS

Legends to Figures.

Figure 1: CONSORT diagram describing screening, recruitment, inclusion, randomization and analysis of patients in the study

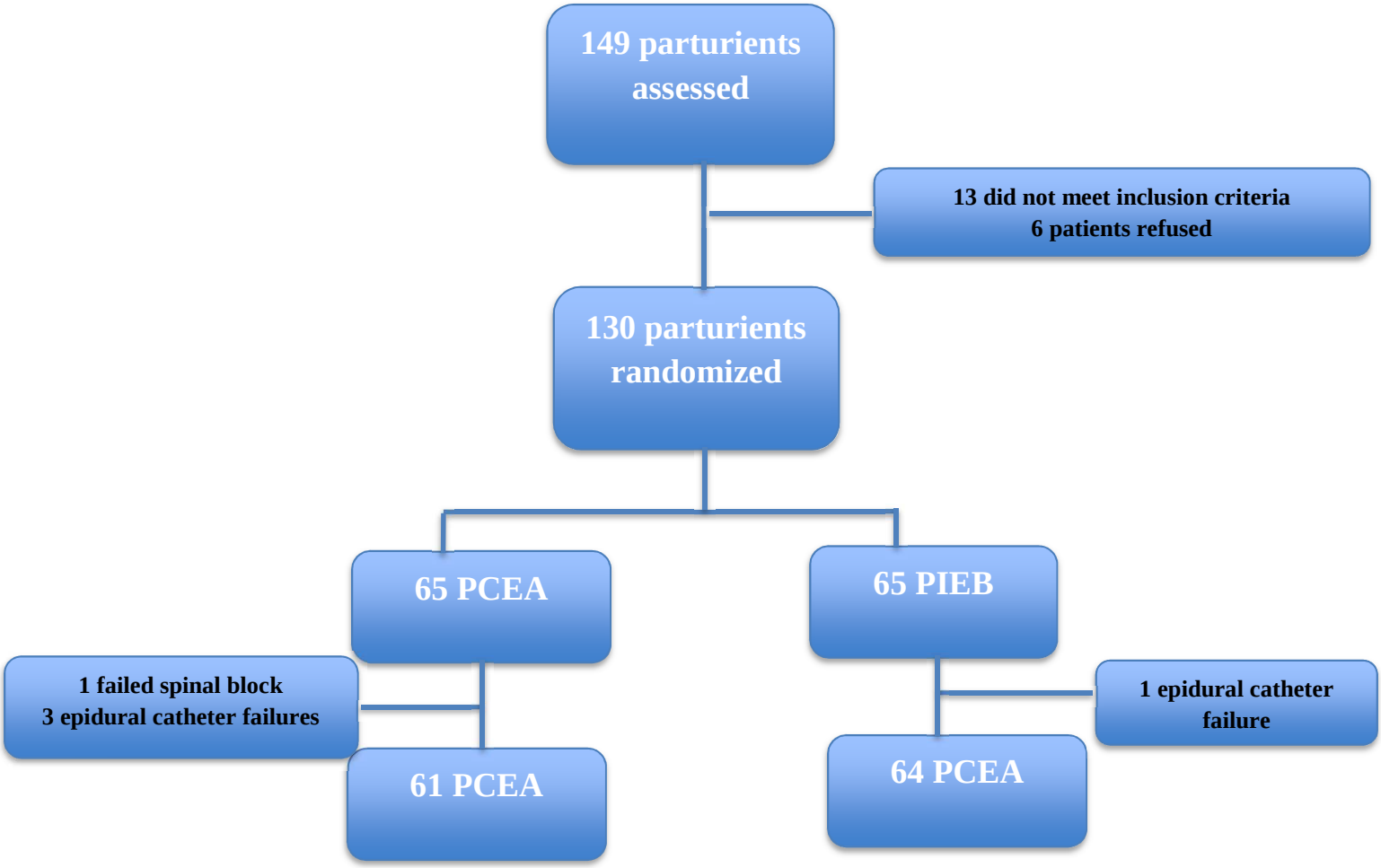


Figure 2: The incidence of breakthrough pain in both the PCEA- and PIEB-groups.

Breaktrough pain	PCEA	PIEB
YES	39/62 (63%)	7/64 (11%)

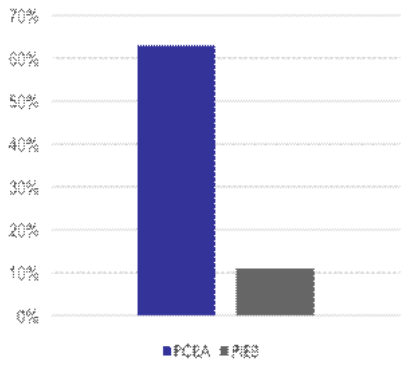


Figure 3: VAS scores for pain on scale from 0-10 in the PCEA- and PIEB groups over time.

1. Observed information of VAS

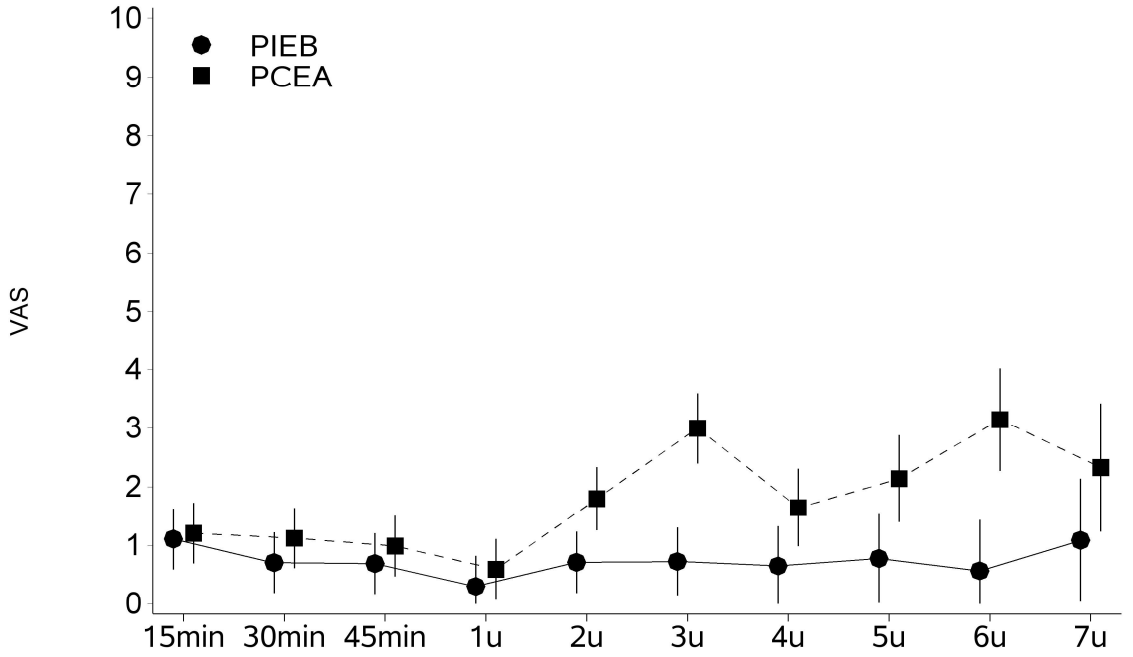
time	group	N	Mean VAS	SD
0	PIEB	64	8.0	1.3
0	PCEA	64	8.7	7.9
15min	PIEB	64	1.1	1.4
15min	PCEA	65	1.2	2.1
30min	PIEB	64	0.7	1.4
30min	PCEA	65	1.1	2.2
45min	PIEB	64	0.7	1.4
45min	PCEA	64	1.0	1.9
1u	PIEB	64	0.3	1.0
1u	PCEA	64	0.6	1.3
2u	PIEB	63	0.7	1.6
2u	PCEA	60	1.8	2.2
3u	PIEB	51	0.7	1.5
3u	PCEA	48	2.9	5.4
4u	PIEB	37	0.6	1.1
4u	PCEA	39	1.5	2.1
5u	PIEB	29	0.7	1.3
5u	PCEA	31	2.0	2.8
6u	PIEB	22	0.5	0.7
6u	PCEA	22	2.9	2.8
7u	PIEB	15	1.1	1.5
7u	PCEA	14	2.1	2.6

2. Means obtained from linear model

Least-squares means and 95%confidence intervals obtained from linear mixed model (plotted in Figure in report Koen VanBrabant)

Time	PIEB Estimate (CI)	PCEA Estimate (CI)	P-value	Bonferroni-Holm
.	0.73 (0.45;1.01)	1.80 (1.52;2.07)	<.0001	.
15min	1.11 (0.59;1.63)	1.21 (0.69;1.72)	0.7920	1.0000
30min	0.70 (0.18;1.22)	1.12 (0.61;1.64)	0.2602	1.0000
45min	0.69 (0.17;1.21)	0.99 (0.47;1.51)	0.4215	1.0000
1u	0.30 (0.00;0.82)	0.59 (0.07;1.11)	0.4337	1.0000
2u	0.71 (0.19;1.23)	1.80 (1.26;2.33)	0.0044	0.0352
3u	0.72 (0.14;1.30)	2.99 (2.40;3.59)	<.0001	<.0001
4u	0.65 (0.00;1.32)	1.65 (0.99;2.31)	0.0385	0.2307
5u	0.78 (0.01;1.54)	2.14 (1.40;2.88)	0.0118	0.0826
6u	0.56 (0.00;1.43)	3.14 (2.27;4.01)	<.0001	0.0004
7u	1.09 (0.04;2.14)	2.33 (1.24;3.41)	0.1078	0.5392

Estimate=mean from a multivariate regression model for longitudinal measures. CI: 95% confidence interval
The first row presents the overall difference (irrespective timepoint).



PIEB (N)	64	64	64	64	63	51	37	29	22	15
PCEA (N)	65	65	64	64	60	48	39	31	22	14