Received: 7 March 2020 | Revised: 16 June 2020 | Accepted: 27 July 2020

DOI: 10.1111/aas.13689

ORIGINAL ARTICLE

acta Anaesthesiologica Scandinavica

Programmed intermittent boluses vs continuous epidural infusion in labor using an adrenaline containing solution: A randomized trial

Felix Haidl[1,2] | Leiv Arne Rosseland[2,3] | Anne-Marte Rørvik[1] | Vegard Dahl[1,2]

[1]Department of Anesthesia, Akershus University hospital, Lørenskog, Norway

[2]Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[3]Department of Research and Development, Division of Emergencies and Critical Care, Oslo University Hospital, Nydalen, Norway

Correspondence
Felix Haidl, Department of Anesthesia, Akershus University hospital, Sykehusveien 25, 1478 Lørenskog, Norway.
Email: felix.haidl@ahus.no

Background: Traditionally, epidural analgesia has been maintained using a continuous infusion (CEI) with the addition of patient-controlled boluses (PCEA). In recent years, programmed intermittent boluses (PIEB) has emerged as an alternative showing better efficacy in randomized studies. In this study, the aim was to test PIEB + PCEA vs CEI + PCEA using an epidural solution containing adrenaline.

Methods: In total, 150 nulliparous and multiparous laboring women were randomized to maintain epidural analgesia with either PIEB + PCEA (5 ml bolus every hour, 5 ml PCEA bolus lockout 20 minutes) or CEI + PCEA (5 ml/h, 5 ml PCEA bolus, lockout 20 minutes) using a solution of bupivacaine 1mg/ml, fentanyl 2 mcg/ml and adrenaline 2 mcg/ml. The primary outcome was total hourly consumption of the epidural solution. Secondary outcomes included hourly pain scores, motor block at 60 minutes and 10 cm cervical dilation, maternal satisfaction, and the need for anesthetist intervention and time to this intervention.

Results: We found no differences in hourly drug consumption between the groups (mean 9.0 ml/h (SD 3.7) (CEI group) vs. 8.1 ml/h (SD 2.0) (PIEB group), $P = .08$). We found a significant difference in number of successfully administered PCEA boluses (mean no. 3.9 (SD 4.1) (CEI group) vs. 1.9 (SD 2.0) (PIEB group), $P < .001$). We found no significant differences in pain score, motor block, maternal satisfaction and the need for anesthetist intervention.

Conclusion: In this study, we found no clinically relevant differences using PIEB + PCEA compared to CEI + PCEA when using an epidural solution containing adrenaline.

Editorial Comment: For labor epidural analgesia infusions, to optimize the analgesic effect, additional programmed intermittent boluses can be used as an alternative to patient-controlled boluses only. In this clinical trial, no differences in drug consumption or analgesic effect was observed when comparing these two different epidural bolus controls programs.

1 | INTRODUCTION

Epidural analgesia is considered the gold standard of pain relief during labor, and is effective with few side effects.[1] The epidural treatment solution normally consists of a low-dose local anesthesia in combination with a lipophilic opioid. Adrenaline is sometimes used as an additive to enhance the efficacy by producing vasoconstriction in the epidural space, hence lowering systemic absorption of the local anesthetic[2] and, in a randomized trial, we have shown that the addition of adrenaline lowered the serum fentanyl concentrations during the first two hours.[3] 30% of all delivery institutions in Norway use an adrenaline containing solution (unpublished data, personal communication, Haidl *et al*, 2020).

Until recently, the most common strategy for administering epidural labor analgesia is through a continuous epidural infusion (CEI), often in combination with patient controlled epidural boluses (PCEA). In recent years, the concept of programmed intermittent epidural bolus injections (PIEB) has been introduced. Previous studies in the field have recently been summarized in a Cochrane systematic review and meta-analysis.[4] The studies included in the Cochrane analysis were heterogeneous (eg combined spinal-epidural (CSE) vs only epidural, epidural solution mixture, basal infusions, patient-controlled boluses (PCEA) vs only basal infusions etc). However, the meta-analysis concluded that PIEB reduced breakthrough pain, reduced hourly local anesthetic consumption and increased maternal satisfaction compared to a continuous infusion. None of the studies included in the meta-analysis included adrenaline in the solutions studied.

The aim of our study has been to investigate the effect of programmed intermittent boluses using an epidural solution containing adrenaline. We hypothesized that programmed intermittent boluses would require less hourly epidural solution consumption than continuous infusion, while giving equipotent analgesia.

2 | METHODS

This study was approved by the regional ethics committee (REK-Sør-Øst, reference number 2016/98), the Norwegian Medicines Agency (EudraCTnr: 2015-004397-14) and registered at clinicaltrials.gov (NCT03043781). All participants gave oral and written informed consent before randomization. Laboring women requesting epidural analgesia were screened for inclusion. Inclusion criteria were adult women (over 18 years old) in American Society of Anesthesia (ASA) class <3, with singleton full term pregnancy (gestational age over 37 weeks) and a maximum of one previous delivery. Patients were excluded if they had poor communication skills in Norwegian or English, body height below 150 cm, had pre-eclampsia or if there was any contraindication to epidural analgesia including any of the medications used. The study was conducted at the labor ward of Akershus University Hospital, Norway between March 2017 and September 2018. This hospital is a university teaching hospital which has approximately 5000 deliveries each year.

The study design was a randomized controlled trial with two parallel groups. Primiparous and multiparous participants were randomized separately to ensure equal distribution of this factor between the two treatment groups. The group assignment was determined by a computer generated algorithm (Randlist®, Datainf, Thübringen, D), and kept in individual sealed envelopes until patients were included. A researcher who did not participate in data collection performed randomization in two groups (sizes1:1), block randomization with varying block size of 2, 4 and 6. The randomization including the block sizes were concealed until all data were entered into the database and the database was monitored and locked. Participants were randomized to receive the epidural solution by either intermittent epidural bolus (PIEB) or continuous epidural infusion (CEI).

At request for epidural analgesia, a multi-orifice catheter was inserted medially or paramedially in the middle lumbar segments (L2-3 or L3-4) via an 18 G Tuohy canula (Portex®, Smiths Medical, Minneapolis, MN, US) using the loss of resistance to saline technique with the patient in the sitting position. The skin was anesthetized using lidocaine 10 mg/ml with adrenaline. The catheter was placed 5 cm in the epidural space, and the catheter was aspirated for signs of intravascular placement. All epidural catheters were placed by the principal investigator (FH). All participants received 5 ml of the epidural analgesia solution consisting of 1 mg/ml bupivacaine, 2 μg/ml fentanyl and 2 μg/ml adrenaline via the epidural catheter as a test-dose. If no signs of intrathecal injection were detected, an additional 5 ml were injected. Fifteen minutes after the second bolus, an infusion pump (Rythmic Pump, Micrel Medical devices SA Pallini, Greece) was started. In the PIEB group, the pump was initiated by giving a 5 ml bolus. Thereafter, the pump gave a 5 ml bolus every hour after initiation, using the pumps maximum bolus delivery speed (ie 100 ml/h). In the CEI group, the pump was started at an infusion rate of 5 ml/h. In both groups, participants had an option of patient controlled epidural (PCEA) boluses of 5 ml with a lockout time of 20 minutes. In the PIEB group, there was an additional lockout time of 20 minutes from the delivery of a programmed bolus by machine default. Furthermore, the basic settings of the pump demanded that a PIEB bolus would be delayed by the PCEA lockout interval in case a PCEA bolus was initiated prior to the next PIEB bolus. The highest possible speed for bolus delivery was used (ie 100 ml/h). Participants were instructed to use the PCEA option if they felt they had inadequate analgesia. This regimen was chosen as it is similar to the institutional protocol, but with the modification of the PCEA bolus lockout time. Midwifes were instructed to contact the anesthetist if analgesia was inadequate despite the use of PCEA boluses, and if needed, the treatment was individualized until satisfactory pain relief.

All participants and study personnel assessing patients were blinded to the intervention. The anesthetist including the patient, and starting the treatment, was not blinded to the intervention. To prevent that any noise from the pump would interfere with the blinding, two parallel pumps were used; one connected to the patient giving the assigned treatment, and one pump connected to itself in a loop with the opposite treatment. Both pumps were kept in

an opaque bag. After the end of the study period, the participants and midwifes assessing the patients were asked if they could guess what treatment group the participant was in (with the option of saying "I don't know"). The answers were examined using the Bang index.[5] The Bang index is scaled in the −1; 1 interval, where 1 indicates complete lack of blinding, 0 indicates perfect blinding and −1 complete opposite guessing.

Participants were assessed for baseline characters, including body metrics and pain on contraction before epidural analgesia initiation. Participants were further assessed for pain on the most recent contractions at the start of treatment and once every hour after start using a numeric rating scale (NRS) ranging from 0 to 10, including worst pain experienced during the delivery phase. If the participant was asleep at the time of pain query, the pain score was assigned "0". If labor continued for more than 8 hours, pain was assessed every second hour. At one hour and at 10 cm cervical dilation, motor block was assessed using a modified Bromage scale (0 = able to lift whole extended leg or standing up, 1 = flexion of the knee, 2 = flexion of the ankle, 3 = no flexion of the knee or ankle).[6] If there was a difference in motor block between the legs, the leg with the most intense block was reported. The day after delivery, a short structured interview was performed by an anesthetist blinded for the study, where the patient's satisfaction with the pain treatment was registered. The patient was asked to rate their overall satisfaction with the treatment, considering treatment effect and possible adverse effects, on a 0-10 numeric rating scale.

2.1 | Statistical analysis

The predefined, primary endpoint of the study, was the average consumption of the epidural solution per hour of treatment including the starting bolus and any extra manually delivered boluses. Secondary outcomes included number of successful PCEA boluses, number of blocked PCEA boluses, pain on contraction during labor and at delivery, maternal satisfactions with the treatment, mode of delivery, motor block at one hour and 10 cm cervix dilation, need for additional anesthetic interventions and time from epidural placement to this intervention. Data were assessed for normality by the Shapiro-Wilks test and visual inspection of histograms and QQ-plots. If variables were found to not be normally distributed, non-parametric statistical tests were used (ie Mann-Whitney U-test), and data were presented by median and percentiles [IQR], rather than Student's *t* test and mean with standard deviations (SD). In categorical variables, Fisher's exact test was used when the expected count in a cell was below 5 rather than the Chi-squared test. The primary endpoint was assessed by Student's *t* test. Time-to-event variables were analyzed using Kaplan-Meier survival analysis and the Log-rank test. Statistical differences in pain score changes over time between groups were tested using a mixed model where the interaction between time and treatment group was used as the outcome test. The data development was not linear throughout the treatment period, and we therefore introduced break points at appropriate time points (ie time = 2 hours and time = 7 hours) after visual inspection of the data. The model consisted of treatment group, the different time variables (from the break points) and the interaction between treatment group and time as dependent fixed effects, and with individual random intercepts and slopes for the effect of time.

A significance level of 5% was used. No correction for multiple comparisons was made, and any significant findings in the secondary outcomes must be interpreted with caution. Data were analyzed using SPSS v. 26 (IBM, Chicago, IL) and STATA/SE v.15 (Stata corp. LLC, College Station, TX).

Sample size was calculated by considering data from previous studies that were similar in dosing to our study[7-9] assuming a mean difference of bupivacaine equivalents of 1 mg/h between groups. With an $\alpha = 0.05$ and a power = 0.8 we estimated that a total of 100 participants were required. To account for possible differences in effect when adrenaline was used in the solution, an additional 50 participants were included in the study.

3 | RESULTS

Of 194 parturients screened, 151 patients were included in the study. One withdrew consent, leaving 150 participants for final analysis (Figure 1). Baseline characteristics for both groups were similar (Table 1). There was an equal amount of multiparous participants in both groups.

There were no significant differences in total consumption of the epidural solution per hour of treatment (mean consumption of 9.0 ml/h in the CEI group vs 8.1 ml/h in the PIEB, $P = .08$) (Table 2). However, there was a significant difference in number of PCEA boluses given in total; (mean no. 3.9 (SD 4.1) in the CEI group vs 1.9 (SD 2.0) in the PIEB group $P < .001$), but no significant differences in number of rejected PCEA boluses between groups ($P = .44$) (Table 2). A total of 20 (13%) participants required any physician assistance after analgesia initiation, 8 (11%) in the CEI group, and 12 (16%) in the PIEB group ($P = .33$). There was a (non-significant) higher proportion of participants in the PIEB group requiring physician administered top up boluses of the study solution (7% in the CEI group vs 12% in the PIEB group, $P = .4$). There were no significant differences in other anesthetic events or interventions (ie rescue bupivacaine boluses through the epidural catheter, supplemental spinal analgesia, unilateral analgesic effect, replacement of epidural catheter etc) or time to first contact to the attending anesthetist($P = .432$) (Figure 2C). After accounting for rescue boluses of bupivacaine given, there were no changes in total bupivacaine consumption between the treatment groups (mean, SD and p-values did not change compared to values derived from epidural solution consumption).

There were no significant differences in temporal development of pain scores between the study groups (Figure 2 A) (time-treatment interaction coefficient −0.05, 95% CI −0.25; 0.15 $P = .64$) or worst experienced pain at delivery (median score 8 IQR [2.5; 9.5] in the CEI group vs 8 [3; 10] in the PIEB group, $P = .54$).

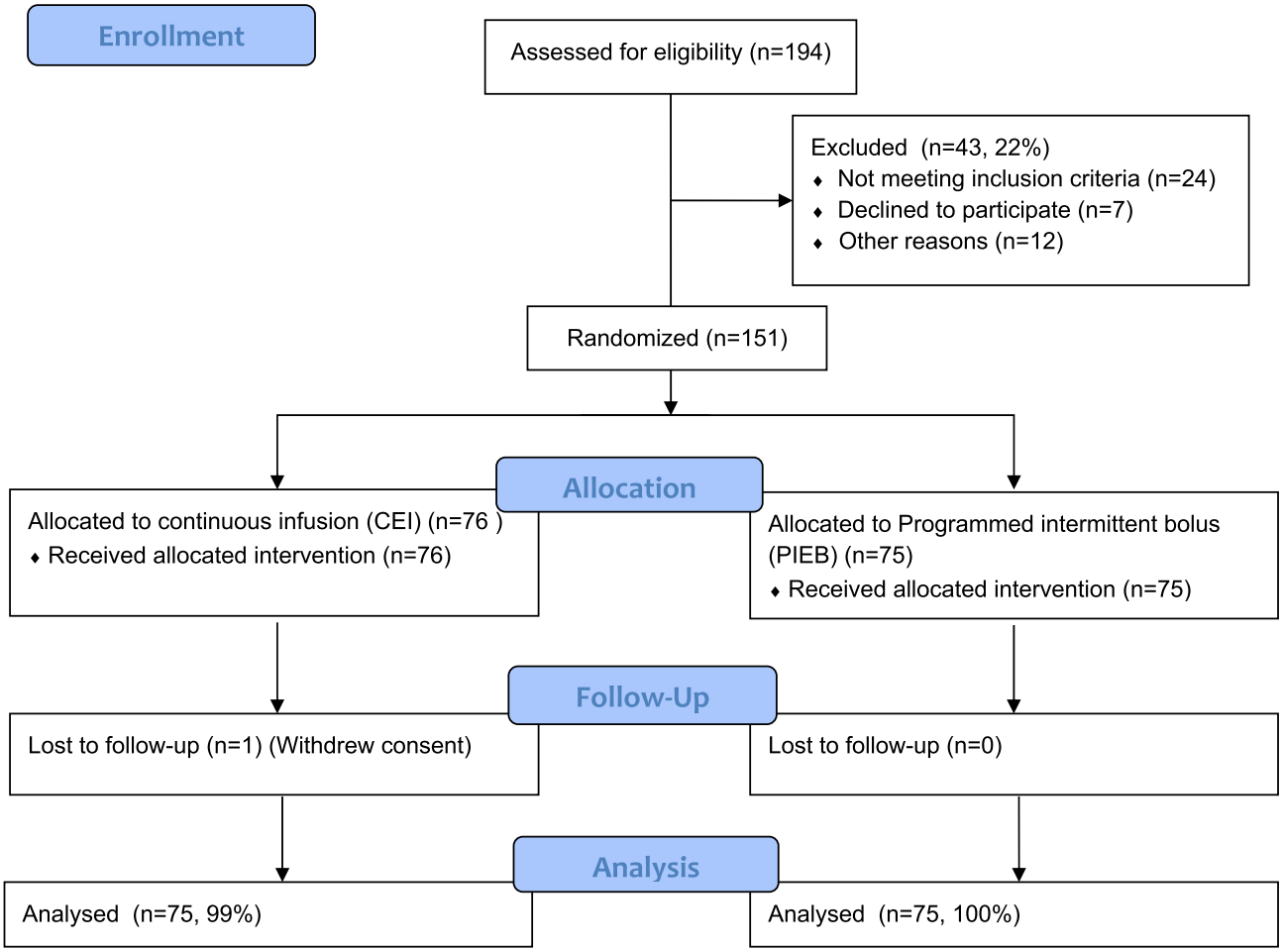

FIGURE 1 Flow of patients during the study [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Baseline characteristics

Variable	CEI group (n = 75)	PIEB group (n = 75)
Age (year)	29.8 (4.25)	30.4 (4.1)
Pre-delivery weight (kg)	82.3 (14.8)	80.8 (12.2)
Height (cm)	165.8 (5.7)	166.7 (6.5)
Gestational age (weeks + days)	40 + 0 (8)*	40 + 0 (9)*
Nulliparous	48 (64%)	48 (64%)
Multiparous	27 (36%)	27 (36%)
Cervical dilation before epidural placement (cm)	4.1 (1.4)	3.9 (1.4)

Note: Data presented as mean (SD), or n (% of treatment group)) unless stated otherwise. *Standard deviation in days.

The duration of treatment (ie from epidural placement until delivery) was not significantly different between groups (median duration 443 minutes, range [67; 1725] (CEI) vs 455 minutes [68; 2209] (PIEB), $P = .76$) (Figure 2B).

There were no significant differences in mode of delivery, or occurrence of side effects (ie hypotension, nausea or pruritus) and no significant differences in overall satisfaction with the treatment (Table 3). There was a non-significant trend toward a higher modified Bromage-score at 60 minutes in group 0, but not at delivery (Table 3).

There were no serious adverse events during the study period. We found no evidence of a lack of blinding (Table 4).

4 | DISCUSSION

In this study, there were no major differences in our primary outcome, that is, total consumption of the epidural solution per hour of treatment. However, there were fewer successful PCEA-boluses in the PIEB-group. This is likely explained by the fact that the PIEB-group had a lock out period after the hourly default bolus. The PIEB-group also had a tendency toward more bupivacaine rescue boluses. These findings reflect the recommendations of Carvalho *et al*;[10] where a shorter PCEA lockout interval was suggested. A shorter lockout period after the hourly bolus would, in our study, likely increase the number of successful PCEA boluses in the PIEB-group, and simultaneously decrease the unsuccessful PCEA-attempts.

Some of the previous randomized clinical trials used two separate pumps, one to deliver the PIEB or CEI maintenance dose, and a

TABLE 2 Epidural treatment outcomes

	CEI group(n = 75)	PIEB group (n = 75)	Mean difference	*P*-value
Total epidural solution consumption (ml/hour)	9.0 (3.7)	8.1 (2.0)	0.9 [−0.1; 1.8]	.08
No. of completed PCEA boluses	3.9 (4.1)	1.9 (2.0)	2.0 [1.0; 3.1]	<.001
No. of rejected PCEA boluses	2.0 (3.9)	2.5 (5.0)	−0.6 [−2.1; 0.9]	.44
No. of participants needing any further physician intervention	8 (11%)	12 (16%)		.33
No. of physician administered manual boluses of the study epidural solution	5 (7%)	9 (12%)		.40[a]
No. of rescue bupivacaine boluses	2 (3%)	2 (3%)		1.0[a]
No. of supplemental spinal injections	0 (0%)	1 (1%)		1.0[a]
No. of unilateral epidural effect	2 (3%)	5 (7%)		.44[a]
No. of new epidural catheter	2 (3%)	2 (3%)		1.0[a]

Note: Data are presented as mean (SD), no (% of treatment group) or mean difference [95% CI]. [a] Fisher's exact test. PCEA, Patient-controlled epidural analgesia.

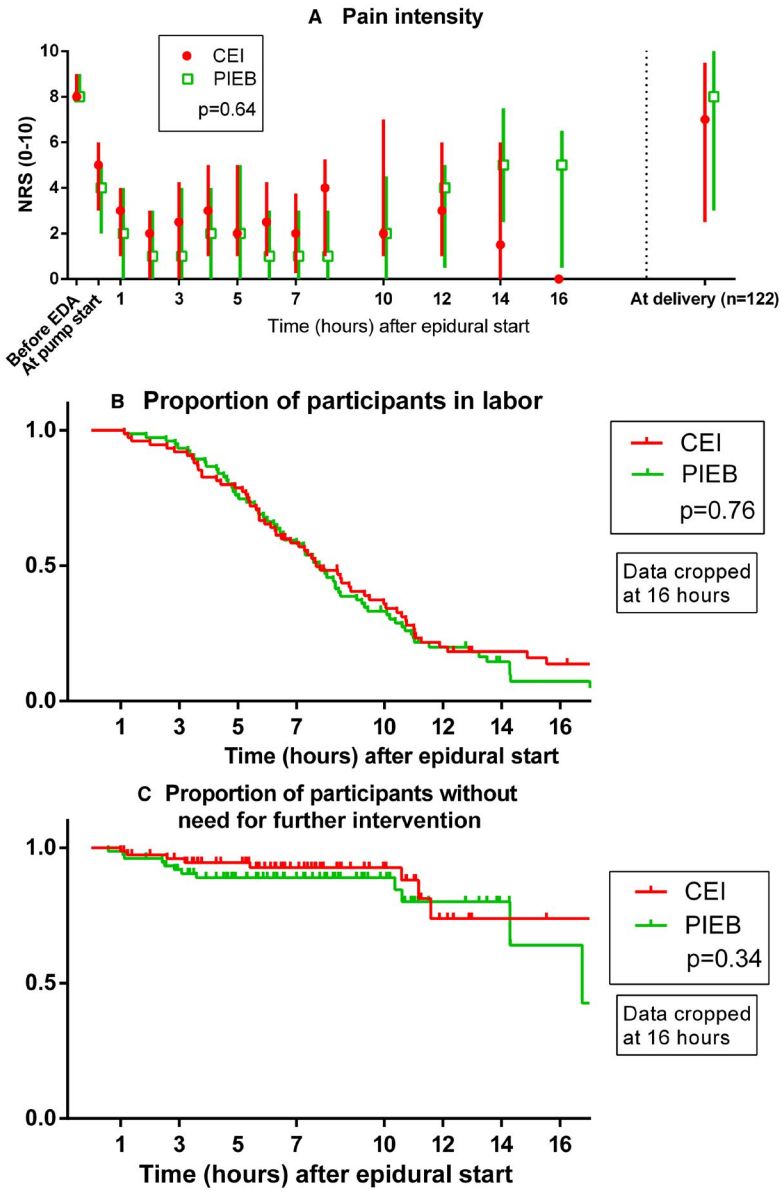

FIGURE 2 A, Pain scores before and during treatment by treatment group. Data presented as median and 25th and 75th percentile. *P*-value from the time*treatment group interaction term in a mixed model. B, Kaplan-Meier curves for participants in labor by treatment group. Participants were censored at cesarean delivery. Data were cropped after 16 hours. *P*-value by the log-rank test. C, Kaplan-Meier curves for participants without the need for further intervention by the attending physician. Participants were censored at delivery. Data were cropped after 16 hours. *P*-value by the log-rank test. CEI, continuous epidural infusion; PIEB, programmed intermittent bolus [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Secondary outcomes

Variable	CEI group (n = 75)	PIEB group (n = 75)	*p*-value
Time from epidural placement to birth (min)	443 [67; 1725][a]	455 [68; 2209][a]	.76[b]
Birth weight (g)	3641 (414)	3695 (425)	.43
Modified Bromage score at 60 minutes			
0	64 (88%)	58 (81%)	
1	7 (9%)	14 (19%)	
2	2 (3%)	0 (0%)	
3	0 (0%)	0 (0%)	.09[c]
Modified Bromage score at delivery			
0	35 (56%)	40 (63%)	
1	14 (22%)	11 (18%)	
2	11 (17%)	8 (13%)	
3	3 (5%)	4 (6%)	.76[c]
Mode of delivery			
Vaginal	43 (57%)	47 (63%)	
Instrumental deliveries	19 (25%)	18 (24%)	
Cesarean section	13 (17%)	10 (13%)	.74
Hypotension			
No hypotension	70 (93%)	73 (97%)	
Mild hypotension	4 (5%)	1 (1%)	
Treated with vasopressors	1 (1%)	1 (1%)	.52[c]
Nausea			
No or mild	72 (97%)	69 (92%)	
Moderate or severe	2 (3%)	6 (8%)	.28[c]
Pruritus			
No or mild	52 (70%)	54 (72%)	
Moderate or severe	22 (30%)	21 (28%)	.82
Satisfaction with treatment	10 [9; 10]	10 [9; 10]	.62[d]

Note: Data presented as mean (SD), median [IQR] or n (% of treatment group)) unless stated otherwise. [a]Median [min.; max.]. [b]Log rank test. [c]Fisher's exact test. [d]Mann-Whitney *U*-test.

separate pump to deliver a PCEA-bolus,[8,11] while some of the studies used various custom-made computer algorithms. In the latter, it was unclear if the PCEA bolus would block or delay the PIEB and if the PIEB would influence the PCEA lock out.[7,12,13] It is possible that the use of two separate pumps in our study would have resulted in a more even distribution of PCEA boluses between the groups. However, the use of two pumps per patients may be ideal in a research context but impractical and costly in an ordinary clinical setting. We have compared the two different methods in an ordinary clinical setting, which would give our results more generalizability.

There is no consensus on the optimal volume and interval of the PIEB dose. Two studies have investigated this in biased coin up-and-down studies using a dilute bupivacaine (0.625 mg/ml) and fentanyl solution, concluding with an 11 ml PIEB bolus[14] and a 40 minutes interval.[15] A further study by Wong *et al* found lower bupivacaine consumption using a 10 ml bolus hourly compared to 5 ml every 30 minutes using a similar solution.[16] It is not clear if these findings are generalizable to different solutions. It has been shown that the addition of adrenaline to manually administered single epidural boluses increases the duration of analgesia,[17,18] and an increased efficacy when added to a continuous infusion.[19] In contrast with previously published studies on PIEB, we found no differences in analgesic efficacy with PIEB compared to CEI. We believe that the prolongation of the analgesic effect of an epidural solution when adrenalin is added, results in a more stable analgesia regardless of method of administration. We speculate if the addition of adrenaline to the solution might affect the optimal PIEB dosing interval.

While the use of adrenaline has proven positive effects in labor analgesia, it has been discredited; hypothesizing it may affect uteroplacental blood flow due to vasoconstriction. However, animal and human studies have shown that adrenaline does not affect uteroplacental blood flow in clinically relevant doses,[20] but this may have reduced the number of institutions using adrenaline in labor. Further studies comparing the effect of adrenaline in the PIEB setting is needed.

TABLE 4 Evaluation of blinding

	Response			
Assignment	**CEI group**	**PIEB group**	**Don't know**	**Total**
Midwife evaluation				
CEI group	22	16	32	70
PIEB group	20	16	33	69
Patient evaluation				
CEI group	14	28	32	74
PIEB group	18	25	32	75

Bang index	**Index**	**95% CI**	***P*-value**
Midwives, CEI group	0.09	[−0.06; 0.23]	.16
Midwives, PIEB group	−0.06	[−0.20; 0.08]	.75
Patients, CEI group	−0.19	[−0.33; −0.05]	.99
Patients, PIEB group	0.09	[−0.05; 0.24]	.14

Note: Data presented as n in the first part of the table. Some midwife and one patient evaluations were missing. The Bang index is scaled in the −1; 1 interval, where 1 indicates complete lack of blinding, 0 indicates perfect blinding and −1 complete opposite guessing. *P*-values evaluate "H0: the study is blinded".

Motor block may lead to increased use of instrumental delivery, an important clinical outcome.[21] While the meta-analysis by Sng concluded with no differences in risk of instrumental delivery, analogous to our findings (motor block was not assessed), a non-randomized impact study have found a reduction in motor block when transitioning from a CEI protocol to a PIEB + PCEA protocol while simultaneously reducing ropivacaine concentration in the solution.[22] Other impact studies have not found the same clear beneficial effects.[23,24]

It is hypothesized that the use of boluses would increase the spread of local anesthesia in the epidural space, thus increasing the chance of good analgesia in the sacral segments. In this study, we assessed the maximum experienced pain at delivery. The maximum pain experienced, and the pain at the end of labor is often remembered.[25] We found individual values within a large range, but with the majority of the pain experienced within the "severe range" (≥7 of 10), with no differences between the groups. To the best of our knowledge, this is the first study examining worst pain at delivery when using PIEB.

Previous studies in the field describes that the patient and the person assessing the outcomes were blinded to the intervention. In the initial preparations before this study, we found that the pump we intended to use made a distinct, albeit quiet sound as the bolus was delivered. This sound made it possible in many cases for the midwife caring for the parturient to unveil the treatment the patient received (unpublished pilots). To counteract this, we implemented the use of two pumps as described in the method section (ie one pump to make "placebo noice"). To further investigate this, we assessed midwifes and participants if they could guess what treatment they received. Our results show that they could not. We do not know whether previous reported studies have made the same efforts to prevent the apparent bias made by educated guesses with regard to this auditory phenomenon. This should be addressed in future studies. Other strengths of our study is uniform participant inclusion, one single anesthetist performing the epidurals, and an extensive data quality control, ensuring high internal validity, and the number of participants included in this study.

There are several limitations to our study. The explicit threshold of pain that mandated contact to the treating anesthetist was not defined, but left to the attending midwife and/or participant to decide. It is possible that an explicit threshold could have resulted in a higher proportion of contacts. However, as a large proportion of participants in both groups were satisfied with the treatment, a mandatory threshold could also have resulted in overtreatment and higher incidence of adverse effects such as extended motor block. Furthermore, it is possible that a larger sample size would have resulted in a statistically significant difference in the primary outcome. Nevertheless, our study is among the largest in the field, and possible statistically significant findings between the groups with a larger sample size might not be clinically relevant. Our approach to assessing satisfaction with treatment was similar to previous studies. However, this field is complex, and satisfaction is often influenced by other factors (such as labor and neonatal outcomes), and these results must therefore be carefully interpreted.

In conclusion, using an epidural solution containing adrenaline, we found no differences in hourly solution consumption, pain scores or maternal satisfaction when using PIEB compared to CEI.

ACKNOWLEDGEMENTS

The authors thank the clinical trial unit, Oslo University Hospital for important input to the study protocol and the midwives at Akershus University Hospital for help with collecting data. The study was funded by departmental funds only. The authors have no conflicts of interest.

ORCID

Felix Haidl https://orcid.org/0000-0001-7225-848X
Leiv Arne Rosseland https://orcid.org/0000-0002-6372-8117

REFERENCES

1. Wong CA. Advances in labor analgesia. *Int J Womens Health*. 2010;1:139-154.
2. Leonard SA, Flynn R, Kelleher N, Shorten GD. Addition of epinephrine to epidural ropivacaine during labour–effects on onset and duration of action, efficacy, and systemic absorption of ropivacaine. *Int J Obstet Anesth*. 2002;11:180-184.
3. Haidl F, Rosseland LA, Spigset O, Dahl V. Effects of Adrenaline on maternal and fetal fentanyl absorption in epidural analgesia: A randomized trial. *Acta Anaesthesiol Scand*. 2018;62:1267-1273.
4. Sng BL, Zeng Y, de Souza NNA, et al. Automated mandatory bolus versus basal infusion for maintenance of epidural analgesia in labour. *Cochrane Database of Systematic Reviews*. 2018;5:CD011344.
5. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. *Control Clin Trials*. 2004;25:143-156.
6. Breen TW, Shapiro T, Glass B, Foster-Payne D, Oriol NE. Epidural anesthesia for labor in an ambulatory patient. *Anesth Analg*. 1993;77:919-924.
7. Leo S, Ocampo CE, Lim Y, Sia AT. A randomized comparison of automated intermittent mandatory boluses with a basal infusion in combination with patient-controlled epidural analgesia for labor and delivery. *Int J Obstet Anesth*. 2010;19:357-364.
8. Capogna G, Camorcia M, Stirparo S, Farcomeni A. Programmed intermittent epidural bolus versus continuous epidural infusion for labor analgesia: the effects on maternal motor function and labor outcome. A randomized double-blind study in nulliparous women. *Anesth Analg*. 2011;113:826-831.
9. Lim Y, Chakravarty S, Ocampo CE, Sia AT. Comparison of automated intermittent low volume bolus with continuous infusion for labour epidural analgesia. *Anaesth Intensive Care*. 2010;38:894-899.
10. Carvalho B, George RB, Cobb B, McKenzie C, Riley ET. Implementation of programmed intermittent epidural bolus for the maintenance of labor analgesia. *Anesth Analg*. 2016;123:965-971.
11. Wong CA, Ratliff JT, Sullivan JT, Scavone BM, Toledo P, McCarthy RJ. A randomized comparison of programmed intermittent epidural bolus with continuous epidural infusion for labor analgesia. *Anesth Analg*. 2006;102:904-909.
12. Sia AT, Lim Y, Ocampo C. A comparison of a basal infusion with automated mandatory boluses in parturient-controlled epidural analgesia during labor. *Anesth Analg*. 2007;104:673-678.
13. Sia AT, Leo S, Ocampo CE. A randomised comparison of variable-frequency automated mandatory boluses with a basal infusion for patient-controlled epidural analgesia during labour and delivery. *Anaesthesia*. 2013;68:267-275.
14. Zakus P, Arzola C, Bittencourt R, Downey K, Ye XY, Carvalho JC. Determination of the optimal programmed intermittent epidural bolus volume of bupivacaine 0.0625% with fentanyl 2 mug.ml(-1) at a fixed interval of forty minutes: a biased coin up-and-down sequential allocation trial. *Anaesthesia*. 2018;73:459-465.
15. Epsztein Kanczuk M, Barrett NM, Arzola C, Downey K, Ye XY, Carvalho JC. Programmed intermittent epidural bolus for labor analgesia during first stage of labor: A biased-coin up-and-down sequential allocation trial to determine the optimum interval time between boluses of a fixed volume of 10 mL of bupivacaine 0.0625% with fentanyl 2 mug/mL. *Anesth Analg*. 2017;124:537-541.
16. Wong CA, McCarthy RJ, Hewlett B. The effect of manipulation of the programmed intermittent bolus time interval and injection volume on total drug use for labor epidural analgesia: a randomized controlled trial. *Anesth Analg*. 2011;112:904-911.
17. Eisenach JC, Grice SC, Dewan DM. Epinephrine enhances analgesia produced by epidural bupivacaine during labor. *Anesth Analg*. 1987;66:447-451.
18. Grice SC, Eisenach JC, Dewan DM. Labor analgesia with epidural bupivacaine plus fentanyl: enhancement with epinephrine and inhibition with 2-chloroprocaine. *Anesthesiology*. 1990;72:623-628.
19. Connelly NR, Freiman JP, Lucas T, et al. Addition of epinephrine to epidural bupivacaine infusions following initiation of labor analgesia with epidural fentanyl. *J Clin Anesth*. 2011;23:265-269.
20. Niemi G. Advantages and disadvantages of adrenaline in regional anaesthesia. *Best Practice & Research Clinical Anaesthesiology*. 2005;19:229-245.
21. Vertommen JD, Vandermeulen E, Aken HV, et al. The effects of the addition of sufentanil to 0.125% bupivacaine on the quality of analgesia during labor and on the incidence of instrumental deliveries. *Anesthesiology*. 1991;74:809-814.
22. Bullingham A, Liang S, Edmonds E, Mathur S, Sharma S. Continuous epidural infusion vs programmed intermittent epidural bolus for labour analgesia: A prospective, controlled, before-and-after cohort study of labour outcomes. *Br J Anaesth*. 2018;121:432-437.
23. Tien M, Allen TK, Mauritz A, Habib AS. A retrospective comparison of programmed intermittent epidural bolus with continuous epidural infusion for maintenance of labor analgesia. *Curr Med Res Opin*. 2016;32:1435-1440.
24. Delgado C, Ciliberto C, Bollag L, Sedensky M, Landau R. Continuous epidural infusion versus programmed intermittent epidural bolus for labor analgesia: optimal configuration of parameters to reduce physician-administered top-ups. *Curr Med Res Opin*. 2018;34:649-656.
25. Carvalho B, Hilton G, Wen L, Weiniger CF. Prospective longitudinal cohort questionnaire assessment of labouring women's preference both pre- and post-delivery for either reduced pain intensity for a longer duration or greater pain intensity for a shorter duration. *Br J Anaesth*. 2014;113:468-473.

How to cite this article: Haidl F, Arne Rosseland L, Rørvik A-M, Dahl V. Programmed intermittent boluses vs continuous epidural infusion in labor using an adrenaline containing solution: A randomized trial. *Acta Anaesthesiol Scand*. 2020;64:1505–1512. https://doi.org/10.1111/aas.13689