Comparing Continuous Epidural Infusion and Programmed Intermittent Epidural Boluses as the Background Infusion for Parturient Controlled Epidural Analgesia: Analysis of the "Real World" Database Using Propensity Score Matching

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Abstract

Background Although the difference in treatment efficacy between programmed intermittent epidural bolus (PIEB) and continuous epidural infusions (CEI) for labor analgesia has been addressed in several previous randomized control trials, observational research on "real world" data is considered as the most important supplement of RCTs about the effectiveness of interventions to guide best clinical practice. We performed a prospective cohort study to compare the efficacy of CEI+PCEA vs. PIEB+PCEA for providing epidural analgesia during labor.

Methods We identified 1807 patients who received epidural analgesia for planned normal vaginal. Propensity score matching with a ratio of 1:1 was implemented to reduce selection bias. The primary outcome of interest was the incidence of motor block assessed with maximum Bromage score, occurring at least once throughout labor. Secondary outcomes included total local anesthetic volume and doses, duration of labor analgesia, the proportion of prolonged second stage of labor, the number of physician-administered epidural boluses, the physician evaluates during labor analgesia, mode of delivery, the incidence of at least one of abnormal vital signs during labor epidural, and Apgar score at 1 or 5 minutes.

Results After propensity score matching, a total of 1328 patients were matched. The motor block occurred less frequently in PIEB group than in CEI group (RR 0.39, 95% CI: 0.29, 0.54,

p<0.0001). PIEB group received more fentanyl dose per hour with the mean difference of 8.85μg (95% CI: 7.79, 9.91, p<0.0001), less bupivacaine per hour with the mean difference of 9.57mg (95% CI: 4.40, 14.57, p<0.0001). We found lower evaluated times per hour in PIEB group (PIEB:0.75 times per hour, CEI: 0.68 times per hour, MD: -0.07 times per hour, 95%CI: -0.10, -0.04, p<0.0001).There is no statistical difference in C-section delivery rate (RR 0.98, 95% CI: 0.84,1.13), instrumental vaginal delivery(RR 0.88, 95% CI:0.69, 1.13), and duration of second stage of labor (RR 0.91, 95%CI: 0.70, 1.18) between PIEB group and CEI group. The low Apgar score at 1-minute incidence was higher in PIEB group, and the risk ratio was 1.15 (95% CI: 0.96, 1.38, p>0.002).

Conclusions Our study showed that PIEB combines with PCEA was superior to CEI combined with PCEA for labor analgesia, including decreasing the incidence of motor block, lessening the local bupivacaine consumption, and reducing the workload of anesthetists. Further investigations into the association between high cumulative dose of fentanyl and increased incidence of low Apgar score in PIEB are needed.

Introduction

Epidural analgesia is considered the most effective and the least depressant method for pain relief with minimal side effects to both the mother and the fetus for the parturient receiving analgesia[1]. Historically, epidural labor analgesia was administered as manual boluses. As technology improved, continuous epidural infusions (CEI) were provided by pumps to provide less intensive labor analgesia. Epidural bolus doses provide better spread as compared to continuous infusions. Subsequently, patient-controlled epidural analgesia (PCEA) allowed for the benefits of bolus dosing while still having the benefit of continuous maintenance of analgesia by a pump. With the introduction of pumps that are capable of automatic boluses, programmed intermittent epidural bolus (PIEB) technology is currently widely used for labor analgesia[2]. The difference in treatment efficacy between PIEB and CEI for labor analgesia has been addressed in previous randomized control trials. George et al. [3] published a well-done systematic review in 2013, which included nine randomized control trials[4-12] with 694 patients, has shown that PIEB compared with CEI may be associated with reduced local anesthetic consumption, the shorter second stage of labor, and higher maternal satisfaction. Wong et al. [8] point out that PIEB may reduce anesthetic use and minimize unintended consequences such as undesirable motor block or toxicity effects.

RCTs are regarded as the most scientifically rigorous study design and considered the gold standard for demonstrating efficacy for the intervention arm. Although RCTs have strong internal validity, they are carefully conducted in controlled research conditions that include strict eligibility criteria that may limits generalizability (external validity) [13]. Observational evidence is considered as the most important supplement of RCTs about the effectiveness of interventions to

guide best clinical practice[14]. An observational study[15] with a larger population has been conducted to show that the benefits of PIEB+PCEA over CEI previously demonstrated in small randomized controlled trials were reproducible on a larger scale in a clinical setting. But these observational effect estimates were vulnerable to confounding bias due to lack of randomization.

Propensity score matching (PSM), one of the propensity score-based methods, is an increasingly popular method used to address confounding by indication in real-world evidence (RWE) studies. The propensity score is defined as the probability of treatment assignment conditional on measured baseline covariates[16,29]. Treated and untreated subjects with the same propensity score will have similar distributions of observed baseline covariates. The propensity score matching allows one to analyze an observational (nonrandomized) study so that it mimics some characteristics of RCTs[18].

We performed a prospective cohort study to compare the effectiveness of CEI+PCEA vs. PIEB+PCEA for providing epidural analgesia during labor using 1:1 propensity score matching.

Methods

Data source

In late May 2018, Brigham and Women's Hospital, located in Boston, Massachusetts, began using PIEB labor analgesia. Since the PIEB technique required nursing, midwife, physician (obstetrician and anesthesiologist) training, practice, and improvement after a period of implementation, it could achieve stable effectiveness. After obtaining Institutional Review Board approval, we included all women who received epidural analgesia for planned normal vaginal

delivery during the January 1st, 2019 and March 31st, 2019 into PIEB group, allowing a comparison period, January 1st, 2018 to March 31st, for CEI group. Women who received combined spinal epidural (CSE) technique or epidural time less than 30minutes were excluded from the study. We extracted data from each participant's original electronic patient records such as the homepage, anesthetic chart, and discharge notes. Data were collected on patient demographics, obstetric data, anesthesia record, delivery data, newborn record.

Epidural procedures

PIEB group pump was programmed to deliver 0.0625% bupivacaine with fentanyl 2μg /ml, 9mL every 45 minutes, beginning 60 minutes after the administration of the initial epidural loading dose. CEI group pump was programmed to deliver bupivacaine 0.125% with fentanyl 2μg /ml at a rate of 6ml/h beginning immediately after the loading dose administration. In both groups, participants were instructed to use the PCEA option if they felt they had inadequate analgesia.

Outcome

The primary outcome of interest was the incidence of motor block assessed with Maximum Bromage score, occurring at least once throughout labor. The degree of motor block was assessed in the right and left legs using the Bromage score[19]: 0=no motor block(compete flexion/extension of the hip, knee, and ankle), 1= partial block (inability to move hip, able to move knee and ankle), 2=partial block (inability to move hip and knee, able to move ankle), 3=complete block (inability to move hip, knee, or ankle).

Secondary outcomes included total local anesthetic volume and doses, duration of labor analgesia, the proportion of prolonged second stage of labor, the number of physician-

administered epidural boluses, the physician evaluates during labor analgesia, mode of delivery, the incidence of at least one of abnormal vital signs during labor epidural, and Apgar score at 1 or 5 minutes.

The prolonged second stage of labor was defined as the duration of the second stage of labor 3 hours for primiparous or 4 hours for nulliparous. Duration of the second stage of labor is recorded as the time from full cervical dilatation on vaginal examination, or the head is visible in the perineum until delivery of the neonate. The mode of delivery is recorded as normal vaginal delivery, instrumental delivery (requiring forceps, vacuum device), and emergency C-section. Duration of labor analgesia, both vaginal and C-section deliveries, was calculated from the epidural placement until the delivery of the neonate. The abnormal vital signs during epidural included hypertension (systolic blood pressure between 130 mmHg or diastolic blood pressure 80mmHg), hypotension (systolic blood pressure <90mmHg) , abnormal heart rates(heart rates<60/per minute or >100 per minute), high body temperature (body temperature38C), abnormal respiration rate (respiration rate < 12 or > 25 breaths per minute) and the low oxygen level (SpO2< 95%).

Statistical analysis

Continuous variables were described as the mean ± standard deviation (SD). These data were analyzed using Student's t-test. Categorical variables were analyzed using the Fisher exact test or the chi-square test. Bonferroni adjustment was applied for multiple testing correction[20]. P-value < 0.002 (0.05 /26) was considered statistically significant, and the value 26 was the total number of the statistical tests in our study.

Propensity score matching was implemented to reduce the possibility of selection bias between two groups. First, we identify all available variables at baseline, which were the predictors of outcome or/and treatment based on expertise and Directed Acyclic Graphs (DAGs). Next, we calculated the propensity score (the probability that a parturient was assigned to the PIEB group or the CEI group as a consequence of these factors) performing a logistic regression with the identified variables mentioned at the first step, including age, BMI, race, height, gestational age, gravida times, parity type, prior labor epidural, prior C-section, twins, neonatal weight, pregnancy comorbidities disease, ASA status, smoker, comorbidities disease at baseline and test before initiating an epidural infusion. Participants in the CEI group were matched according to propensity scores, leading to an even distribution of potential confounding to the PIEB groups with a ratio of 1:1. Finally We assessed the post-matching balance by calculating standardized difference before and after PSM, with meaningful imbalance set at values>0.1, and post-matching C-statistics, which was expected to be close to 0.5 when the balance was present. All statistical analyses were performed in software R 4.1.2.

Results

The final eligible study cohort included 1807 participants, of whom 888 received CEI+PCEA (CEI group), and 919 received PIEB+PCEA (PIEB group). Table1 summarized the participants' characteristics stratified by labor epidural procedure, before and after propensity score matching. Before PSM, CEI group tended to have less prior labor epidural history, a greater number of using the test prior to initiating an epidural infusion, and had a greater of comorbidities such as

pulmonary disease, GI/hepatic disease, neurologic/muscular disease with the exception of a fewer number of hematologic/oncology disease. After PSM, a total of 1328 patients (664 in each group) were matched. All standardizes differences for covariates were less than 0.1, indicating that they were well balanced. The post matching C-statistic was 0.504, presenting the balance.

The motor block (maximum Bromage score ≥1) occurred less frequently in PIEB group than in CEI group (Table 2). The risk ratio for the occurrence of motor block in PIEB group vs CEI group was 0.39 (95% CI: 0.29, 0.54, p<0.0001).

The total volume of bupivacaine and fentanyl, including initial dose and physician-administered epidural bolus, was higher in PIEB group than in CEI group (Table 3). The mean difference was 38.66ml (95% CI: 32.71, 44.91, p<0.0001). PIEB group received more fentanyl dose per hour with the mean difference of 8.85μg (95% CI: 7.79, 9.91, p<0.0001), less bupivacaine per hour with the mean difference of 9.57mg (95% CI: 4.40, 14.57, p<0.0001), and less evaluated times with the mean difference 0.07 times per hour (95% CI: 0.04, 0.10, p<0.0001).

Table 4 showed the risk ratio of secondary outcomes comparing the two groups. The incidence of instrumental vaginal delivery was 6.93% for CEI group and 5.57% for PIEB group (p=0.308). The risk ratio for the incidence of c-section in PIEB group vs CEI group was 0.98 (95% CI: 0.84, 1.13, p=0.763). The incidence of the low Apgar score at 1 minute (Apgar score at 1 minute<7) was higher in PIEB group, and the risk ratio was 1.15 (95% CI: 0.96, 1.38, p=0.145).

Discussion

We found a significantly decreased incidence of motor block from 19.92% in PIEB group to 4. 67% in CEI group, the risk ratio was 0.39 (95% CI: 0.29, 0.54, p<0.0001). Our findings supported the findings of a meta-analysis[3], including nine RCTs that has presented markedly reduce incidence in motor block in PIEB (2.8%) compared with that in CEI (16%).The significant reduction in the incidence of motor block observed in our study is consistent with the lower bupivacaine concentrations (0.0625%) and hourly bupivacaine doses (8.87mg per hour) of PIEB. Recent reports have demonstrated that lower hourly bupivacaine doses (7.5–10.3 mg) are effective when administered with higher volume PIEB[4,21]. Those findings suggested that lower bupivacaine concentrations (0.0625%) may be necessary for successful PIEB protocols to minimize motor block.

PIEB group had statistically significantly lessened use of bupivacaine. The total bupivacaine used in PIEB group was lower than that in CEI group (MD, -9.57mg, 95% CI: -14.53, -4.40 p<0.0001). The hourly bupivacaine doses in the PIEB were 8.87mg, which is lower than that (10.94mg) in CEI group (MD, -2.07mg, 95%CI: -2.48, -1.67, p<0.0001). Ronald B et al.[15] reported, with eight studies (n = 652) in a meta-analysis, there was a statistically significant reduction in total local anesthetic delivered with PIEB (MD, –1.2 mg bupivacaine equivalents per hour; 95% CI: –2.2, –0.3 p<0.0001).

Results presented no statistical difference in C-section delivery rate (RR 0.98, 95% CI: 0.84,1.13), instrumental vaginal delivery(RR 0.88, 95% CI:0.69, 1.13), and duration of second stage of labor (RR 0.91, 95%CI: 0.70, 1.18) between PIEB group and CEI group. This was consistent with the meta-analysis of nine RCTs comparing PIEB and CEI finding no difference

in the rates of C-section (OR 0.87, 95% CI: 0.56, 1.35) or instrumental delivery (OR 0.59, 95% CI: 0.35,1.00)[3].

However, PIEB group had statistically significantly increased use of fentanyl. The total fentanyl used in PIEB group was nearly twice that in CEI group (PIEB 214.82μg vs. CEI 130.11μg). The hourly fentanyl doses in the PIEB were 26.86μg, which was also higher than that (18.01μg) in CEI group (MD, 8.85μg, 95%CI: 7.79, 9.91, p<0.0001). These results were inconsistent with previous studies. Findings in previous RCTs[3] showed no statistically significant difference in fentanyl consumption between the two groups. We speculated that there were three reasons. Firstly, the bupivacaine concentrations for PIEB protocol in our study was 0.0625%, which is half of that in CEI group. The total volume of local anesthetic consumption increased with the decrease in bupivacaine concentrations(PIEB: 107.25ml vs. CEI 80.33ml, MD, 38.66ml, 95%CI: 32.71, 44.94, p<0.0001), but the fentanyl concentration of neither of two groups changed, was still 2mg/ml. Secondly, the total local anesthetic dose included the physician-administered epidural bolus. It is worth noting that 32.3% of participants in our study received physician-administered epidural bolus, including fentanyl and/or bupivacaine. The third reason was that our study data came from a "real world" clinical population with more diversity and complexity.

Recently new findings on fentanyl epidurals during labor published in the Journal of Applied Laboratory Medicine, researchers found that the likelihood of fentanyl passing on to babies correlated with the duration and cumulative dose of the epidural. Mothers who received fentanyl for less than 5 hours at a cumulative dose of <100μg did not have children who tested positive for fentanyl. In contrast, mothers treated for more than 10 hours with a cumulative dose

of >100μg had children with positive fentanyl tests. Wong CA et al. [22] reported a prevalence of low Apgar score at the birth of 16.7% at one minute in the group that received 20μg of intrathecal fentanyl. We found the incidence of low Apgar score at 1 minute (Apgar score at 1 minute 7) was higher in PIEB group (PIEB: 8.58% vs. CEI: 6.48%, the risk ratio was 1.15 (95% CI: 0.96, 1.38, p>0.002), although this did not reach statistical significance. Our study was not designed to detect the relationship between a higher cumulative dose of fentanyl and increased incidence of low Apgar score in PIEB group compared to CEI group. Therefore, we may not include all necessary covariables for further analysis.

In our study, we noted lower evaluated times per hour in PIEB group (PIEB:0.75 times per hour, CEI: 0.68 times per hour, MD: -0.07 times per hour, 95%CI: -0.10, -0.04, p<0.0001). It showed that PIEB might reduce the workload of anesthetists. Previous studies have mainly focused on the comparisons of the effectiveness of two labor epidural procedures, and few studies have findings on this issue.

There are several limitations to this study. First, residual confounding by some unmeasured variables can't be ruled out, although it is likely to be minor. The potential for residual confounding by unmeasured factors not included in the PS model was evaluated by inspecting the balance in key baseline lab results in the population subset with thin information available. After PSM, results showed that it was still unbalanced in selected lab test results. Second, the study data is dependent on the documentation in the electronic medical records. For instance, PCEA boluses were not recorded in the documentation, and there may have been differences in the number of PCEA boluses. In addition, the Bromage scale scores were not routinely checked

at regular intervals, and some of the motor blocks may not be identified. Moreover, this was a single center study. BWH is a teaching affiliate of Harvard Medical School. There were some differences in parturients characteristics compared with that of general medical institutions. We found that about 50% of parturients in our study have comorbidities disease, which was much higher than that of general institutions. Finally, findings might not be generalizable to regimens using different bupivacaine concentrations. However, the strength of this study is a large sample size, a "real world" research population that actually be treated in practice, and appropriate use of statistical approaches. We analyzed our study by applying the PSM approach to observational data, allowing us to minimize selection bias and improve data interpretation.

In conclusion, this large prospective cohort study was designed to compare continuous epidural infusion and programmed intermittent epidural boluses on labor analgesia using a "real world" database. We found that PIEB combines with PCEA was superior to CEI combined with PCEA for labor analgesia, including decreasing the incidence of motor block, lessening the local bupivacaine consumption, and reducing the workload of anesthetists. Further investigations into the association between high cumulative dose of fentanyl and increased incidence of low Apgar score in PIEB are needed.

Table 1. Baseline characteristics of study participants before and after PSM

	Before PSM			After PSM		
	CEI n=888	PIEB n=919	St. Diff	CEI n=664	PIEB n=664	St. Diff
Age, mean (SD), years	33.10(5.36)	32.88(5.24)	0.041	33.09(5.42)	32.95(5.08)	0.027
Height, mean (SD), m	1.64(0.07)	1.64(0.07)	0.011	1.64(0.07)	1.64(0.07)	0.009
Body mass index, mean (SD), kg/m^2	30.4(5.3)	30.45(5.5)	0.013	30.42(5.56)	30.47(5.37)	0.002
Race			0.047			0.031
White, n (%)	658(74.1)	685(74.5)		484(72.9)	487(73.3)	
African American, n (%)	104(11.7)	101(11.0)		75(11.3)	76(11.4)	
Asian, n (%)	103(11.6)	114(12.4)		88(13.3)	87(13.1)	
Others, n (%)	23(2.6)	19(2.1)		17(2.6)	50(7.5)	
Single, n (%)	222(25.0)	222(24.2)	0.020	163(24.5)	501(24.2)	0.007
Gestational age, mean (SD), m	39.0(1.8)	38.8(1.9)	0.065	39.02(1.84)	38.95(1.78)	0.040
Gravida, mean (SD), times	2.3(1.6)	2.3(1.5)	0.012	2.28(1.43)	2.27(1.44)	0.004
Parity			0.067			0.082
Nulliparous(P=0)	511 (55.6)	470 (52.9)		361(54.4)	358(53.9)	
Primiparous(P=1)	293 (33.0)	295 (32.1)		210(31.6)	227(34.2)	
Multiparous(P≥2)	119 (13.4)	109 (11.9)		89(13.4)	77(11.6)	
Grand Multiparous(P≥ 5)	6 (0.7)	4(0.4)		4(0.6)	2(0.3)	
Prior labor epidural (≥ 1), n (%)	328(36.9)	448(48.7)	0.109	229(34.5)	229(34.5)	<0.001
Prior C-section (≥ 1), n (%)	49(5.5)	38(4.1)	0.065	27(12.0)	30(4.5)	0.022
Neonatal weight(g)			0.060			0.099
<2500	52(5.9)	61(6.6)		39(5.9)	39(5.9)	
<4000	790(89.0)	800(87.1)		591(89.0)	575(86.6)	
≥4000	46(5.2)	58(6.3)		34(5.1)	50(7.5)	
Twins, n (%)	15(1.7)	7(0.8)	0.084	7(1.1)	7(1.1)	<0.001
Pregnancy Comorbidities	102(11.5)	112(12.2)	0.022	80(12.0)	72(10.8)	0.038
ASA status			0.107			0.026
1, n (%)	13(1.5)	7(0.8)		8(1.2)	7(1.1)	
2, n (%)	810(91.2)	823(89.6)		605(91.1)	602(90.7)	
3, n (%)	65(7.3)	89(9.7)		51(7.7)	55(8.3)	
Smoker (before pregnant), n (%)	112(12.6)	117(12.7)	0.004	81(12.2)	84(12.7)	0.014
Comorbidities disease at baseline						
Cardiovascular disease, n (%)	86(9.7)	68(7.4)	0.082	55(8.3)	53(8.0)	0.011
Pulmonary disease, n (%)	135(15.2)	92(10.0)	0.157	84(12.7)	80(12.0)	0.018
GI/Hepatic disease, n (%)	242(24.3)	76(8.3)	0.513	72(12.8)	76(11.4)	0.019
Endocrinologic disease, n (%)	89(10.0)	86(9.4)	0.022	69(10.4)	67(10.1)	0.010
Hematologic/Oncology disease n (%)	80(9.0)	143(15.6)	0.201	70(10.5)	77(11.6)	0.034
Neurologic/Muscular disease n (%)	45(5.1)	22(2.4)	0.141	18(2.7)	21(3.2)	0.027
Renal disease, n (%)	2(0.2)	3(0.3)	0.019	1(0.2)	0(0.0)	0.055
Psychologic disease, n (%)	187(21.1)	190(20.7)	0.009	134(20.2)	136(20.5)	0.007
Test before initiating an epidural infusion, n (%)	812(91.4)	697(75.8)	0.198	632(95.5)	632(95.5)	<0.001

Table 2. Motor block

	CEI Group (n=664) Events (%)	PIEP Group (n=664) Events (%)	Risk ratio (95% CI)	P value
Motor block (Maximum Bromage score ≥1)	115 (19.92)	31 (4.67)	0.39 (0.29, 0.54)	<0.0001
Partial motor block (Maximum Bromage score =1)	73 (10.99)	25 (3.76)	0.49 (0.35, 0.69)	<0.0001
Partial motor block (Maximum Bromage score =2)	35 (5.27)	5 (0.75)	0.24 (0.11, 0.56)	<0.0001
Complete motor block (Maximum Bromage score =3)	7 (1.05)	1 (0.15)	0.25 (0.04, 1.56)	0.069*

*Fisher's exact test

Table 3. The mean difference (MD) of continuous secondary outcomes

Outcome	CEI Group (n=664) Mean (SD)	PIEB Group (n=664) Mean (SD)	Mean difference (95% CI)	P value
Analgesia				
Total volume (ml)	68.59 (42.02)	107.25 (68.45)	38.66 (32.71, 44.94)	<0.0001
Total bupivacaine dose (mg)	80.33 (47.49)	70.76 (46.56)	-9.57 (-14.53, -4.40)	0.0002
Total fentanyl dose (μg)	130.11 (70.76)	214.82 (80.10)	84.71 (72.36, 97.06)	<0.0001
Hourly bupivacaine dose (mg per hour)	10.94 (4.69)	8.87 (2.51)	-2.07 (-2.48, -1.67)	<0.0001
Hourly fentanyl dose (μg per hour)	18.01 (11.15)	26.86 (8.38)	8.85 (7.79, 9.91)	<0.0001
Duration of labor epidural (hour)	8.33 (5.55)	8.47 (5.82)	0.14 (-0.47, 0.79)	0.663
Received physician-administered epidural bolus (times)	0.56 (0.97)	0.45 (0.88)	0.11 (0.0003,0.20)	0.049
Hourly received physician-administered epidural bolus (times per hour)	0.062 (0.11)	0.061(0.14)	0.001(-0.013, 0.014)	0.962
Total evaluated times	5.80 (3.72)	5.25 (3.31)	-0.55 (-0.93, 0.16)	0.0046
Hourly evaluated times (times per hour)	0.75 (0.28)	0.68(0.28)	-0.07 (-0.10, -0.04)	<0.0001

Table 4. The risk ratio of dichotomous secondary outcomes

Secondary Outcomes	CEI Group (n=664) Events (%)	PIEB Group (n=664) Events (%)	Risk ratio (95% CI)	P value
At least one of abnormal vital signs	277 (41.72)	271 (40.81)	0.98 (0.87, 1.10)	0.738
Hypertension	71 (10.69)	63 (9.49)	0.93 (0.77, 1.13)	0.446
Hypotension	132 (19.88)	153 (2.30)	1.09 (0.96, 1.24)	0.160
Abnormal heart rates	42 (6.32)	54 (8.13)	1.13 (0.94, 1.37)	0.204
High body temperature	12 (1.81)	11 (1.66)	0.96 (0.62, 1.47)	0.833
Abnormal respiration rates	1 (0.15)	5 (0.75)	1.67 (1.16, 2.40)	0.218*
Low oxygen level	56 (8.43)	41 (6.17)	0.83 (0.66, 1.06)	0.114
Prolonged Second stage of labor	38 (5.72)	32 (4.82)	0.91 (0.70, 1.18)	0.461
Instrumental vaginal delivery	46 (6.93)	37 (5.57)	0.88 (0.69, 1.13)	0.308
C-section	106 (15.96)	102 (15.36)	0.98 (0.84, 1.13)	0.763
Apgar score at 1 minutes (<7)	43 (6.48)	57 (8.58)	1.15 (0.96, 1.38)	0.145
Apgar score at 5minutes (<7)	9 (1.36)	13 (1.96)	1.19 (0.83, 1.69)	0.389

*Fisher's exact test

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