Regular intermittent bolus provides similar incidence of maternal fever compared with continuous infusion during epidural labor analgesia

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ABSTRACT

الأهداف: لمقارنة آثار بولس المتقطعة مقابل التسريب المستمر لتخدير الولادة حول الجافية العمل لدرجة حرارة الأم ومستوى مصل انترلوكين 6 (IL–6).

الطريقة: أجريت هذه التجربة العشوائية في نانجينغ مستشفى الولادة ورعاية الطفل الصحية ونانجينغ بمقاطعة جيانغسو. الصين خلال الفترة ما بين أكتوبر 2012م وفبراير 2014م. أما بولس المتقطعة (RIB، ن = 66) أو التسريب المستمر (CI، ن = 66) كانت تستخدم لتخدير ولادة حول الجافية. جرعة بولس (10 مل من 0.08% ropivacaine + 0.4 μg·ml-1 sufentanil) ميكروغرام• أعطيت يدويا مرة واحدة لمدة ساعة في المجموعة RIB، في حين أعطي المحلول بشكل مستمر بمعدل ثابت من 10 مل H–1 في مجموعة CI. تم قياس درجة عن طريق طبلة الأذن ومستوى المصل انترلوكين IL–6 بعد ساعة واحدة بعد الولادة. واحتسب حالات الحمى (≥38ºC).

النتائج: كان حدوث الحمى للأمهات مماثل بين المجموعتين. وكان هناك ارتفاع في متوسط درجة الحرارة مع مرور الوقت في كلا المجموعتين، ولكن لم يم الكشف عن الفروق الإحصائي بين المجموعات في فترة زمنية ؛ أظهرت الأمهات المصل انترلوكين IL–6 تغييرات مماثلة.

الخاتمة: مقارنة مع التسريب المستمر، تقدم بولس المتقطعة مع نفس حدوث حمى الولادة لتخدير حول الجافية. يمكن أن تشارك انترلوكين 6 في الارتفاع مع متوسط زيادة درجة حرارة الأم.

Objectives: To compare the effects of regular intermittent bolus versus continuous infusion for epidural labor analgesia on maternal temperature and serum interleukin-6 (IL-6) level.

Methods: This randomized trial was performed in Nanjing Maternity and Child Health Care Hospital, Nanjing, Jiangsu Province, China between October 2012 and February 2014. Either regular intermittent bolus (RIB, n=66) or continuous infusion (CI, n=66) was used for epidural labor analgesia. A bolus dose (10 ml of 0.08% ropivacaine + 0.4 μg·ml^{-1} sufentanil) was manually administrated once an hour in the RIB group, whereas the same solution was continuously infused at a constant rate of 10 ml·h^{-1} in the CI group. Maternal tympanic temperature and serum IL-6 level were measured hourly from baseline to one hour post partum. The incidences of fever (≥38ºC) were calculated.

Results: The incidence of maternal fever was similar between the 2 groups. There was a rising trend in mean temperature over time in both groups, but no statistical difference was detected between the groups at respective time points; maternal serum IL-6 showed similar changes.

Conclusion: Compared with continuous infusion, regular intermittent bolus presents with the same incidence of maternal fever for epidural labor analgesia. Interleukin-6 elevation could be involved in mean maternal temperature increase.

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The relationship between epidural labor analgesia and maternal intrapartum temperature was investigated, and several lines of studies found that epidural labor analgesia was significantly associated with maternal fever.[1-6] Although an antipyretic effect

of opioids and altered maternal thermoregulation partly explain the etiology, inflammation is involved in the most likely mechanism of fever, such as elevation of maternal serum interleukin-6 (IL-6) levels.[7,8] Regular intermittent epidural bolus, with smaller local anesthetics consumption and better patient satisfaction compared with continuous infusion, is becoming increasingly used for labor analgesia.[9-12] On-demand intermittent epidural injections showed a lower incidence of intrapartum fever in the first 4 hours of labor analgesia than continuous infusion, with similar maternal serum IL-6 levels at respective time points.[13,14] However, the association between regular intermittent epidural bolus and intrapartum fever is still unclear. The aim of the present study was to compare the effects on maternal temperature and serum IL-6 level of regular intermittent bolus versus continuous infusion for epidural labor analgesia.

Methods. We searched for prior related research on the PubMed website using the key words: intermittent, continuous, intrapartum, fever, epidural, labor, analgesia, and interleukin-6. The study protocol was approved by the Institutional Ethics Committee (Nanjing Maternity and Child Health Care Hospital, Nanjing, Jiangsu Province, China) and registered with ClinicalTrials.gov (NCT01708668). All research participants provided written informed consent following the principles of the Helsinki Declaration. Participants consisted of healthy, American Society of Anesthesiologists grade I or II, nulliparous, term women with singleton, vertex pregnancies, and cervical dilatation of 1-3 cm. Parturients were recruited between October 2012 and February 2014. Exclusion criteria included a contraindication to epidural analgesia, a baseline temperature of ≥37.5°C, age <20 years or >45 years, drug abuse, an indication for cesarean delivery, and high-risk pregnancies such as preeclampsia, placenta previa, placental abruption, diabetes mellitus, and hypertension.

One hundred and thirty-two subjects were randomly allocated to receive either regular intermittent bolus (RIB) or continuous infusion (CI) epidural labor analgesia during the latent phase of labor, 66 in each group. Sequentially numbered opaque sealed envelopes containing computer-generated random numbers were used for the group allocation. The unblinded investigator opened the envelopes at the time of randomization; other study personnel and the parturients were all blinded to group allocation. After entering the labor room, the women were intravenously given normal saline warmed to 37°C at a rate of 100 $ml \cdot h^{-1}$ throughout labor. The labor and delivery rooms were maintained at a temperature of 22°±2°C. Maternal tympanic temperature (first temp Genius® thermometer, Sherwood Medical, St. Louis, MO, USA), epidural sensory levels, visual analogue scale (VAS, 0=no pain; 10=worst imaginable pain), and modified Bromage scale (MBS, 0=no motor block; 1=hip blocked; 2=hip and knee blocked; 3=hip, knee, and ankle blocked) were recorded and maternal peripheral venous blood was drawn before epidural insertion and hourly thereafter until one hour post partum. The thermometer, which was calibrated and validated before measurement, was placed lightly in the ear canal according to the manufacturer's guidelines. Maternal fever was defined as a temperature greater than 38 degrees Celsius. Neonatal rectal temperature was collected at one h after delivery. Umbilical venous cord blood was sampled post placental delivery. The blood samples were immediately centrifuged at 3000 g for 10 minutes. The serum was then immediately frozen at -70°C until assay for IL-6. Serum levels of IL-6 were measured in duplicate by enzyme-linked immunosorbent assay (ELISA) with commercially available kits (Quantikine, R&D Systems, Minneapolis, MN, USA). The limit of detection was 0.95 pg/ml for IL-6, and inter- and intra-assay coefficients of variation were below 5%. Additional umbilical cord venous and artery blood were collected for blood gas analysis.

Epidural analgesia was initiated at the L3-4 or L2-3 interspace, and the catheter was inserted 3 cm into the epidural space. A 3 ml test dose of 1.5% lidocaine with 1: 200,000 epinephrine was given, followed by 10 ml of 0.125% ropivacaine + 0.4 $\mu g \cdot ml^{-1}$ sufentanil. Parturients whose VAS scores were larger than 3 mm 15 minutes after the use of a loading dose were excluded from the study. Two syringe pumps (Graseby 3300; Graseby Medical Ltd., Watford, UK) were connected via a 3-way stopcock to the epidural catheter, one (covered

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with black paper) set up for either RIB or CI while the other for patient-controlled analgesia (PCA). The epidural solution for both pumps consisted of 0.08% ropivacaine + 0.4 μg·ml^{-1} sufentanil. In the RIB group, a bolus dose of 10 ml solution was manually given hourly beginning 75 minutes post analgesia. In the CI group, the same solution was continuously infused at a constant rate of 10 ml·h^{-1} beginning 15 minutes post analgesia. The PCA pump was set to deliver a 5 ml bolus dose with a lockout time of 30 minutes. We advised the parturient to push the PCA button whenever she felt uncomfortable. If the pain relief were inadequate 15 minutes after having activated the PCA bolus, a bolus dose of 5-10 ml of 0.15% ropivacaine was manually given until the VAS was <3 mm. The 2 pumps were discontinued one hour after delivery. Consumption of epidural drugs and number of epidural boluses was noted.

Demographic data were recorded. Obstetric characteristics included group B streptococcus (GBS) colonization, number of vaginal examinations, use of oxytocin augmentation, duration from rupture of the membranes to delivery, mode of membranes ruptured, the durations of labor (epidural insertion to delivery) and analgesia (epidural insertion to discontinuation of the pumps), and mode of delivery. Neonatal weight, Apgar scores, and umbilical cord acid-base status were examined. After delivery, placenta was taken for histopathological examination for inflammation with a grade of 2 or higher according to the previously described method.[15]

Statistical analysis. Because the incidence of maternal fever during continuous infusion for epidural labor analgesia varied from 10-33%,[13,16-19] we presumed that the incidence in the CI group was 22%. We calculated that the sample size of 66 patients per group would maintain an 80% power at a 2-tailed significance level of 0.05 to detect a difference in the incidence of maternal fever between the 2 groups, with an incidence of 5% in the RIB group, and a dropout rate of 10%. Continuous variables were compared between the groups using the Student's t test, or the Mann-Whitney U test as appropriate. Categorical data were analyzed by x^2 or Fisher's exact test where appropriate. To detect differences of temperature between 2 groups over time, a repeated measures analysis of variance with Bonferroni correction was performed. Statistical analyses were performed using the Statistical Package for Social Sciences for Windows version 17.0 (SPSS Inc., Chicago, IL, USA). A p-value of less than 0.05 was considered statistically significant.

Results. One hundred and twenty-five subjects completed the study protocol and were finally included in the analyses (**Figure 1**). Three subjects in the RIB group, and 4 women in the CI group were excluded from the study because they opted for a cesarean section without specific reason, with their babies' Apgar scores ≥9 at one minute, and 10 at 5 minutes. The 2 groups were similar regarding maternal age, height, weight, gestation, and baseline cervical dilatation (**Table 1**). The VAS pain scores were significantly higher at 3 and 4 hours post analgesia in the CI group compared with those in the RIB group (**Figure 2**). There were no differences in the epidural sensory levels between the 2 groups (**Table 2**). For the MBS, all subjects had a score of 0 during the study. There was no difference in the incidence of maternal fever (**Table 3**) between the 2 groups. In both groups, a rising trend of mean temperatures over time was found, but did reach statistical significance at any time points compared with corresponding baselines (**Figure 3**). We did not find any statistical difference between the 2 groups at respective time periods regarding mean temperature. Similarly,

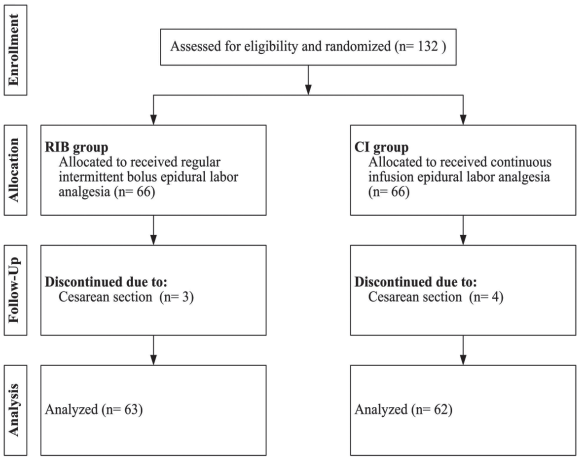

Figure 1 - Flow diagram among 132 subjects that completed the study protocol. RIB - regular intermittent bolus, CI - continuous infusion

Table 1 - Baseline demographic characteristics of epidural labor analgesia patients.

Characteristics	RIB group (n=63)*	CI group (n=62)†	*P*-value
Maternal age, years	27±5	28±5	0.348
Maternal height, cm	159±4	161±5	0.095
Maternal weight, kg	67±9	70±10	0.121
Maternal gestational age, weeks	39.4±0.9	39.7±1.2	0.102
Baseline cervical dilatation, cm	2.2±0.9	2.0±0.8	0.357

Values are mean ± standard deviation.
RIB - regular intermittent bolus, CI - continuous infusion

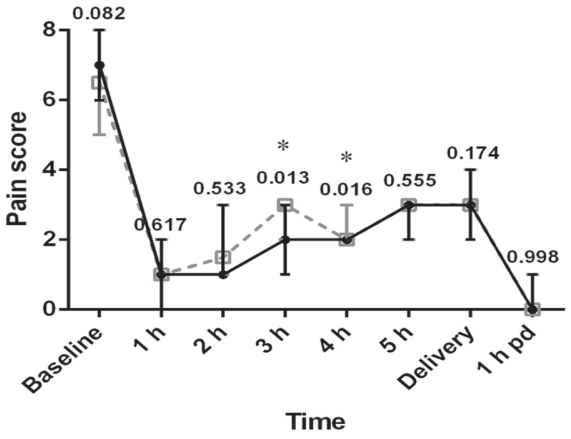

Figure 2 - Visual analogue scale pain scores in RIB (black solid line) or CI group (grey dotted line) over time. Error bars are interquartile range. Compared with RIB group, **p*<0.05. *P*-values are presented at corresponding time point. RIB - regular intermittent bolus, CI - continuous infusion, pd - post delivery.

Table 2 - Sensory block levels (thoracic vertebral level).

Time	RIB group	CI group	*P*-value
1 hour	8 [8- 9] (63)	8 [8- 9] (62)	0.467
2 hour	9 [8- 9] (63)	9 [8- 9] (62)	0.103
3 hour	9 [8- 9] (57)	9 [8- 10] (58)	0.093
4 hour	9 [8- 10] (47)	9 [9- 10] (50)	0.162
5 hour	9 [9- 9] (31)	9 [9- 10] (33)	0.191
Delivery	9 [9- 10] (63)	9 [9- 10] (62)	0.139
1 h post delivery	9 [9- 10] (63)	10 [9- 11] (62)	0.128

Values are median [interquartile range] (denominator).
RIB - regular intermittent bolus, CI - continuous infusion.

Table 3 - Incidence of maternal fever.

Time	RIB group	CI group	*P*-value
1 hour	0 (63)	0 (62)	-
2 hours	1 (63)	2 (62)	0.989
3 hours	0 (57)	2 (58)	0.496
4 hours	2 (47)	4 (50)	0.731
5 hours	4 (31)	5 (33)	1.000
Delivery	6 (63)	7 (62)	0.746
1 h post delivery	4 (63)	5 (62)	0.980
Total	6 (63)	8 (62)	0.549

Values are positive (total). RIB - regular intermittent bolus, CI - continuous infusion.

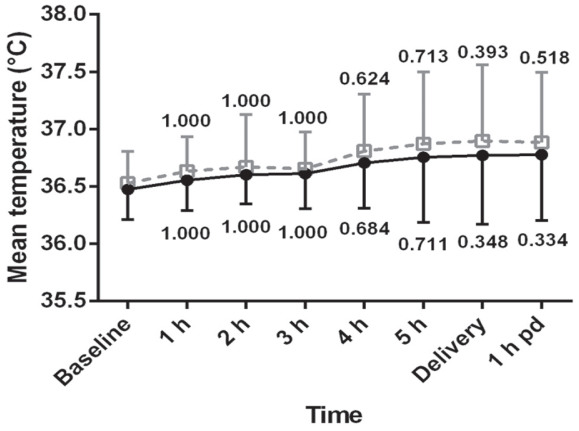

Figure 3 - Maternal mean temperatures in RIB (black solid line) or CI group (grey dotted line) over time. Error bars are mean and standard deviation. Compared with baseline, *p*-values are presented at corresponding time point. RIB - regular intermittent bolus, CI - continuous infusion, pd - post delivery.

maternal serum IL-6 levels showed an elevation trend during labor, and reached statistical significance 2 hours post analgesia compared with the respective baselines in the 2 groups (**Figure** 4). There were no differences in maternal serum IL-6 levels at any time points between the 2 groups. Obstetric, neonatal, and epidural outcomes are listed in **Table** 4, the number of epidural boluses, consumption of ropivacaine, and sufentanil in the RIB group decreased significantly compared with the CI group. No differences were found between the 2 groups with respect to other outcomes. We did not observe statistical differences between the 2 groups with regard to umbilical cord blood gases analyses (data not shown), which were within normal range in all cases.

Discussion. The underlying mechanism of intrapartum maternal hyperthermia during epidural analgesia for labor remains undetermined. However, some studies found that corticosteroids inhibited epidural-associated maternal temperature elevation and reduced the rise of maternal/cord blood IL-6 levels.[19,20] The dominant view of epidural-associated hyperthermia rests on maternal inflammation (elevated levels of maternal serum and cord blood IL-6).[7] Our study demonstrated that maternal mean temperature increased after initiation of epidural analgesia in both groups despite no significant difference, and was accompanied by a rise in maternal serum IL-6 concentrations, which is similar to a previous study.[14] We did not find any difference in neonatal rectal temperature and umbilical venous serum IL-6 between the groups. We compared maternal mean temperature and serum IL-6 hourly following epidural analgesia initiation, and found that IL-6, a marker of the acute inflammation response, more significantly than mean temperature did. Taking into account normal umbilical cord blood gases analyses, we suggest that an increase of maternal serum IL-6 is associated with physical stress and noninfectious inflammation, irrespective of the mode of epidural analgesia.[8,21]

In the present trial, we employed regular intermittent bolus epidural labor analgesia, which provided lower pain scores and fewer narcotics consumption compared with continuous infusion. This finding is in accordance with earlier observations in which intermittent epidural boluses reduced the incidence of breakthrough pain or local anesthetic consumption.[9,12]

We found no difference in the incidence of maternal fever between the 2 groups at any time point. This is not consistent with a similar study[13] that showed intermittent epidural injections lead to a lower incidence of intrapartum fever in the first 4 hours post analgesia compared with continuous infusion. One reason for this may be due to the difference of bolus interval. Epidural analgesia restrains lower body sweating via blocking sympathetic nerves. In the previous study,[13] intermittent boluses were injected at the patients' request on average every 75 minutes, which was longer than our intervals by 15 minutes. The longer bolus interval perhaps allows more restoration of heat loss, thereby avoiding heat retention resulting from sympathetic blockade. By contrast, continuous epidural infusion continuously produces heat retention, which explains the higher maternal mean temperature compared with intermittent boluses, although no statistical difference was found. The other potential reasons include the differences in analgesic type and labor room temperature.

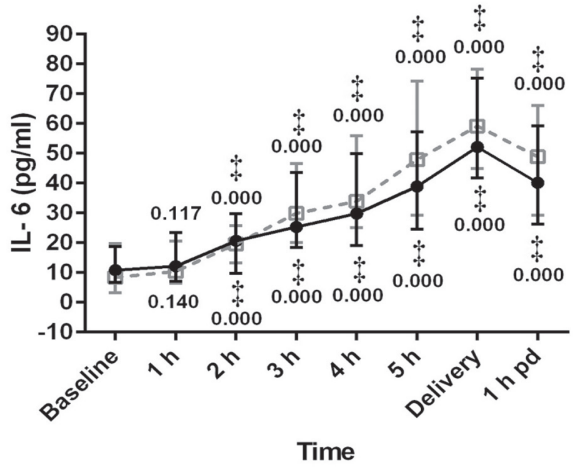

Figure 4 - Maternal serum IL-6 levels in RIB (black solid line) or CI group (grey dotted line) over time. Error bars are interquartile range. Compared with baseline, ‡p<0.001. P-values are presented at corresponding time point. RIB - regular intermittent bolus, CI - continuous infusion, pd - post delivery, IL-6 - interleukin-6

There is little evidence that intrapartum fever is attributed to placental infection in parturients who received epidural labor analgesia or not.[8,22] The present study also showed that epidural-associated fever is not necessarily linked to placental inflammation. Despite the presence of clear contrary evidence that epidural-associated fever only developed in those with placental inflammation, still other risk factors (length of labor) are involved.[23] Our present study investigated the association between regular intermittent bolus for epidural labor analgesia, which was the optimized method of epidural labor analgesia, and maternal

Table 4 - Obstetric, neonatal, and epidural outcomes among 125 subjects.

Outcomes	RIB group (n=63)	CI group (n=62)	*P*-value
Group B streptococcus positive	1 (1.6)	2 (3.2)	0.989
Number of vaginal examinations	2.3±0.6	2.5±0.8	0.155
Oxytocin augmentation	40 (63)	44 (71)	0.373
Rupture of the membranes to delivery, min	206±100	230±107	0.186
Artificial rupture of membranes	32 (51)	40 (65)	0.121
Duration of labor, min	302±91	322±102	0.251
Duration of analgesia, min	362±91	382±102	0.251
Instrumental delivery	3 (5)	5 (8)	0.697
Placental inflammation	4 (6)	5 (8)	0.980
Neonatal weight, g	3406±337	3313±325	0.118
Apgar score (1 min)	10 [10-10]	10 [10-10]	0.766
Apgar score (5 min)	10 [10-10]	10 [10-10]	0.551
Neonatal rectal temperature, °C	36.6±0.3	36.7±0.5	0.248
Umbilical venous serum IL-6, pg/ml	12.4 [8.9-18.8]	10.1 [3.3-19.8]	0.088
Consumption of ropivacaine (mg)	60±16	70±20	0.003
Consumption of sufentanil (μg)	27±8	32±9	0.003
Number of epidural boluses	1.0±0.8	1.5±1.0	0.002

Values are number (percentage), mean ± standard deviation, or median [interquartile range]. RIB - regular intermittent bolus, CI - continuous infusion

temperature, and the results showed that it did not reduce the incidence of maternal fever when compared with continuous infusion. Although a negative result was indicated, this provides further understanding of the mechanism of intrapartum fever induced by different epidural injection methods, and provides implication for further research.

There are some limitations in our trial. Firstly, we did not use programmable infusion pumps because they were unobtainable, which provide more precise administration of drugs than manual administration. Secondly, sweating was not measured in our study, which may play an important role in fever. Finally, although we recorded maternal temperature from epidural until one hour postpartum, the subsequent temperature change was unknown.

In conclusion, regular intermittent bolus shows a similar incidence of maternal fever and better analgesia compared with continuous infusion during epidural labor analgesia. The epidural-related rise in maternal temperature could be attributed to noninfectious inflammation, such as IL-6 level elevation.

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