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S100 β in Newborns after C-Section with General versus Epidural Anesthesia: a prospective observational study

Zhendong Xu¹, Zhiqiang Liu^{1,*}, Yueqi Zhang¹, Chunhong Jin¹, Fuyi Shen¹, Yibing Yu¹, Ted Cheek², Onyi Onuoha², Ge Liang², Richard C Month², Joshua Atkins², Kha M Tran³, and Huafeng Wei^{2,*}

¹Department of Anesthesiology, Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine, Shanghai, 201204, China

²Department of Anesthesiology and Critical Care, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, United States of America

³Department of Anesthesiology and Critical Care, Children Hospital of Philadelphia, Philadelphia, PA 19104, United States of America

Abstract

Background—Preclinical evidence suggests that general anesthetics can dose-dependently induce neurodegeneration in the developing brains of animals which can be reliably determined by measurement of blood S100 β , but this correlation remains unclear in humans. We hypothesized that S100 β would not be increased in cord arterial blood of fetuses exposed briefly to general anesthetics during a C-section, compared to epidural anesthesia.

Methods—A prospective observational clinical study comparatively measured changes of brain damage biomarker S100 β ratio of umbilical artery over vein (changes after fetus circulation) immediately after delivery under C-section with either epidural or general anesthesia. Newborn blood gas measurements, APGAR scores and maternal wellbeing were also compared.

Results—Compared to epidural anesthesia, general anesthesia resulted in the lower S100 β ratio of umbilical artery over the vein (medium 2.64, [quartiles 1.39, 3.45] vs. medium 1.59, [quartiles 0.88, 2.01], $P=0.031$), without changing the S100 β level in the vein of the mother. There was no significant difference between general and epidural anesthesia when comparing other maternal and newborn parameters.

Conclusion—S100 β levels in newborn after C-section is lower with general anesthesia than epidural anesthesia, with unclear mechanisms.

Keywords

Anesthesia; S100 β ; Neurodegeneration; C-section; Newborn

*Corresponding author: Huafeng Wei, Department of Anesthesiology and Critical Care, Perelman School of Medicine, University of Pennsylvania, 305 John Morgan Building, 3620 Hamilton Walk, Philadelphia, PA 19104, United States of America, wei@uphs.upenn.edu. Zhiqiang Liu, Department of Anesthesiology, Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine, 2699 Gaoke West Road, Shanghai, 201204, China, drliuzhq@hotmail.com. DR ZHENDONG XU (Orcid ID : 0000-0002-2696-3492)

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Introduction

Preclinical data from both tissue cultures and animal studies suggest a neuroprotective effect of general anesthetics (GAs) against various stresses including hypoxia and ischemia^{1,2}. On the other hand, GAs have also been shown to be especially neurotoxic to the developing brain of various animal species in a dose- and time-dependent manner and may be associated with long-term learning or developmental disorders^{3–5}. Unfortunately, neither the neuroprotective nor the neurotoxic effects of GAs have been clearly confirmed in human subjects. The mechanisms of general anesthesia-mediated dual effects of both neuroprotection and neurotoxicity in preclinical studies are unclear, although several hypotheses have been proposed.

It is therefore essential that the dual effects of neuroprotection and neurotoxicity by GAs in the developing brain are clearly defined and confirmed in human studies. The high sensitivity of the developing brain to the neurotoxic properties of GAs as described in preclinical studies^{6,7}, is concerning to parents whose children receive general anesthesia for various surgeries. However, there is controversial retrospective clinical data on whether GAs used in the developing brain cause long-term learning disability or developmental disorders, with some supporting^{8–10} and refuting evidence in the literature^{11,12}. Two recent international multicenter prospective clinical trials (detected no general anesthesia-associated neurodevelopmental or neurobehavioral disorders^{13,14}, although the possible long-term neurotoxic effects of GAs at high concentration for prolonged use could not be excluded.

Both prospective and retrospective clinical trials have examined the long-term learning and behavioral disability resulting from anesthetic exposure to the developing brain using a battery of complex behavioral tests. Availability of a reliable biomarker to detect anesthesia neurotoxicity acutely in the developing brain can advance the research in this area positively. A commonly used biomarker for brain damage is a calcium binding protein primarily from glial cells, S100 β , which has been considered a sensitive biomarker to detect brain damage after various stresses, including ischemia¹⁵ and trauma^{16,17}. S100 β is a sensitive and reliable biomarker to predict fetus hypoxia and ischemia damage in pregnant patients and has been used for such purposes¹⁵. Our previous studies have also demonstrated the use of plasma S100 β as a sensitive biomarker to detect brain damage when the fetus brain is exposed to a high concentration of general anesthetics, with a good correlation between the level of apoptosis and the exposure to general anesthesia detected in the fetus brain¹⁸. S100 β has been shown to be valuable in animal models for detecting general anesthesia-mediated acute neurologic damage in the developing brain^{18–20}. However, its effectiveness and usefulness to reflect anesthesia associated brain damage in human subjects is yet to be confirmed.

Although most cesarean sections (C-sections) are completed under epidural anesthesia, emergent and elective cesarean deliveries occasionally need to be completed under general anesthesia. In such instances, the fetus brain may be briefly exposed to GAs during the C-section. It is not clear whether a brief exposure of the developing fetal brain to general anesthesia is harmful. Umbilical artery blood come from the fetus circulation and reflects

changes on fetus side, while the umbilical vein blood originate from the placenta and demonstrate changes on mother side. Utilizing the brain damage biomarker, S100 β , we compared the ratio of S100 β from umbilical artery over vein (UA/UV) immediately after delivery (after fetus circulation) from newborn delivered with C-section under either epidural or general anesthesia. We hypothesized that the brain damage biomarker, S100 β , would not be increased in cord arterial blood of fetuses exposed briefly to general anesthetics during a C-section, compared to epidural anesthesia.

Materials and Methods

Two similar clinical study protocols were approved by the Institutional Review Board (IRB) from the Shanghai First Maternity and Infant Hospital (SFMIH), Tongji University School of Medicine, Shanghai, China, and the Hospital of the University of Pennsylvania (HUP), Philadelphia, USA separately. The study protocol was registered in the Chinese Clinical Trial Registry (registration no. ChiCTR-OOC-15007163). Written informed consent was obtained from patients scheduled for C-section under epidural or general anesthesia. The inclusion criteria included American Society of Anesthesiologists physical status I or II, and term gestation at 36 weeks or more. Exclusion criteria included age <18 years, known maternal neurologic abnormality, known fetal neurologic defect; preeclampsia, diabetes mellitus, intrauterine growth retardation, or allergy to any study medication.

The indications for general anesthesia (GA) in this patient population were as follows: obstetrician request based on maternal and fetus status for emergent C-section. Elective C-section were elected secondary to maternal request after failed regional block, coagulopathy/bleeding risk, history of lumbar traumatic injuries or operation, severe lumbar disc protrusion and rachioscoliosis, history of bad back pain and/or laminectomy, back infection, scare of needle on back. All C-sections under GA in SFMIH were elective while all cases at HUP were emergent. A total of 160 patients were screened and 77 recruited at SFMIH, while 86 patients were screened and 24 recruited at HUP for the study between February 2012 and May 2015.

Anesthesia

During the C-section, patients were maintained in the supine position with a 15-degree left lateral tilt. Electrocardiogram measurements, noninvasive blood pressure (NBP) readings of the left upper arm and pulse oxygen saturation (SpO₂) were obtained. A baseline NBP reading including systolic, diastolic and mean blood pressures (SAP, DAP, MAP) were measured and documented.

Patients in the epidural anesthesia (EA) group were placed in the right lateral or sitting position. EA was administered at the L2–L3 vertebral interspace through an epidural catheter, which was secured at 3–5 cm into the epidural space. The parturient was thereafter returned to the supine position with a 15° left lateral tilt. EA induction and maintenance was achieved with 1.5% lidocaine, sodium bicarbonate and 1: 200,000 epinephrine. Oxygen at 4 L/min was administered via nasal catheter. Surgery was initiated when the sensory block level was above T6 and Bromage score was grade 3.

Patients in the GA group were induced with propofol 2 mg/kg and succinylcholine 2 mg/kg intravenously, and maintained with 0.75 MAC of sevoflurane at SFMIH or 0.75 MAC of desflurane at HUP. Surgery was initiated after verification of the appropriate placement and position of the endotracheal tube by capnography. An observer collected all intraoperative data. Occurrence of hypotension and hypoxia were recorded. Hypotension was defined as a greater than 20% decrease in SAP below the baseline value and was treated with intravenous phenylephrine. Hypoxia was defined as $SpO_2 < 95\%$. Time from anesthesia induction to incision, and time from incision to delivery were also noted.

After the delivery of the baby, the neonatal condition was evaluated by the pediatricians and Apgar scores (at 1 and 5 min) were assigned and documented. Immediately after delivery of baby from the uterus, a portion of umbilical cord (~10–15 cm) was clamped on both side to prevent loss of blood and the newborn baby was then separated from the placenta by cutting the cord between the clamp away from the placenta side and the newborn baby. The placenta was delivery shortly after baby delivery, and 1–5 ml of blood was taken from the umbilical vein and artery between two clamped sides immediately after placenta delivery. This protocol will assure that cord arterial blood S100 β between two clamps was not contaminated by the placenta S100 β after the clamping and reflected true S100 β concentrations in cord arterial blood originated from the newborn. A portion of the blood was immediately injected into a blood gas/electrolyte analyzing system (ABL-80 FLEX, Radiometer) for blood partial pressure of CO_2 (PCO_2), blood partial pressure of O_2 (PO_2), blood pH and base excess (BE), and the remaining blood sample was used for the S100 β study assay. 5 ml of blood was also taken from the mother via the existing peripheral intravenous catheter for S100 β assay. The blood samples were immediately centrifuged at 2500 RPM for 10 minutes and the supernatant collected and stored at minus 80-degree temperature until the measurement of S100 β level.

S100 β serum concentrations were measured using ELISA assay. Commercially available ELISA kits were used: EZHS100B-33K, Human S100 β ELISA, EMD Millipore, Billerica, MA, USA was used at SFMIH, and Sangtec ® 100 ELISA, DiaSorin Inc., Stillwater, MN, USA was used at HUP. Following the manufacturer's protocol, each sample was incubated with the tracer from the kit for 2h. Then tetramethylbenzidine was added. The reaction was then stopped with stop solution and the absorbance of the samples read at 450 nm and 590nm using Spectramax M5 plate reader (Molecular Devices, Sunnyvale, CA, USA) at SFMIH, and read at 450 nm by Synergy H1 microplate reader (Bio-Tek Instruments Inc., Winooski, VT, USA) at HUP. The standard concentration curve was plotted to determine the concentrations of the samples.

We had a deviation from original study protocol. The concentration of S100 β in maternal amniotic fluid was not reported, for it is extremely low and could not be measured by S100 β kit.

Statistical Analyses

The primary outcome was the group differences of S-100 β level in umbilical blood in the GA group and EA group. The secondary outcomes were group differences in umbilical blood gas measurements and neonatal outcomes.

Based on previous study²¹, a sample size of 32 per group calculated by power analysis PASS 11 (NCSS, Kaysville, UT) was required to achieve a statistical power of 91%, at a 5% level of significance. Univariate intergroup data were tested for normality using the Kolmogorov–Smirnov test. Demographic data and blood gas parameters were presented as means, if normally distributed, or as median and range, if not normally distributed, and group differences were compared using Student t test or the Mann–Whitney U test when appropriate. Nominal data were compared using the chi-square test or Fisher’s exact test. Analyses were performed using GraphPad Prism Software (Version 6.1) for Windows. Two-sided P values less than 0.05 were considered statistically significant.

Results

Patient recruitment and flow are presented in Fig 1. Seventy-seven patients at SFMIH and twenty-four patients at HUP were recruited for the study but after exclusions, data were analyzed from 63 patients at SFMIH and 23 patients at HUP. Twenty-seven patients received general anesthesia and 36 patients received epidural anesthesia at SFMIH. Three patients received general anesthesia and 20 patients received epidural anesthesia at HUP. Although initial design intended to combine data from two hospitals as a two centers clinical trial, the pattern of inclusion and the practical details of the assay prevented this possibility. The difficulty includes the variation in patient population and the different measurement kits for S100 β by the different staff and the unbalanced patient population for general anesthesia for elective or emergent C-section. Therefore, we have presented the data from the two different hospitals separately. Nonetheless, parallel comparisons between the two hospitals, especially for the trend of changes, are analyzed and discussed.

Demographics and clinical characteristics of patients at SFMIH are shown in table 1. Patients in both groups were similar in age, weight, height, body mass index, parity, gestational age and incidence of hypotension or hypoxia after anesthesia induction. Time from anesthesia induction to incision in the EA group was longer than the GA group (25 ± 3.4 vs. 4.1 ± 0.8 min, $P<0.001$), and time from incision to delivery (min) was also significantly longer in the EA group compared to the GA group (5.9 ± 1.8 vs. 5.0 ± 1.1 min, $P=0.039$).

Neonatal outcome at SFMIH was also summarized in table 2. All Apgar scores at 1 and 5 min were similar. The mean neonatal weight and gender were not significantly different between the EA and GA groups. Blood gas readings of the umbilical artery (UA) and umbilical vein (UV) in the SFMIH patients only are presented in table 2. There were no differences in the pH, PCO₂, PO₂ and base excess (BE) between both groups at SFMIH. Fetal blood gas measurements were unavailable at HUP.

Demographics and clinical characteristics (maternal and neonatal) of the patients at HUP are presented in Table 3. Patients in the EA group were older than those in the GA group ($P=0.046$). Apgar scores (1 min and 5min) of neonates in GA group were significantly lower than those in the EA group. Time from anesthesia induction to incision in the EA group was significantly longer when compared to the GA group (21.0 ± 5.2 vs. 3.3 ± 2.6 min, $P=0.001$). There were no significant differences in weight, height, body mass index, parity, gestational age and incidence of hypotension or hypoxia between two groups.

As shown in figure 2, although there were no significant differences in the UA or UV S100 β concentration between the EA and GA groups in both hospitals (Fig. 2A and B), the S100 β UA/UV ratio was significantly lower with GA than EA (Fig. 2C) in SFMIH. Interestingly, the changes in the trend of S100 β UA/UV ratio at HUP (Fig. 2D) were similar to the results seen at SFMIH although statistical difference was not achieved most likely due to the sample size, which was underpowered. Although no statistical difference ($P=0.061$), UA and UV difference (UA-UV) in GA group ($0.059 [-0.012, 0.165] \mu\text{g/L}$) clearly trended to be lower than that in EA group ($0.198 [0.038, 0.394] \mu\text{g/L}$) in SFMIH (Fig. 2E). The absolute UA and UV difference (UA-UV) in HUP was also presented in Fig. 2F, with same trend as in SFMIH. There was no significant difference in the maternal venous S100 β of the patients at SFMIH (Figure 3).

These results demonstrated a significant decrease of UA/UV S100 β ratio after general anesthesia compared to epidural anesthesia, but no significant changes of S100 β in maternal mother vein, suggesting that the short exposure of general anesthetics to the fetus developing brain does not increase neurodegeneration biomarkers acutely.

Discussion

It is generally accepted that properly designed prospective controlled clinical trials provide more valuable information for clinical practice than retrospective clinical studies. Given the multiple controversial results from available retrospective studies about anesthetic neurotoxicity in the developing human brain, it is essential that more prospective clinical trials be performed for definitive or better conclusions on this subject matter. Primary outcomes of two currently ongoing international randomized controlled clinical studies (GAS and PANDA studies) are focused on studying learning and developmental disorders by the use of a battery of behavioral tests^{13,14,22}. The use of biomarkers as a reliable diagnostic tool for identifying acute damage by general anesthetics in the developing brain would be desirable. With animal studies suggesting a good correlation between elevated plasma S100 β and pathological neurodegeneration in the developing brain^{18–20,23}. In addition to its high sensitivity to detect fetal brain damage from asphyxia or stresses before birth^{15,24–26}, S100 β is clearly a good candidate to be tested in related clinical studies. This study suggests that S100 β can be used to detect general anesthesia-mediated neurodegeneration in the developing brain because the trend of S100 β changes of UA, UV and UA/UV from two different hospitals are the same, suggesting it is a reliable peripheral biomarker from different patient populations. In addition, these results are also consistent with previous retrospective clinical studies indicating that multiple exposures rather than a single exposure to GAs during infancy contributes to increased learning disability⁸. A previous study has demonstrated that children born via C-section under general anesthesia did not have increased long-term developmental disorders when compared to those born under epidural anesthesia¹². The range of S100 β in umbilical cord blood during normal delivery without anesthesia varied widely in different studies, for examples, $0.32 \mu\text{g/L}$ (range $0.18–5.27 \mu\text{g/L}$)²⁷, $0.4 \pm 0.05 \mu\text{g/L}$ ²⁸, and $1.10 \mu\text{g/L}$ (range $0.38–5.50 \mu\text{g/L}$)²⁹ etc. In this study, the median level of S100 β level in UA and UV under general vs epidural anesthesia are $0.230 \mu\text{g/L}$ vs $0.310 \mu\text{g/L}$ and $0.133 \mu\text{g/L}$ vs $0.113 \mu\text{g/L}$ respectively, higher S100 β in UA with epidural anesthesia than general anesthesia. The UA/UV ratio will reflect the

percentage change after fetus blood circulation, presumably after CNS circulation also. One explanation of general anesthesia mediated lower level of S100 β is that short exposure of general anesthetics may cause mild to moderate elevation of cytosolic calcium concentration via activation of InsP3 or ryanodine receptors, inducing endogenous neuroprotective mechanisms³⁰ and reduce the release of S100 β into blood stream. More clinical trials in the future are needed to confirm the sensitivity and specificity of S100 β to detect possible anesthesia-mediated harmful effects to the developing brain when used at extreme high concentrations, such as during fetal surgery^{31,32}.

It is not clear why UA/UV S100 β ratio is significantly lower in newborns delivered with C-section under GA than EA. One possible explanation is that the short exposure to GA may provide neuroprotection against stresses during delivery by preconditioning^{1,23,33}. If the dual effects of neuroprotection and neurotoxicity of GAs are based on the concentration and duration of anesthesia as proposed in the preclinical studies^{30,34}, it is speculative that extreme high concentration and prolonged duration of GA used during fetal surgery^{31,32} may have an increased risk of anesthesia-related neurotoxicity in the fetal developing brain. Another possible reason could be due to the duration from start of induction of anesthesia to the delivery of the newborn, which is much faster under GA than EA, hence decreasing the exposure of the developing brain to various stress factors that could subsequently increase S100 β . Nevertheless, the results from this study at least suggest that short exposure of general anesthetics to fetus developing brains during C-section was less likely to cause fetal brain damage, although the mechanisms why GAs decreased S100 β , compared to EA, is not clear.

It is interesting to note that the S100 β level in the maternal vein was not significantly different between GA and EA, contrary to the significant decrease with the newborn UA/UV S100 β ratio after general anesthesia. Considering the fact that the adult brain is much less vulnerable to anesthesia neurotoxicity than the developing brain^{7,35,36} in conjunction with the short exposure of GA to the maternal CNS during C-section, it is possible that the differences in the changes of S100 β between the fetus and mother reflect the high vulnerability of the developing brain to anesthesia neurotoxicity demonstrated in preclinical studies^{5,7}. On the other hand, the level of plasma S100 β in the mother's vein may be affected by multiple factors, such as contribution from the fat or muscle due to the incision of the abdominal wall and the uterus. In other words, the S100 β level in the mother's vein may not be as specific as its indication of brain neurodegeneration as in the fetus UA/UV ratio. A previous study had demonstrated that EA during C-section may significantly suppress the level of stresses in both mother and fetus³⁷, which may also contribute to the decreased level of S100 β compared to the GA during C-section in this study.

Limitations

Although the clinical protocols utilized in both institutions (University of Pennsylvania Hospital (HUP) and the Shanghai First Maternity and Infant Hospital (SFMIH)) were the same, the kits used to measure S100 β were not from the same company. This may contribute to the different baseline level of S100 β and thus, made it difficult to combine the data from the two hospitals. However, the trend changes of S100 β in UA, UV and the UA/UV ratio

were similar in both hospitals, a strength supporting the reliability of utilizing S100 β as a brain damage biomarker in this clinical protocol. It is obvious that the number of GAs at HUP were too low to perform any meaningful statistical analysis. This is mostly due to the considerably decreased probability of using GA for elective C-sections in the United States of America and the significant time restraint involved in obtaining study consent before an emergent C-section. The percentage of patients who received EA for labor analgesia at SFMIH (40~60%) is obviously lower than HUP (>90%), hence increasing the likelihood of receiving GA for urgent C-section much higher at HUP. Nevertheless, the parallel comparison of S100 β data from two hospitals and the similar changes in trend observed strengthen the reliability of S100 β as a brain damage biomarker in this patient population. Due to the lack of desflurane at SFMIH, a different volatile anesthetic (sevoflurane) was used however, at equivalent concentration (0.75 MAC). This may have had a confounding effect if data from the two different hospitals were combined for statistical analysis. Although S100 β is a highly sensitive biomarker to detect brain damages by various harmful factors¹⁷, it is relatively less specific as there are S100 β . Extra-neural sources of S100 β also include muscle, kidney and heart^{38,39}. So the specificity of S100 β for acute brain injury is generally low⁴⁰. A combination of different biomarkers, such as neuron-specific enolase (NSE), glial fibrillary acidic protein (GFAP) and tau protein etc., will be needed to improve predictive ability of brain injury in further work. S100 β in blood is regarded as extracellular S100B passing into the blood through a disrupted blood–brain barrier (BBB)⁴¹. Hence, increased blood concentrations of S100B is considered an early marker of the disruption of BBB after head injury, thus not always as a sign of neuronal damage. Measures are necessary to minimize S100 β contribution from other source other than CNS. The relatively high Apgar score of newborn baby from elective C-section at SFMIH versus low APGAR scores in newborn from emergent C-section at HUP under general anesthesia warrant future studies with more emergent cases for adequate power to perform proper statistical analysis.

Because this is not a randomized controlled study, it is difficult to eliminate some confounding factors that cause fetal stress and changes in S100 β . Nevertheless, we have tried our best to compare the most commonly seen cofounders that may cause fetal stress during or after C-section, such as maternal hypoxia or hypotension, fetal blood gas and Apgar score. There was no significant difference between general versus epidural anesthesia on these monitored parameters.

In summary, general anesthesia during C-section did not increase but decreased biomarker S100 β in newborn blood compared to epidural anesthesia, implicating a decreased likelihood for GA-mediated fetus brain damage during C-section.

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Fig 1. Trial diagram of enrolled patients

SFMIH=Shanghai First Maternity and Infant Hospital in China; HUP=Hospital of the University of Pennsylvania; C-section=cesarean section; GA=general anesthesia; EA=epidural anesthesia; UA= umbilical artery; UV= umbilical vein.

Fig 2. The S-100β levels in umbilical vein (UV) and in umbilical artery (VA) blood and the ratio of S-100β (UA/UV) at SFMIH and HUP

Median, quartiles, and the highest and lowest values were shown. The Mann-Whitney U-test was used for comparison between groups of data. Data were presented as median (interquartiles). A P value of less than 0.05 was considered Statistical significance.

(A) S100β in UV were not significantly different between EA (0.113 [0.093, 0.165] μg/L, 95% CI [0.110, 0.196] μg/L) and GA group (0.133 [0.098, 0.235] μg/L, 95% CI [0.138, 0.242] μg/L) at SFMIH. No significant difference was found in UA between EA (0.310 [0.148, 0.549] μg/L, 95% CI [0.311, 0.568] μg/L) and GA group (0.230 [0.146, 0.365] μg/L, 95% CI [0.216, 0.523] μg/L) at SFMIH.

(B) S100β in UV was not significantly different between EA (0.311 [0.212, 0.587] μg/L, 95% CI [0.268, 0.668] μg/L) and GA group (0.972 [0.332, 1.863] μg/L, 95% CI [-0.855, 2.966] μg/L) at HUP. No significant difference was found in UA between EA (1.379 [0.799, 1.987] μg/L, 95% CI [1.040, 1.704] μg/L) and GA group (1.626 [1.287, 1.973] μg/L, 95% CI [0.777, 2.480] μg/L) at HUP.

(C) The ratio of S100β was significantly higher in EA group (2.64 [1.39, 3.45], 95% CI [2.25, 5.16]) than in GA group (1.59 [0.88, 2.01], 95% CI [1.24, 4.03]) at SFMIH,

*P=0.031. EA group: N=36, GA group: N=27.

(D) Ratio of S100 β (UA/UV) in EA (3.57 [1.76, 6.07], 95%CI [2.80, 5.91]) and GA group (1.32 [0.87, 5.94], 95%CI [-4.26, 9.69]) was not significantly different at HUP. EA group: N=20, GA group:N=3.

(E) The absolute UA and UV difference (UA-UV) in EA (0.198 [0.038, 0.394] $\mu\text{g/L}$, 95%CI [0.151, 0.422] $\mu\text{g/L}$) and GA group (0.059 [-0.012, 0.165] $\mu\text{g/L}$, 95%CI [0.017, 0.342] $\mu\text{g/L}$) was not statically different at SFMIH, P=0.061. EA group: N=36, GA group:N=27.

(F) The absolute UA and UV difference (UA-UV) in EA (0.893 [0.437, 1.361] $\mu\text{g/L}$, 95%CI [0.637, 1.172] $\mu\text{g/L}$) and GA group (0.315 [-0.237, 1.641] $\mu\text{g/L}$, 95%CI [-1.825, 2.970] $\mu\text{g/L}$) was not different at HUP, P=0.276. EA group: N=20, GA group:N=3.

HUP=Hospital of the University of Pennsylvania; SFMIH=Shanghai First Maternity and Infant Hospital in China; EA= epidural anesthesia; GA=general anesthesia.

Fig 3. The S-100 β levels in maternal vein (MV) blood at SFMIH

Median, quartiles, and the highest and lowest values were shown. The Mann-Whitney U-test was used for comparison between groups of data. Data were presented as median (interquartiles). A P value of less than 0.05 was considered Statistical significance. S100 β was not significantly different between EA (0.011 [0.008, 0.017] $\mu\text{g/L}$, 95%CI [0.008,0.032] $\mu\text{g/L}$) and GA group (0.016 [0.007, 0.036] $\mu\text{g/L}$, 95%CI [0.016,0.036] $\mu\text{g/L}$). SFMIH=Shanghai First Maternity and Infant Hospital in China; EA= epidural anesthesia; GA=general anesthesia.

Table 1

Maternal demographics and clinical characteristics (SFMIH)

	EA group (N=36)	GA group (N=27)	P value
Age	31.8±3.9	31.9±3.3	0.898
Weight (kg)	69.7±6.8	71.5±9.6	0.382
Height (cm)	161±49	161±54	0.955
Body mass index (kg/m ²)	26.7±2.3	27.4±3.6	0.316
Parity (primiparous/multiparous)	25/11	17/10	0.589
Gestation (weeks)	38.9±1.0	38.5±0.8	0.141
Hypotension after anesthesia induction (n)	15(41.7%)	8(29.6%)	0.326
Hypoxia (n)	0	0	1
Time from anesthesia induction to incision (min)	25±3.4	4.1±0.8	<0.001
Time from incision to delivery (min)	5.9±1.8	5.0±1.1	0.039

Data presented as mean±SD or n (%).

Group differences were compared using Student t test. Nominal data were compared using the chi-square test.

SFMIH=Shanghai First Maternity and Infant Hospital in China; EA= epidural anesthesia; GA=general anesthesia.

Table 2

Neonatal Data (SFMIH)

	EA group (N=36)	GA group (N=27)	P value
Apgar score (1 min)	10(9,10)	10(8,10)	0.745
Apgar score (5 min)	10(10,10)	10(10,10)	0.390
Male / Female	18/18	14/13	1
Weight (g)	3407 ± 406	3407 ± 363	0.999
UV blood			
pH	7.30 ± 0.07	7.28±0.05	0.259
PCO ₂ (mmHg)	49.12±8.28	47.89±7.66	0.55
PO ₂ (mmHg)	53.31±15.74	56.20 ±13.62	0.448
BE	-4.17±1.64	-4.79±1.29	0.112
UA blood			
pH	7.27±0.07	7.25±0.06	0.271
PCO ₂ (mmHg)	50.91±7.94	49.50±8.00	0.492
PO ₂ (mmHg)	44.53±13.65	43.60±11.88	0.779
BE (mmol/L)	-4.92±1.14	-5.12±1.24	0.497

Data presented as Mean±SD or n. Apgar scores presented as median (interquartile).

Group differences were compared using Student t test, and Apgar score were compared using Mann-Whitney U test. Nominal data were compared using the chi-square test. SFMIH=Shanghai First Maternity and Infant Hospital in China; EA= epidural anesthesia; GA=general anesthesia; UA= umbilical artery; UV= umbilical vein; BE=Base excess.

Table 3

Maternal and neonatal demographics and clinical characteristics (HUP)

	EA group (N=20)	GA group (N=3)	P value
Age	27.4±6.9	18.7±1.2	0.046
Weight (kg)	87.9±20.1	96.0±38.0	0.564
Height (cm)	163.3±6.3	158.2±1.6	0.210
Body mass index (kg/m ²)	32.9±6.9	39.1±13.4	0.211
Parity (primiparous/multiparous)	12/8	3/0	0.525
Gestation (weeks)	38.5±2.5	39.4±1.1	0.572
Hypotension after anesthesia induction(n)	10(50%)	1(33.3%)	1
Hypoxia (n)	0	0	1
Time from anesthesia induction to incision (min)	21.0±5.2	3.3±2.6	0.001
Time from incision to delivery (min)	9.0±5.7	2.5±0.9	0.068
Apgar score (1 min)	8(6,3,9)	2(2,5)	0.001
Apgar score (5 min)	9(9,9)	8(6,8)	0.011
Neonatal Gender (Male/Female)	10/10	2/1	1
Neonatal Weight (g)	3474±525	3667±315	0.547

Data presented as Mean±SD or n. Apgar scores presented as median (interquartile). Group differences were compared using Student t test, and Apgar score were compared using Mann–Whitney U test. Nominal data were compared using Fisher's exact test.

HUP=Hospital of the University of Pennsylvania; EA= epidural anesthesia; GA=general anesthesia; UA= umbilical artery; UV= umbilical vein; BE=Base excess.