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The impact of route of anesthesia on maternal and fetal ischemia modified albumin levels at cesarean section: a prospective randomized study

Abstract

Objective: Ischemia modified albumin has been shown to increase in ischemic situations, and has also been shown to increase in fetal cord blood in deliveries by cesarean section. The aim of this study is to reveal whether anesthesia has an impact on maternal and fetal cord ischemia modified albumin levels.

Methods: Seventy two women with uncomplicated term pregnancies were randomized to spinal (n=37) or general anesthesia (n=35) groups. The blood pressure, oxygen saturation, and pulse rate of the patients were recorded during the procedure. Maternal blood samples of ischemia modified albumin (IMA) were taken 10 min from the start of the procedure. The fetal cord blood samples of IMA were taken immediately after birth.

Results: Maternal (0.99±0.19 vs. 0.80±0.27) and fetal (1.00±0.21 vs. 0.70±0.26) IMA levels were significantly higher in the general anesthesia group. Fetal IMA levels were positively correlated with maternal gravidity (r=0.31; P=0.008), parity (r=0.25; P=0.028), and fetal birth weight (r=0.23, P=0.045). Also, as time from incision to delivery lengthens, fetal IMA levels increase (r=0.29, P=0.012).

Conclusion: Fetal cord ischemia modified albumin levels were higher in the general anesthesia group, therefore, it is proposed that regional anesthesia should be the preferred route of anesthesia for an elective cesarean section, at least until the impact of high fetal cord IMA levels are manifested.

Keywords: Cesarean section; general anesthesia; ischemia modified albumin; regional anesthesia.

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Introduction

Recently, ischemia modified albumin (IMA) has been proposed as a valuable marker of ischemia [21]. Ischemia with free radical generation causes structural changes in the N terminus of albumin, leading to IMA production [4]. This change in structure reduces binding of albumin to nickel, copper and cobalt, this is a feature used in determining IMA levels with the albumin cobalt-binding test (ABSU). A higher sensitivity and a very short half-life makes this marker more favorable in cardiac ischemia when compared with conventional tests, such as electrocardiography (ECG), and troponin-I [5]. Other than cardiologic events, IMA has been reported to increase in other clinical situations comorbid with ischemia, such as systemic sclerosis [6], ischemic stroke [22], strenuous exercise [16], gastrointestinal or delayed muscle ischemia [2], and trauma [9]. Moreover, increased oxidative stress in metabolic syndrome [11], obesity [20], and polycystic ovary syndrome [7] were also reported as being associated with elevated IMA levels. Thus, any situation leading to ischemia might lead to an increase in IMA levels.

Pregnancy on its own has been shown to be an incremental factor for IMA levels [21]. Guven at el. reported that IMA levels were higher than reference values for non-pregnant adults during all trimesters, but especially in the third [13]. The authors claimed that higher IMA and lower malondialdehyde levels may be a sign of oxidative stress in pregnancy [13]. Few studies evaluated maternal IMA levels in different obstetric entities, such as trophoblast invasion [21], preeclampsia [19], and intrauterine growth restriction [14]. Additionally, in case of recurrent early pregnancy loss, higher IMA levels were reported in the first trimester of pregnancy compared to healthy pregnant controls [18]. The authors suggested that high IMA levels in cases with recurrent early pregnancy loss might

be related to abnormal placentation and an abnormally hypoxic uterine environment [18].

Finally, delivery by cesarean section was reported to be associated with higher fetal IMA levels [14]. The studies in the literature evaluating whether the mode of delivery effects maternal and fetal IMA levels did not consider the route of anesthesia. Neuraxial anesthesia for cesarean delivery is usually preferred to general anesthesia because it minimizes the risk of failed intubation, ventilation, and aspiration. In the latest Cochrane review of 22 studies comparing neuraxial blockade vs. general anesthesia in otherwise uncomplicated cesarean deliveries reported no significant difference in terms of neonatal Apgar scores of 6 or less and of 4 or less at 1 and 5 min, and need for neonatal resuscitation [1]. Therefore, this study was designed to clarify if IMA levels differ between routes of anesthesia chosen for cesarean section by measuring both maternal and umbilical cord blood IMA levels during the operation.

Materials and methods

This study was conducted in a university clinic between September 2011 and July 2012. All women that attended the Obstetrics and Gynecology Department were offered to participate in the study. During the study period, 72 women were enrolled into this prospective randomized study. The study protocol was approved by the Ethics Committee of the University Hospital. All the women participating in the study gave informed consent. All women received prenatal care in the same institution. All the participants had uncomplicated term gestations at 37 and 40 completed weeks. Before randomization, obstetric ultrasound examinations were performed to determine the amniotic fluid volume, the lie, and position of the fetus. The estimation of the gestational age was on the basis of ultrasonographic examination performed between 11 and 14 weeks of gestation. The women without a first trimester scan were excluded from the study. In all cases delivery by cesarean section was performed for a previous cesarean section or for fetal malpresentation. All cesarean sections were performed by the same operators. Patients were randomized to spinal (n=37) or general anesthesia (n=35) groups according to a computer generated randomization list.

The exclusion criteria composed of complicated pregnancies (e.g., intrauterine growth retardation, gestational diabetes mellitus, preeclampsia, fetal congenital anomaly, oligohydramnios, placenta previa), mothers with chronic illnesses (e.g., hypertension, diabetes mellitus), and any history of maternal cardiac symptoms, such as angina, myocardial infarction, coronary artery disease, vascular disease, and inflammatory disease. Oligohydramnios was defined as the deepest vertical pocket of amniotic fluid <2 cm. In addition, smokers and alcohol consumers, cases with abnormal albumin levels (<3.5 g/dL and >5.5 g/dL), and multiple pregnancies were also excluded from the study. The patients with contraindications of neuroaxial anaesthesia (coagulopathy, infection, hypovolemia, patient reluctance) were excluded from the study.

As soon as the patients were taken to the operating room, all were monitored (GE Heathcare Finland Oy, Helsinki, Finland). Thereafter, ECG, blood pressure, oxygen saturation (SpO_2), and pulse rate were all recorded. All patients were given 2 L/min O_2 inhalation by nasal cannulation. In the regional anesthesia group, 500 mL Ringer lactate solution was infused 15 min before spinal anesthesia by left hand venous cannulation. Patients were positioned in left lateral position to avoid aorta-caval syndrome; 2 mL 0.5% hyperbaric bupivacaine was administered through L 2–3 or L 3–4 inervertebral space by a 25-gauge spinal needle (Quincke, Braun Melsungen AG, Melsungen, Germany) for spinal anesthesia. In case of hypotension (systolic blood pressure 20% lower than basal level) or bradycardia (heart rate <60/min), 2–3 mg ephedrine (50 mg at maximum dose) and 0.5 mg atrophine were administered. Level of the neurological blockage was evaluated with a pinprick test 5 min after each procedure. Blockage level between thoracal 4–6 dermatomes were accepted as appropriate for surgical intervention. Patients in the general anesthesia group were not premedicated. Induction for general anesthesia was held by 2–3 mg/kg propofol, 0.6 mg/kg rocuronium infusion. Anesthesia was maintained by 50% O_2–50% N_2O, and 1%–1.5% sevoflurane. The time required for application of spinal anesthesia and the time for induction in general anesthesia were recorded. Systolic and diastolic blood pressures, SpO_2, and pulse rate were also recorded at 1, 2, 3, 4, 5, and 10 min of both groups. Additionally, incision to delivery intervals were recorded in both groups.

Maternal blood samples were collected from the antecubital vein into a non-heparinized tube at the 10^{th} min of induction. Cord blood was collected immediately after the delivery for umbilical cord acid base analyses, and an extra umbilical cord blood sample was taken for the analysis of fetal IMA. Maternal and fetal blood IMA samples were immediately centrifuged, and serum was separated and frozen at −80°C until assayed for IMA analysis. IMA concentrations were analyzed by measuring the complex composed of dithioerthreitol and cobalt, and unbound to albumin by the colorimetric method in a spectrophotometer. First, a mixture of 200 μL of patients serum and 50 μL cobalt chloride (Sigma Aldrich, St Louis, MO, USA) was prepared in glass tubes. The mixture was left to incubate at room temperature for 10 min. After that, 50 μL of dithiothreirol (1.5 mg/mL) was added to the tubes and incubated at room temperature for 2 min. At the final stage 1000 μL of sodium chloride (0.9%) was added to the mixture. A blank specimen was prepared with distilled water for control. The analyses in the spectrophotometer (Human Humalyzer 2000, Germany) was performed at 470 nm for detection of absorbance of the specimens, and the results were given as absorbance units (ABSU).

Statistical analyses

Data analysis was performed by using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA). Whether the distributions of continuous variables were normal or not was determined by the Shapiro Wilk test. Data were shown as mean±standard deviation (SD) or median (minimum–maximum), where applicable. While the mean differences between groups were compared by Student's *t*-test, otherwise Mann Whitney *U*-test was applied for the comparisons of the median values. Nominal data were analyzed by χ^2 or Fisher's exact test, where appropriate. Multiple logistic regression analysis was used to determine the independent predictors that mostly affected IMA levels. Any variable whose univariable test had a P-value <0.25 was accepted as a candidate for the multivariable model along with all variables of known clinical importance. Odds ratio and 95% confidence intervals for independent variables were calculated.

A P-value <0.05 was considered statistically significant. A power analysis was performed to estimate the number of patients needed in each group. It was assumed that 0.1 ABSU change (SD=0.1) in serum IMA concentrations was clinically significant. Assuming a two-sided test with a probability of a type-I error of 0.05, a statistical power of 80%, 32 patients were required in each group.

Results

The mean age of the patients and the gestational age at birth in the general and regional anesthesia groups are given in Table 1. The median (min–max) gravidity and parity of the patients were 2 (1–6) and 0 (0–4), respectively (Table 1). When the groups were compared for demographic characteristics (maternal age, gravidity, parity, gestational age at birth) no significant difference were found (P>0.05, Table 1). Incision-to-delivery intervals were similar in both groups (P>0.05). The time for induction was significantly shorter in general anesthesia when compared with the time required for spinal anesthesia (Table 1). None of the umbilical artery acid base parameters were abnormal in either group. No significant difference was found when two groups were compared for umbilical arter acid base parameters (Table 1). Maternal (0.99±0.19 vs. 0.80±0.27) and fetal (1.00±0.21 vs. 0.70±0.26) IMA levels were significantly higher in the general anesthesia group (Table 1). Fetal gender was male in 57.1% (n=20) of the newborns in general anesthesia and 50% (n=18) in the spinal anesthesia group. Additionally, fetal IMA levels were higher in male fetuses compared to females (0.90±0.26 vs. 0.77±0.28; P=0.039).

Systolic and diastolic blood pressure, SpO_2 and pulse rate values at 0, 1, 2, 3, 4, 5, and 10 min for both groups are listed in Table 2. Both systolic and diastolic blood pressures declined during the procedure. Neither the changes in systolic or diastolic blood pressures differed in the general and regional anesthesia groups (P=0.875 and P=0.141, respectively). Systolic blood pressure was significantly higher at 0, 1, and 2 min in the general anesthesia

Table 1 Characteristics of general anesthesia and regional anesthesia groups.

Parameters	General anesthesia (n=35)	Regional anesthesia (n=37)	P-value
Age (years)			
Mean±SD	30.17±5.31	28.10±4.68	0.084
Gravidity			
Median (min–max)	2 (1–6)	2 (1–4)	0.087
Parity			
Median (min–max)	0 (0–4)	0 (0–2)	0.773
Gestational age at birth (weeks)			
Mean±SD	38.5±1.1	38.6±0.9	0.497
Time required for anesthesia[a] (min)			
Mean±SD	1.81±0.96	2.44±1.42	0.037[b]
Incision to delivery interval (min)			
Median (min–max)	2.5 (0–12)	3 (0–6)	0.121
Maternal IMA levels (ABSU)			
Mean±SD	0.99±0.19	0.80±0.27	0.001[b]
Fetal IMA levels (ABSU)			
Mean±SD	1.00±0.21	0.70±0.26	<0.001[b]
Umbilical cord acid base parameters			
pH			
Mean±SD	7.31±0.04	7.33±0.06	0.330
pO_2			
Mean±SD	17.48±8.40	17.21±6.70	0.881
pCO_2			
Mean±SD	51.97±6.65	50.51±8.43	0.420
BE			
Median (min–max)	−0.41(−5.5–2.8)	0.2 (−11.8–4.7)	0.575
Lactate			
Mean±SD	1.47±0.61	1.68±1.04	0.483

[a]Induction period in general anesthesia, time for regional anesthesia. [b]P<0.05. SD=standard deviation, IMA=ischemia modified albumin, ABSU=absorbance unit, pO_2=partial oxygen pressure, pCO_2=partial carbon dioxide pressure, BE=base excess.

Table 2 Blood pressures, O_2 saturation and pulse rates in general (Group 1) and regional anesthesia (Group 2) groups.

Time	Systolic blood pressure (mm Hg)		P-value	Diastolic blood pressure (mm Hg)		P-value	Saturation		P-value	Pulse rate		P-value
Median (min–max)	Group 1	Group 2		Group 1	Group 2		Group 1	Group 2		Group 1	Group 2	
0 min	130 (100–173)	126 (95–155)	0.012[a]	80 (55–108)	76 (53–92)	0.220	99 (85–100)	99 (97–100)	0.141	95 (76–132)	99 (40–133)	0.344
1 min	130 (100–163)	124 (90–154)	0.040[a]	80 (53–97)	72 (44–98)	0.035[a]	99 (96–100)	99 (96–100)	0.030[a]	100 (65–132)	96 (62–133)	0.972
2 min	124 (99–162)	116 (75–146)	0.016[a]	76 (54–104)	63 (37–97)	<0.001[a]	99 (98–100)	99 (97–100)	0.044[a]	91 (72–149)	96 (64–140)	0.454
3 min	125 (90–168)	111 (85–143)	0.050	74 (42–104)	62 (42–91)	0.002[a]	99 (97–100)	100 (96–100)	0.050	99 (71–155)	97 (65–145)	0.767
4 min	121 (90–175)	111 (67–169)	0.073	73 (49–104)	63 (38–94)	0.001[a]	99 (97–100)	100 (94–100)	0.051	93 (62–135)	91 (58–130)	0.989
5 min	117 (86–164)	110 (83–147)	0.143	72 (41–103)	60 (36–88)	0.004[a]	99 (97–100)	100 (73–100)	0.022[a]	99 (60–135)	91 (56–162)	0.848
10 min	122 (93–157)	112 (78–169)	0.244	71 (51–96)	65 (29–94)	0.004[a]	99 (94–100)	100 (75–100)	0.038[a]	88 (69–126)	92 (55–143)	0.918

[a]Statistically significant.

group. Diastolic blood pressures were significantly higher in the general anesthesia group at all times (1, 2, 3, 4, 5, and 10 min) except initiation of anesthesia (0 min).

SpO_2 was stable during the procedure in both groups. The changes in SpO_2 values were similar between groups (P=0.841). Significantly higher values of SpO_2 were found at 1, 3, 5, and 10 min in the regional anesthesia group when compared with the general anesthesia group (P=0.030, P=0.050, P=0.022, and P=0.038, respectively). The changes in pulse rate were similar between groups (P=0.077). The pulse rate did not change during the procedure, and no significant difference were found in the pulse rate when the two groups were compared for 0, 1, 2, 3, 4, 5, and 10 min values.

According to the Spearman's rank correlation analyses, the baseline characteristics (age, gravidity, parity, and gestational age at birth) were not correlated with maternal IMA levels. However, fetal IMA levels were positively correlated with gravidity (r=0.31; P=0.008), and parity (r=0.25; P=0.028). In addition, fetal birth weight and fetal IMA levels were also found to be positively correlated (r=0.23, P=0.045). An important finding was that as time from incision to delivery lengthens, fetal IMA levels increase (r=0.29, P=0.012). However, no correlation exists between fetal umbilical cord acid base parameters and fetal IMA levels (Table 3). In the general anesthesia group, systolic blood pressure at 2 min was negatively correlated with fetal IMA levels, while no correlation existed in the regional anesthesia group.

The correlation analyses were repeated to clarify the parameters recorded during anesthesia (systolic blood pressure, diastolic blood pressure, SpO_2, and pulse rate) that might elevate maternal and fetal IMA levels. The results revealed that neither maternal nor fetal IMA levels were correlated with SpO_2 values (P>0.05). Among blood pressure values only 2 min systolic blood pressure was negatively correlated with fetal IMA levels in the general anesthesia group (r=0.035; P=0.037). However, none of the blood pressure values were found to be correlated with fetal IMA levels in the regional anesthesia group.

Discussion

This study is the first in the literature evaluating maternal and fetal IMA levels in different anesthesia types used for a cesarean section in uncomplicated term gestations. The results showed significantly higher maternal and fetal IMA levels in the general anesthesia group. Moreover, in the general anesthesia group lower systolic

Table 3 The results of Spearman rank correlation analysis.

Parameters	Maternal IMA		Fetal IMA	
	Correlation coefficient (r)	P-value	Correlation coefficient (r)	P-value
Maternal age	0.076	0.526	0.157	0.187
Gestational age	0.134	0.262	−0.091	0.448
Gravidity	0.181	0.129	0.310	0.008[a]
Parity	0.090	0.453	0.259	0.028[a]
Fetal birth weight	0.311	0.008[a]	0.237	0.045[a]
pH	0.011	0.929	−0.044	0.715
pO_2	−0.027	0.820	0.089	0.456
pCO_2	−0.032	0.790	−0.007	0.951
BE	−0.015	0.899	−0.109	0.367
Hb	−0.032	0.787	0.064	0.596
Htc	−0.030	0.805	0.066	0.582
Lactate	−0.155	0.193	−0.150	0.209
Time required for anesthesia[b]	−0.114	0.355	−0.131	0.285
Incision to delivery interval	−0.118	0.327	−0.296	0.012[a]

[a]$P<0.05$. [b]"Induction period" in general anesthesia, "time required" for regional anesthesia. IMA=ischemia modified albumin, pO_2=partial oxygen pressure, pCO_2=partial carbon dioxide pressure, BE=base excess, Hb=hemoglobin, Htc=hemotocrit.

blood pressure during delivery of the baby was found to be correlated with increased fetal IMA levels. A previous report [12, 14] documented that cord blood IMA levels of neonates from complicated deliveries are significantly higher than uncomplicated term deliveries. Complicated delivery causes an almost 50% increase in fetal cord blood IMA levels compared with the normal delivery group. However, severe fetal hypoxia was related with a 300% increase in IMA levels [12]. All these accumulating data indicate that IMA can be a valuable marker in perinatology in the future.

During abdominal entry in a cesarean section, manipulation and traction of the anterior abdominal muscles can be the explanation for higher maternal IMA levels of women delivered by cesarean section when compared with women who delivered vaginally [8]. As previously reported by Troxler et al., ischemia in skeletal muscles causes an increase in IMA [24]. Cesarean section is a process needing external forces, and can also lead to abdominal muscle injury to some extent. The operation itself or anesthesia related factors can be the cause of elevated maternal IMA levels. However, our results suggest other factors rather than muscle injury contribute to elevated maternal IMA levels. Mothers from the general anesthesia group had significantly higher IMA levels when compared with the regional anesthesia group. A result supported by studies on rat models where laparotomy by transperitoneal anesthesia, on its own, did not obviously change IMA levels pre- and postoperatively, in the sham group [3]. The higher maternal IMA levels in the general anesthesia group can be as a result of significantly lower values of SpO_2 in this group when compared with the regional anesthesia group.

According to our study, one of the subjects of importance is the correlation of fetal weight with fetal IMA levels. The results of our study documented a positive correlation of fetal weight with fetal IMA levels. Regarding these results, small for gestational age fetuses are expected to have lower IMA levels. The clinical importance of this finding is that in cases of intrauterine growth restriction, higher IMA levels might be detected as fetal hypoxia is related to increased IMA levels. Hence, a previous study that compared umbilical cord blood IMA levels of intrauterine growth restricted and appropriate for gestational age fetuses, reported no significant difference in IMA levels [14]. Another major point found in our study is the correlation between gravidity, parity and IMA levels. This was reported by Iacovidou et al. [14] and others [17, 23], previously. All the factors, such as fetal weight, gravidity, and parity that might have an influence on IMA levels need to be clarified by large population based studies to prevent misinterpretation of the results.

Some authors suggest that oxidative stress in the fetal circulation does not depend on the mode of delivery [10]. Others report higher fetal cord blood IMA levels in neonates delivered by cesarean section compared with vaginal deliveries, although arterial blood gas analysis and Apgar scores were in the normal range [14]. This study evaluated the maternal and fetal IMA levels during

different anesthesia types and our results showed that the general anesthesia group had significantly higher blood pressures at all times when compared with the regional anesthesia group. Moreover, newborns from the general anesthesia group had significantly higher levels of IMA with normal fetal cord blood arterial blood gas values and neonatal Apgar scores. Cesarean section under anesthesia might elevate IMA levels causing hypotension and uterine hypoperfusion, which is a very similar mechanism as in tourniquet and revascularization surgery reports. Consequently, hypotension and blood pressure alterations might not be the sole factors affecting fetal IMA levels. Oxygenation might be another contributing factor for elevated fetal IMA levels of fetuses delivered by elective cesarean section. Breathing room air under regional anesthesia or 30% oxygen under general anesthesia is usually adequate for maternal or fetal oxygenation [15]. In the presence of a hypoxic fetus, providing supplementary oxygen could lessen the severity of fetal hypoxia but can also lead to reperfusion injury. All the previous literature documenting elevated IMA levels from complicated deliveries might be due to reperfusion injury caused by maternally high inspired oxygen fraction [15]. The clinical importance and long-term consequences of fetuses with normal umbilical cord acid base status and elevated IMA levels is not yet clear.

In conclusion, cord blood IMA is a marker of transient ischemia and the unknown long-term consequences of neonates with high IMA level necessitates follow-up of these children. Concerning our results, if general anesthesia is to be applied for elective cesarean sections then blood pressure and maternal oxygenation should be strictly controlled as systolic blood pressure before, and during, the delivery of the baby is negatively correlated with fetal IMA levels.

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