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Umbilical cord blood coagulability, acidosis and intracranial hemorrhage

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1 Introduction

It is well known that, despite remarkable advances in perinatal medicine in recent years, intracranial hemorrhage is still a common neonatal finding and is a major problem to be solved.

Intracranial hemorrhage in the newborn has been traditionally discussed, based on the rough classification into hemorrhage caused by the external pressure on the head of the newborn during the birth procedure (mechanical or traumatic) and that associated with intrauterine metabolic disorder (hypoxic or chemical). Due to recent developments in perinatal, maternal and newborn care and to technical improvements in obstetrical care, the incidence of intracranial hemorrhage due to the first reason, i.e. birth trauma associated hemorrhage has decreased. Regarding the second cause of hemorrhage, accurate estimation of the fetal metabolic status is so difficult that it is rather common clinical experience to detect intracranial hemorrhage after birth in cases which had shown no specific abnormality during the perinatal period. Thus, the connection between metabolic disorder and intracranial hemorrhage needs further investigation.

We have devoted considerable attention to the fetal acid-base balance, and in this paper we have studied intracranial hemorrhage from the viewpoint of the relationship between blood coagulability and acid-base balance.

Curriculum vitae

MAMORU SAKURABA, *M.D. was born in Tokyo, Japan, in 1934 and graduated from Hokkaido University School of Medicine, in 1959. His Doctorate in Medicine was awarded by Hokkaido University Graduate School of Medicine, and in 1964, he received the Doctor of Medical Science degree with a thesis concerning fetal and neonatal hematology. From 1973 to 1985, he was appointed as a university lecturer in the Asahigawa Medical College, and currently he is head of Depart. of Obstet. and Gynecol. of Mikawa Municipal Hospital. His main scientific interests include perinatology especially acid-base balance and blood coagulability.*

2 Material and methods

Of 1324 pregnant women admitted to the Department of Obstetrics of the Berlin-Neukölln Women's Hospital between October 1982 and February 1983, 178 women with a singleton pregnancy who had a normal gestational course, were chosen at random and agreed to participate in this study.

Immediately after delivery the umbilical cord was clamped with two forceps and the cord blood was drawn from the umbilical artery into both a disposable syringe and a SALING's capillary.

For measurement of blood coagulability we used the hepaplastin test (Normotest), for determination of fibrinolytic activity, measurement of fibrin degradation products (FDP), soluble fibrin monomer complex (SFMC) and anti thrombin III (AT-III) were utilized for the index of the circulating inhibition system.

The Corning Model 178 and SALING–TUROWSKI pH-apparatus were used for umbilical arterial blood gas analysis. After sampling, 109 m mol/l tri-sodium citrate (9 volumes of blood to 1 volume of the reagent) were added to blood for the hepaplastin test and immediately centrifuged at 2500 rpm for 5 minutes.

Hepaplastin test was performed using Hepaplastin-Kit (EIZAI) [20]. For measurement of FDP, SFMC and AT-III 0.04 ml of anti plasmin reagent was added to the sample blood and after 30 minutes centrifuged at 1000 rpm for 10 minutes. An FDPL-KIT of TEIKOKU ZOKI [7] was used for FDP measurement, the ethanol gelation test was employed for measurement of SFMC. The AT-III level was determined using the BOEHRINGER-MANNHEIM's reagent [1].

The significance of difference was statistically analysed by Student "t" test. Intracranial hemorrhage in the newborn was diagnosed based on the ultrasonic findings and neurological evaluation performed on days 1 and 3 after birth, in cooperation with Dr. MARIA BRAND, a pediatrician specialized in this field.

3 Results

3.1 Hepaplastin test (N-test)

As shown in figure 1, the hepaplastin values of the cord blood decreased as the arterial pH fell in the normal group showing an arterial pH of 7.30 or higher, the hepaplastin value was 54.7 ± 11.2%, while in cases of acidosis where the arterial pH was 7.19 or less, the hepaplastin value decreased to 24.2 ± 7.3%, suggesting a significant difference between these two groups. A significant reduction in the hepaplastin value was also noted in the preacidotic group (pH 7.24–7.20).

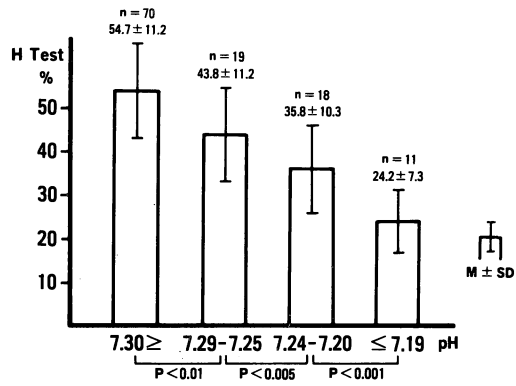

Figure 1. Hepaplastin values and pH.

3.2 FDP values

Figure 2 shows the relationship between the FDP levels and arterial pH. In the normacidic group 12 (48%) of 25 cases showed the FDP level of ⩾80 μg/ml, and of these, it was 160 μg/ml in four (16%) cases.

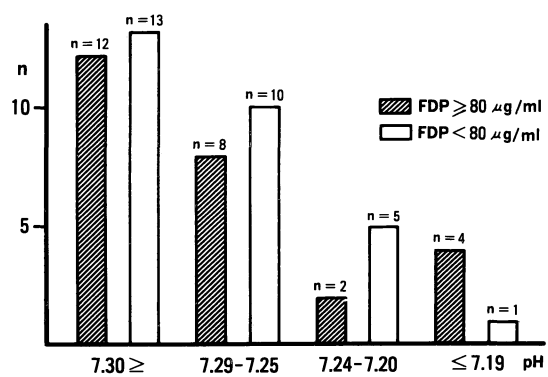

Figure 2. FDP values and pH.

Meanwhile in the acidosis group where the arterial pH was 7.19 or lower, the FDP level was 80 μg/ml or higher in four (80%) of five cases and of these, it was as high as 320 μg/ml in three cases. In the preacidotic group the cases showing a FDP level of 80 μg/ml or higher accounted for only 30%, but the value was raised up to 160 mg/ml in all these cases.

3.3 SFMC values

As demonstrated in table I, the SFMC value was 46.1% in the group with an arterial pH of 7.30 or higher and 66.7% in the group with an arterial pH of 7.19 or lower, suggesting no obvious difference between these two groups. The analysis of the relationship between the FDP levels and SFMC positivity rate disclosed that in cases showing the FDP of 40 μg/ml or lower, only 11.1% were SFMC positive, while the SFMC positivity rate was 56.2%, 81.8% and 100% in three groups showing the FDP of 80 μg/ml and 320 μg/ml respectively.

3.4 AT-III levels

As can be seen in table II, no obvious changes were observed partly because of the small number of cases studied.

3.5 Cases of intracranial hemorrhage as diagnosed by ultrasonography

Ultrasonography was performed in all infants by Dr. M. BRAND, and as shown in table III, intracranial hemorrhage was diagnosed in five cases.

Of 14 cases of acidosis with an arterial pH of 7.19 or less, two cases (14%) had intracranial hemorrhage. Of 164 cases with an arterial pH 7.20 or higher, three cases (1.8%) had hemorrhage and, when the preacidotic infants within the arterial pH range of 7.20–7.24 were added to the acidotic infants, the incidence of intracranial hemorrhage in this group with increased acidity was 8.1% (3/37 cases), suggesting a clearly higher incidence as complared with 1.4% in the control group.

Regarding the relationship between hemorrhage and blood coagulability, marked reductions in the

Table I. SFMC and pH

pH / SFMC	7.30 or higher	7.29 ~ 7.25	7.24 ~ 7.20	7.19 or lower
positive	18 cases	8 cases	6 cases	4 cases
negative	21 cases	9 cases	3 cases	2 cases
positive ratio (%)	46.1	47.0	66.7	66.7

Table II. AT-III and pH

pH / At-III	7.30 or higher	7.29 ~ 7.25	7.24 ~ 7.20	7.19 or lower
M	187.5	200.9	135.4	120.2
S. D.	56.4	47.8	138.7	–
n	11	12	– 2	1

Table III. I. C. H. Diag by Cranial US (Dr. BRAND)

Case	Age	P.	G. A. W D	B. W. g	S. S.	pH	H. Test %	F. D. P. μg/ml	FSMC	AT-III
1	34	1	37.6	2.640	9	7.35	58	40	–	
2	27	2	40.2	3.160	10	7.36	60	80	–	
3	27	1	38.1	2.980	8	7.22	30	80	+	
4	26	1	40.3	3.100	4	6.88	14	320	+	
5	24	1	40.1	3.620	6	7.19	31	100	+	229.8

P = Para, G. A. = Gest. age, B. W. = Birth weight, S. S. = Saling's score

hepaplastin values, markedly high SFMC positivity rate and high FDP levels were observed in the acidotic cases. Because of the small number of cases studied, it was not possible to make any definite conclusions regarding this matter.

4 Discussion

Due to the remarkable advance in medical techniques in recent years, the fetal and neonatal mortality rates and the incidence of severe sequela of obstretrical central nervous system have decreased. For the physicians committed to perinatal medicine, the aim of which lies in the intact survival of the infants, the early detection and prevention of disorders of the central nervous system is of prime importance.

Intracranial hemorrhage in particular is one of the most serious causes of the poor prognosis of the affected newborns, and has been studied by many researchers in various fields. Although the different clinical manifestation of intracranial hemorrhage constitutes a definite disease entity, the diversity of its etiology does not allow a generalized discussion on the severity of the damage and its prognosis, since these vary with the maturity of individual infants, the site and size of the hemorrhage, the number of risk factors and chronological factors.

This issue needs to be studied further. At the Third Japanese National Congress of Perinatal Medicine held in 1985, ZINBO [25] et al. presented the results of their studies on cases of intracranial hemorrhage which provide overall information of this disease entity in the recent Japanese experience. They investigated by birth weight, the number of fatal cases which had the complication of intracranial hemorrhage encountered over the last 20 years in Tsukiji Municipal Obstetric Hospital. By dividing the two decades into 4 periods of five years, they studied changes in the number of deaths occurring in each five year period. According to them, among the extremely small sized premature infants weighing 999 g or less, 20% or more of the infants died of intracranial hemorrhage in all the four periods, despite a marked drop in the mortality rate among those extremely tiny infants. Among the infants born underweight between 1000 g and 2499 g, both the number of neonatal deaths and incidence of intracranial hemorrhage tended to decrease. In the group of infants born with normal birth weight 2500 g or more, both the number of fatal cases and incidence of intracranial hemorrhage decreased, but the absolute number of hemorrhagic cases still remains to be substantially large. They concluded that intracranial hemorrhage is of major clinical importance both for extremely tiny premature infants and newborns of normal birth weight. Investigating risk factors for intracranial hemorrhage, SCHOENBERG [22] evaluated 30 items from the perinatal period in 12 instances of intracranial hemorrhage chosen from 10850 cases seen between 1965 and 1974. He reported that a significant correlation was found only between prematurity and respiratory distress syndrome. Cerebral hypoxia and acidosis have been reported to play an important role in the occurrence of intracranial hemorrhage in the neonate.

COLE [5] and HAMBELTON et al. [9] demonstrated that the hypoxic or acidotic condition may cause hemorrhage due to stasis, thrombus formation and breakdown of the venous system. This is because capillaries in the brain may be ruptured by a rise in arterial pressure, particularly in condition of hypercapnia and hypoxia. *Hill* et al. [12] reported that with intrauterine hypoxia, abnormal glucose metabolism and accumulation of lactic acid occur, leading to acidosis in peripheral blood and then in tissues. This in turn causes vasodilation, increased blood flow, and formation of small thrombi in the peripheral vasculature, resulting in DIC and an enhanced bleeding tendency. Based on these findings, they highlighted the significance of intrauterine asphyxia. Evaluation of impaired cerebrovascular autoregulation after asphyxia shows that there is a direct relationship between systematic blood pressure and cerebral blood flow. LOU et al. [15] also demonstrated pressure-passive relationship between systematic blood pressure and cerebral blood flow in asphyxiated term fetal sheep. Increase of systematic blood pressure to 60–70 mmHg was related to a six fold increase in cerebral blood flow.

GOLDSTEIN [8] describes the mechanism of the autoregulation disorder as follows: histologically, the endothelial cells in the brain capillaries are unlike those in other organs; tightly joined together, they contribute in maintaining the stable composition of the brain extracellular fluid and various components; thus the breakdown of these tight endothelial junctions results in the increased capillary permeability to water-soluble molecules and irons in plasma, leading to brain tissue edema, vascular wall impairment and eventually hemorrhage.

BUCCIARELLI [3] performed an in-vivo experiment on the relationship between blood flow and blood pH in goats. He showed that the cerebral blood flow increases linearily during acidosis, and changes in blood flow are correlated to both pH and $PaCO_2$ ($r = 0.64, 0.79$).

JOHNSON [13] also demonstrated in his experiments in fetal lambs that a drop in pH from 7.40 to 7.04 was associated with a marked increase in the cerebral blood flow and, particularly in the brain stem, such a drop caused a 275% increase in blood flow from the control value as well as an increase in blood pressure (58 mmHg − 71 mmHg).

As described above, acidosis and hypoxia have been known to have substantial effects on the autoregulation of the cerebral circulatory system and to constitute one of several causes of intracranial hemorrhage.

Next, blood coagulability in the presence of acidosis and hypoxia will be discussed. Although many reports are available on this issue, little agreement has been reached with respect to the involvement of acidosis and hypoxic conditions in blood coagulability. *Shirahata* et al. [23] reported that prolongation of activated partial prothrombin time (APPT) and decrease in fibrinogen, hepaplastin value and platelet counts were observed in cases of intracranial hemorrhage, and that these changes were marked particularly in the presence of acidosis and RDS. SUZUKI [24] pointed out increases in FDP and SFMC, significant decreases in factor VII and kininogen levels and a decrease in 6-Ket-$PGF_{\alpha 1\alpha}$ in asphyxiated infants. COLE [5] who studied 22 cases reported that acidosis or hypoxia produced no systemically distinct difference in blood coagulability, but prolonged prothrombin time, prolonged partial thromboplastin time (PTT), decreases in fibrinogen level and thrombocytopenia were noted in 15, 11, 4, and 6 cases respectively. The prolongation in prothrombin time suggests the consumption of factor VII and X.

CHESSELS [4] reported thrombocytopenia and decreases in fibrinogen level and thromboblast value in 16 of 48 cases, and also reported that coagulation abnormalities were more frequent in infants with intracranial hemorrhage than in those infants with hyaline membrane disease. ANDERSON [2] and EKELUND [6], who also obtained similar findings, investigated these abnormalities from the viewpoint of DIC. They explain that the liberation of tissue thromboplastin causes the formation of small thrombi in the peripheral vasculature which in turn, causes consumption of the coagulation factors leading to secondary hemorrhage. Similarly, HAUPT [11] describes that in the hypoxic newborns, the generation of the coagulation factors, particularly that of factor V, is inhibited, and this induces the activation of some unknown mechanism and produces bleeding. According to OGAWA [19] and MAKI et al. [17] changes in cord blood pH, Po_2 and Pco_2 were not associated with significant changes in thrombotest value, fibrinogen level and plasminogen level, however, severely asphyxiated infants, the fibrinogen concentration was markedly decreased. In experimental acidosis, prolongation of r and k time and shortening of ma were noted on Thromboelstgram (TEG), thrombocytopenia and falls in fibrinogen and plasminogen levels were also detected. Based on these findings, they concluded that acidosis is associated with alternations in blood coagulability, altered hemodynamics, and liberation of tissue thromboplastin accompanying this impaired coagulability, which induces the onset of DIC.

NIEDNER et al. [18] who performed match tests in 20 cases, showed that, in the acidosis group where decreased platelet counts and factors II and V concentrations are noted as well as marked prolongation of thrombin time and PTT occur, these changes are correlated to changes in blood pH, particularly when pH drops to 7.09 or lower. DIC occurred in all such cases. KISKER [14] reported that hypoxia experimentally induced in fetal lambs does not lead to significant alternations in blood coagulation factors, and he postulated that this absence of alternations during hypoxic conditions may be due to the adaptation to lower intrauterine Po_2 levels and immature coagulation system unable to respond to such a hypoxic state. As regards changes in AT-III, HATHAWAY [10] reported that the AT-III levels decrease in premature infants or in newborn with IRDS. In the present study, we failed to show any consistent results, but three cases with a lower pH (below 7.20) value indicated low activity of AT-III. MAHASANDANA [16] described that the lowest levels of AT-III were seen in infants with idiopathic respiratory distress syndrome, and other high risk groups, such as preterm infants and asphyxiated infants also demonstrated lower activity. PETERS [21] discussed the low activity of the AT-III levels in the infants with reduced blood flow resulting from hyperviscosity initiated hypoxia and local acidosis. Both of these phenomena contribute to activation of the coagulation

system. Venous stasis with acidosis and local hypoxia caused increased secretion of tissue plasminogen activators and consumption of inhibitor.

The relationship between intracranial hemorrhage and acidosis was discussed in the above paragraphs centering around the effects of acidosis on the autoregulation of cerebral blood flow and blood coagulability. Although involvement of various factors such as the duration of the acidotic condition and the rate of progression of acidosis has yet to be studied, a reasonable hypothesis may be that acidosis leads to the breakdown of capillary endothelium with simultaneous tissue circulation insufficiency and release of tissue thromboplastin. This, in turn, causes alternations in hemodynamics and autoregulation of blood flow, reduction in blood coagulability and increased activity of fibrinolytic system, and eventually to a rise to DIC and enhancement of secondary hemorrhage.

No consistent findings have been obtained yet regarding the identification of the unknown factor which, as HAUPT [11] describes, affects the blood coagulation system in the presence of acidosis. It is necessary to explore not only the changes in the coagulation and fibrinolytic system but in the biochemical changes taking place in the body during acidosis. As reported by SUZUKI [24] changes in the kinin/prostaglandin system seen during acidosis, may provide some clue for our future exploration. Beside this, the mechanism by which asphyxia and acidosis interfere with the hepatic synthesis of vitamin K dependent factors, remains unknown and has yet to be elucidated.

Abstract

The relationship between blood pH and blood coagulability and alternations in the fibrinolytic system was studied using blood samples obtained from the umbilical artery of 178 cases. Further studies were performed on this relationship in 5 cases of intracranial hemorrhage detected by ultrasonography, and the following results were obtained:

1. A definitely significant correlation was noted between the hepaplastin value and blood pH and these values markedly decreased in the acidosis group.
2. Changes in FDPs and SFMC were not so obvious as changes in the hepaplastin values, but activation of the fibrinolytic system was noted in the acidosis group.
3. No consistent finding was obtained with respect to changes in At-III.
4. Among five cases of intracranial hemorrhage, abnormalities in the coagulation and fibrinolytic system were noted in cases of acidosis, indicating that presence of acidosis is associated with severe intracranial hemorrhage.
5. The necessity of future studies on biochemical changes during acidosis was discussed.

Keywords: Acidosis, AT-III, cord blood coagulability, FDP, hepaplastin test, intracranial hemorrhage, SFMC, ultrasonography.

Zusammenfassung

Gerinnung im Nabelschnurblut, Azidose und intracranielle Blutungen

Von Oktober 1982 bis Februar 1983 untersuchten wir an der Freien Universität Berlin die Korrelation zwischen der Gerinnung im Nabelschnurblut, einer Azidose und intracraniellen Blutungen. 178 Frauen mit Einlingsschwangerschaften, normalem Schwangerschaftsverlauf und normaler Entbindung wurden zufallsmäßig ausgesucht und in die vorliegende Studie einbezogen.

Gemessen wurden der pH-Wert in der Umbilikalarterie, der Hepaplastin-Wert, Fibrinabbauprodukte (FDP), lösliche Fibrin-Monomer-Komplexe (SFMC) und Antithrombin-III (AT-III). In dem o. g. Zeitraum wurden in der Gruppe bei 5 Kindern ultrasonographisch (durch Dr. M. BRAND) intracranielle Blutungen diagnostiziert. Wir kamen zu folgenden Ergebnissen: 1. die Hepaplastin-Werte korrelierten signifikant mit dem Blut-pH; in der Azidose-Gruppe kam es zu einem deutlichen Abfall. 2. Veränderungen der FDP's und SFMC's waren nicht so deutlich wie bei den Hepaplastin-Werten, jedoch konnte in der Azidose-Gruppe eine Aktivierung des fibrinolytischen Systems beobachtet werden. 3. Hinsichtlich des AT-III ließ sich kein Zusammenhang erkennen. 4. Bei den 5 Fällen mit intracraniellen Blutungen wurden bei Vorliegen einer Azidose Veränderungen der Gerinnung und des fibrinolytischen Systems beobachtet, was auf den Zusammenhang zwischen einer Azidose und schweren intracraniellen Blutungen hinweist. 5. Diskutiert wurde die Notwendigkeit weiterer Untersuchungen über biochemische Veränderungen während einer Azidose.

Schlüsselwörter: AT-TII, Azidose, FDP, Gerinnung im Nabelschnurblut, Hepaplastin-Test, intracranielle Blutung, SFMC, Ultraschall.

Résumé

Coagulabilité au sang du cordon, acidose et hémorragie intra-cranienne

Nous avons étudié la corrélation entre la coagulabilité du sang du cordon ombilical, l'acidose et les hémorragies intra-craniennes à l'université libre de Berlin d'octobre 1982 à février 1983. 178 femmes avec une grossesse unique, avec un déroulement et un accouchement normaux ont été choisies par randomisation et acceptées pour cette étude.

Nous avons mesuré le PH artériel ombilical, les valeurs de l'hépaplastine, les produits de dégradation de la fibrime (P D F) les complexes de monomères de fibrine solubles (SFMC) et l'antithrombine III (AT III). Au cours de cette période nous avons porté chez 5 patientes le diagnostic d'hémorragie intra-cranienne par échographie (Dr M. BRAND) dans le même groupe.

Les résultats sont les suivants:
1) Il existe une corrélation significative nette entre les valeurs de l'hépaplastine et le PH sanguin, et ces valeurs chutent de façon importante dans le groupe avec acidose.
2) Les modifications des PDF et les SFMC ne sont pas aussi évidentes que celles des valeurs de l'hépaplastine, mais on a noté une activation du système fibrinolytique dans le groupe avec acidose.
3) Il n'a pas été obtenu de résultats consitants pour les variations d'Antithrombine III.
4) Parmi les 5 cas d'hémorragie intra-cranienne, on a noté des anomalies de la coagulation et des systèmes fibrinolytiques en cas d'acidose, que l'existence d'une acidose s'accompagne d'hémorragie intra-cranienne graves.
5) On discute la nécessité d'études ultérieures sur les modifications biochimiques au cours de l'acidose.

Mots-clés: Acidose, A. T. III, coagulabilité au cordon, échographie, F. D. P., hémorragie intra-cranienne, hépaplastintest, SFMC.

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