Increased Serum Potassium and Intraventricular Hemorrhage Revisited

Dror Mandel MD MHA, Yoav Littner MD, Francis B. Mimouni MD, Zahava Stavarovsky MD and Shaul Dollberg MD

Department of Neonatology, Lis Maternity Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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Abstract

Background: Increased serum potassium and intraventricular hemorrhage occur frequently in preterm infants.

Objective: To retrospectively analyze data obtained on infants with severe IVH in relation to blood K^+ concentrations.

Methods: We identified all patients with severe IVH born between July 1997 and July 2000. Each patient was pair-matched with a control infant of the same gestational age ($\pm$1 week) without IVH in terms of head ultrasound findings on day 5 and whole blood K^+ on days 3–5.

Results: There were 24 infants in each group. The IVH group had significantly lower 1 minute Apgar scores and pH and higher blood K^+ than the control group. Blood pH and K^+ were inversely correlated. Stepwise regression analysis, taking into account blood pH and 1 minute Apgar score, showed a correlation only between blood K^+ and IVH status.

Conclusions: Severe IVH is significantly associated with higher blood K^+ concentrations. A causal relationship cannot be ascertained at this point.

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Hyperkalemia (blood potassium in excess of 6.7 mmol/L) has been reported to occur in as many as 32–50% of extremely low birth weight infants (<1,000 g at birth) [1–8]. The rate of intraventricular hemorrhage in the same group of high risk infants has been reported to be approximately 23% [9]. Several authors have reported a temporal relationship between these two serious complications of extreme prematurity [10–13]. The purpose of this study was to retrospectively analyze the data obtained in our institution since 1 July 1997 and to critically review the literature on this topic.

Patients and Methods

Patients

We retrospectively identified all patients with severe IVH (grades 3 and 4) born in our institution between July 1997 and July 2000. Each patient was pair-matched with a control infant of the same gestational age ($\pm$1 week) without IVH and born immediately after the birth of the study infant.

Methods

- *IVH screening.* In our institution, small preterm infants are routinely screened for IVH on day 5 of life (in order to detect nearly all patients with IVH), and in week 3–4 of life (in order to detect patients with periventricular leukomalacia) [14,15], using ultrasonography (Aloka SSD-2200, Japan). The grade of IVH was determined by a single radiologist (Z.S.) according to the Papile classification [16].
- *Fluid management.* In our institution, fluids are managed according to a strict protocol. In very low birth weight infants (< 1,500 g), intravenous fluids are started at 80–100 ml/kg birth weight/day, as a non-K^+ containing electrolyte solution on day 1, followed by a K^+ containing solution after sufficient urine output is demonstrated, at an infusion rate of 2 mEq/kg birth weight/day. Total parenteral nutrition providing the same daily K^+ infusion rate is started on day 2 of life. Feeds are started between day 2 and 5, depending on the presence or not of risk factors for necrotizing enterocolitis, at daily increments of 20 ml/kg birth weight.
- *Electrolyte measurement.* Whole blood K^+ was routinely obtained from umbilical catheters on days 3, 4 and 5 of life in all infants, using a Nova M electrode (Nova Biomedical Corporation, Waltham, MA, USA). This instrument is calibrated twice daily and maintained according to the manufacturer's standards. Normal standard neonatal values with this instrument have been published elsewhere by us [17].

Data collection and analysis

All patients' charts were individually reviewed by a single investigator (D.M.) according to a predetermined protocol. In particular, the following demographic, diagnostic and therapeutic or procedural variables were recorded: maternal demographics, preterm rupture of membranes, prenatal steroid treatment, magnesium sulfate treatment, birth weight, Apgar scores, presence of umbilical artery catheter and umbilical vein catheter, use of mechanical ventilation, presence of patent ductus arteriosus, laboratory data, and presence and grade of IVH.

Statistical analysis

Paired Student *t*-tests were used to study differences between infants with IVH and those without. Backward stepwise regression analysis was used to study the independent impact of hyperkalemia and other selected independent variables on IVH. A P value <0.05 was considered significant.

Results

There were 24 infants in each group. No significant differences were found between the two groups in any of the obstetric characteristics

IVH = intraventricular hemorrhage

Table 1. Obstetric characteristics

	With IVH (n=24)	Without IVH (n=24)
Maternal age (yrs)	30 ± 4.9	29 ± 4.5
Prolonged rupture of membranes	9 (37.5)	3 (12.5)
Magnesium treatment	0	2 (8.3)
Celestone treatment	16 (67)	10 (42)
Meconium-stained amniotic fluid	2 (8.3)	1 (4.2)
Mode of delivery		
Vaginal	16 (67)	15 (62)
Cesarean	8 (33)	9 (38)

Data are expressed as mean ± SD or No. (%). No statistically significant differences were found between the two groups.

Table 2. Clinical characteristics

	With IVH (n=24)	Without IVH (n=24)
Birth weight (g)	1030 ± 671	1021 ± 606
Gestational age (wks)	26 ± 4.3	27 ± 3.8
Gender		
Male	10 (42)	9 (37)
Female	14 (58)	15 (63)
1 minute Apgar*	5 (3–7)	7 (5–9)
5 minute Apgar	8 (6–10)	9 (8–9)
Albumin treatment on the 1st day of life	13 (54)	11 (46)
Dopamin treatment on the 1st day of life	5 (21)	8 (33)
Presence of umbilical vein catheter	22 (92)	23 (96)
Presence of umbilical artery catheter	23 (96)	21 (88)
Mechanical ventilation	24 (100)	21 (88)
Maximum mean airway pressure (cmH_2O)	11 ± 3.2	10 ± 4.1
Presence of patent ductus arteriosus	20 (83)	20 (83)
Indomethacin treatment	21 (88)	19 (79)

Data are expressed as mean ± SD or No. (%), except for Apgar scores that are expressed as a median (range).
* $P < 0.04$.

Table 3. Patients' laboratory characteristics

	With IVH (n=24)	Without IVH (n=24)	*P* value
Potassium (mmol/L)			
Day 3 of life	5.8 ± 1.1	4.5 ± 0.6	<0.001
Day 4 of life	6.2 ± 1.3	4.5 ± 0.5	<0.006
Day 5 of life	5.8 ± 0.9	4.5 ± 0.7	<0.001
pH			
Day 3 of life	7.28 ± 0.11	7.32 ± 0.07	<0.005
Day 4 of life	7.28 ± 0.13	7.34 ± 0.06	<0.01
Day 5 of life	7.2 ± 0.11	7.35 ± 0.04	<0.006

Data are expressed as mean ± SD

considered [Table 1]. With regard to the infants, the only significant difference between groups was the 1 minute Apgar score, which was significantly lower in the IVH group [Table 2]. Table 3 presents the laboratory data: the IVH group had a significantly lower blood pH and a higher blood K^+ during the 3 days preceding the head ultrasound. Blood pH and K^+ on day 1 were inversely correlated (R^2 = 9.2%, $P < 0.04$). Stepwise regression analysis – taking into account blood K^+ (on days 3, 4 or 5), 1 (or 5) minute Apgar score, and gestational age – demonstrated a correlation only between the blood K^+ and IVH status (e.g., K^+ on day 4: R^2 = 44.5%, $P < 0.001$).

Discussion

We found that infants with severe IVH have significantly higher blood K^+ concentrations than gestational age pair-matched controls. This was also consistently reported in four other studies [10–13], although the authors mostly considered this relationship to be coincidentally, rather than causally, related.

The first group of investigators to report a high incidence of hyperkalemia and "cerebral lesions" on ultrasonography was Shortland et al. [10], who also noted the association with cardiac arrhythmias. The relationship between arrhythmias and hyperkalemia is not new and has long been recognized in adults [18], children [18] and neonates [19]; it is likely due to the repolarization defect induced by hyperkalemia. Shortland and collaborators [10], however, were the only ones to suggest a causal relationship between arrhythmias, hyperkalemia and cerebral lesions because of the temporal relationship that existed between these three complications of extreme prematurity in some infants. They based their conclusion on the fact that PVL occurred in three infants shortly (within 24 hours) after cardiac arrhythmia, which, they suggested, supported the theory that ischemic brain lesions were a *consequence* of the arrhythmia [10]. We find this theory intriguing, even though it was not based on a very large number of observations or supported by the fact that PVL even preceded the arrhythmia in at least one other infant of their study [10].

Brion et al. [11] identified a group of 7 very low birth weight infants who developed hyperkalemia in excess of 7.0 mmol/L, out of a group of 1,552 VLBW infants. In all seven infants, hyperkalemia was of early onset (9–70 hours of age), was not accompanied by oliguria, and was associated with a high incidence of IVH, i.e., 6 of the 7 infants (86%) developed IVH. A control group of seven infants did not differ in many perinatal outcome variables but had a much lower incidence of IVH: only 1 of 7 (14%).

In a more recent study, Perlman and Risser [12] aimed to determine whether elevated uric acid concentrations, an index of hypoxanthine catabolism after ischemia reperfusion, can predict the later occurrence of IVH and PVL. In their study, higher uric acid concentrations on day 1 of life were significantly associated with the subsequent development of severe IVH/PVL and subsequent hyperkalemia. The authors observed that hyperkalemia developed uniformly, when it occurred, on day 2 of life, in 13 of the 58 infants (22%) and did not correlate with urine output. In contrast, of the 10 infants who developed severe IVH, the IVH was present on day 2 in 7 infants, on day 3 in 2 infants, and on day 5 in 1 infant [12]. Thus, while there is a large overlap between hyperkalemia and severe IVH, it appears that 3 of 13 infants with hyperkalemia did not have severe IVH, and in 3 of 10 infants with severe IVH, hyperkalemia developed

PVL = periventricular leukomalacia
VLBW = very low birth weight

after IVH, while in 7 of 10 infants the two events seemed to occur at the same time. Thus, in their study the two events appear to be related more coincidentally than causally. Our study did not address the issue of a possible association between hyperkalemia and PVL, since we elected to study only infants with severe IVH, and IVH is quantifiable (Papile classification [16]) while PVL is not.

The last study to address (indirectly) this issue is that of Kluckow and Evans [13]. In that study the investigators hypothesized that low systemic blood flow may be an important factor in the pathogenesis of hyperkalemia in preterm infants through reduced urinary output and reduced K^+ excretion. The authors measured superior vena cava flow in 119 preterm infants born before 30 weeks of gestation. Hyperkalemia, defined as a peak K^+ concentration >6.5 mmol/L, occurred in 17 of 119 infants (14.3%). Urine output was significantly lower in the hyperkalemic infants during the first 24 hours of life. A K^+ rate rise exceeding 0.12 mmol/L/hour in the first 12 hours of life predicted low SVC flow with 93% accuracy. Moreover, the peak K^+ occurred after the lowest measured SVC flow in 84% of infants. A significant relationship was noted between both the peak and mean K^+ during the study period and the grade of IVH. The 18 infants with significant IVH (grade 2 or more in their study) had both higher peak and mean K^+. The time of peak K^+ concentration measurement was *before* the maximum grade of IVH was documented in 83% of these infants. Thus, according to the findings of Kluckow and Evans, it is also likely that hyperkalemia and significant IVH were coincidental events, non-causally related. However, it should be noted that those authors may have addressed a subgroup of hyperkalemic infants, that is, those who had at least some degree of oliguria. Most articles relating to hyperkalemia in preterm infants address the issue of *non-oliguric* hyperkalemia, where hyperkalemia is believed to result from a greater intracellular to extracellular K^+ shift, which occurs immediately after birth in some extremely low birth weight infants [5].

Since our study was retrospective in nature, the exact timing of IVH cannot be determined as sonograms were initially performed only on day 5 of life. Also, our study addressed blood potassium values as a continuous variable, rather than hyperkalemia, a discrete variable. Reports of non-oliguric hyperkalemia refer to values of K^+ greater than 6 mmol/L [20], 6.5 mmol/L [13,21], 7.0 mmol/L [11], or 7.5 mmol/L [10]. When present, hyperkalemia was reported to occur early, usually on day 2 of life [10]. In our study, by protocol, electrolyte measurements were not done within the first 24–48 hours of life in most infants because these measurements are believed to reflect maternal electrolyte status [22,23]. Blood K^+ increased in most infants to reach peak values on day 4 of life, whereas in the studies of Shortland [10] and Omar [21] they reached a peak on day 2 of life. The reason for this rise has not been elucidated to date. Omar's more recent study, showing that prenatal steroids significantly prevented this elevation, favors the theory of a contribution of deficient cell membrane sodium, potassium-adenosinetriphosphatase activity, in these small infants. Nevertheless, we were not able to determine whether rising K^+ values preceded the development of IVH, were coincidental to it, or followed it. Both our review of the literature and our own data are suggestive of a strong association between the development of significant IVH and that of hyperkalemia in small premature infants. However, a causal relationship is unlikely, particularly since hyperkalemia in excess of 6.7 mmol/L has been reported to occur in as many as 32–50% of extremely low birth weight infants (<1,000 g at birth) [1–8], while the rate of IVH in the same group of high risk infants has been reported to be approximately 23% [9]. Nevertheless, we cannot rule out that hemolysis of the enclosed intraventricular blood clot may contribute an *additional* K^+ load to the intravascular space.

SVC = superior vena cava

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Correspondence: Dr. S. Dollberg, Dept. of Neonatology, Lis Maternity Hospital, Tel Aviv Sourasky Medical Center, 6 Weizmann Street, Tel Aviv 64239, Israel.
Phone: (972-3) 692-5690
Fax: (972-3) 692-5681
email: dollberg@tasmc.health.gov.il