Retinal Hemorrhages in Critically Ill Children – a Prospective Study

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SUMMARY

In this observational study, we aimed to define the prevalence, distribution, and extent of retinal hemorrhage (RH) in critically ill children, defining demographic characteristics, clinical features and outcome of patients with RH, excluding those with trauma. We also aimed to describe the impact of age, gender, admission diagnosis, risk factors of respiratory failure, requirement of mechanical ventilation, presence of an endotracheal/tracheostomy tube, cardiopulmonary resuscitation, arrhythmia, hyperkalemia, pneumothorax, sepsis, heart failure, hypo/hypertension, presence of seizures, and presence of coagulation disorders on this distribution as secondary results. Data were collected prospectively, consecutively from April 2013 to April 2014. A total of 150 patients were identified during the study period for the study purposes. The male to female ratio was 1.05. There was no detectable impact of age, age group, gender, admission diagnosis, respiratory failure, requirement of mechanical ventilation, presence of an endotracheal/tracheostomy tube, arrhythmia, sepsis, hypo/hypertension, presence of seizures, pneumothorax, and presence of coagulation disorders/coagulopathy on the prevalence of RH. The study demonstrated that risk factors of hyperkalemia, cardiopulmonary resuscitation and heart failure were significantly associated with RH. Any child found to have RH might have an underlying medical condition that requires further investigations. In addition, a study focused on the effects of RH on visual acuity and visual outcome in the future will be helpful for understanding the long term impact of RH.

KEYWORDS

Children, critically ill, pediatric intensive care unit, retinal hemorrhages

Introduction

Retinal hemorrhage (RH) is a common finding in child abuse/shaken baby syndrome, but the presence of RH may also be considered with cardiopulmonary resuscitation due to thoracic compression, trauma, intracranial hemorrhages, raised intracranial pressure, and a wide range of illnesses such as blood disorders, infections (i.e., cytomegalovirus, herpes simplex virus, rickettsia, toxoplasmosis, endocarditis), and seizures[1-4]. In addition, birth-related RH is common in neonates due to spontaneous vaginal delivery (25%) and delivery with forceps and vacuum (43%-57%), while the lowest rate of RH occurs with cesarean section (7%)[5,6]. RH is a condition that has important medical, social and legal consequences. The current practice of determining RH in critically ill pediatric population in the developing world is not well characterized, and existing studies describing RH mostly focus on abusive head trauma[7,8], and the presence of RH raises the question of preceding trauma/child abuse[9].

Some studies state that RH might result from resuscitative efforts due to chest compression[10,11]. According to Agrawal *et al*., RHs were seen in critically ill children with a prevalence of 15.1%, and mainly (66%) were mild. Severe multilayered RH is uncommon (3.7%) and is only seen in patients with severe head trauma, fatal coagulopathy, sepsis, or a combination of these factors[12]. The aim of this prospective observational study was to define the prevalence, distribution, and extent of RH in critically ill children, defining demographic characteristics, clinical features and outcome of patients with RH, excluding newborns and patients with trauma. Furthermore, we also aimed to describe the impact of age, gender, prevailing diagnosis at admission, risk factors of respiratory failure, requirement of mechanical ventilation, presence of an endotracheal/tracheostomy tube, arrhythmia, hyperkalemia, pneumothorax, sepsis, heart failure, hypo/hypertension, presence of seizures, and presence of coagulation disorders on this distribution as secondary results.

Materials and Methods

Upon approval from the local Ethics Committee, the study was performed in a pediatric intensive care unit (PICU) which has 14 pediatric intensive care beds and is one of the largest referral centers for multidisciplinary tertiary care. It admits nearly 500-600 patients *per* year from all pediatric specialties. Patients between 1.5 month and 18 years of age with no historical or physical evidence of preceding trauma were included in the study. Data were collected on all patients with various diagnoses who had been admitted to our unit consecutively over a time period of one year, from April 2013 to April 2014.

During this period, 498 children were admitted to our unit. Among them, 150 patients were identified to meet the study inclusion criteria and their parents provided a written informed consent for the study. Demographic data such as age, gender, admission diagnosis, risk factors such as respiratory failure, requirement of mechanical ventilation, presence of an endotracheal/tracheostomy tube, cardiopulmonary resuscitation (CPR), arrhythmia, hyperkalemia, pneumothorax, sepsis, heart failure, effects of systolic and diastolic blood pressure values (mm Hg), presence of seizures, presence of coagulation disorders and platelet count, prothrombin time (PT) and partial thromboplastin time (PTT) levels were collected for statistical analysis. Coagulopathy was defined as PT of more than 3 seconds above normal, and/or twice normal PTT, and/or platelet count <50 000/mm^3 [13]. Blood potassium level was determined according to its reference range to define hypokalemia or hyperkalemia[14]. In addition, hypotension and hypertension were

defined according to its reference ranges according to age and gender[14].

We classified RH by using laterality (unilateral or bilateral), severity (mild when less than 5 RH were identified, moderate when there were 5-20 RH, and severe when there were more than 20 RH), and single or multilayered based on their location in the retina[5]. All data were gathered and documented prospectively for statistical evaluation. All study patients underwent history taking, physical examination and routine laboratory investigations according to diagnosis, and these pediatric intensive care admissions had dilated retinal fundoscopic examination by an experienced ophthalmologist using an indirect ophthalmoscope. Eye examination was performed as soon as possible within the first 24-48 hours of admission. All children were monitored for vital functions such as heart and respiratory rate, blood pressure, pulse-oximeter, electrocardiogram (ECG), and urine output. Medical records of the patients were evaluated and prospective chart reviews were performed. Patients younger than 1.5 months (to exclude birth-related RH) and those older than 18 years, patients with suspected/proven abusive head trauma or penetrating eye trauma, all other trauma patients (i.e., road traffic accidents, fall down from height by accident or suicide, physical abuse), patients who were not personally observed by the authors, and patients meeting the inclusion criteria that could not be enrolled to the study due to refusal of informed consent were excluded from the study.

Statistical analysis

All data were analyzed using Statistical Package for Social Sciences (SPSS) for Windows 20 (SPSS Inc., Chicago, IL, USA) statistical software. The normality of data distribution was evaluated with Kolmogorov-Smirnov and Shapiro-Wilk tests. Variables showing normal distribution were expressed as mean ± standard deviation (SD), and variables not showing normal distribution were expressed as median (minimum-maximum). Mann Whitney *U* test was used for comparison of groups in variables not showing normal distribution. Pearson χ^2-test was used for comparison of categorical variables. Multivariate analysis of independent variables was performed using logistic regression analysis. The level of statistical significance was set at $p<0.05$.

Results

A total of 498 patients were admitted to PICU during the study period, and 150 patients met the inclusion criteria. The male to female ratio was 1.05, with 77 (50.3%) male and 73 (47.7%) female patients. The mean age of the patients was 5.2±5.6 (min 0.1, max 17, median 2.4) years. Demographic data are summarized in Table 1. Neurological diseases were the most frequent admission diagnosis (n=54, 36%), followed by metabolic disorders (n=19, 12.7%) and pulmonary diseases (n=18, 12%). According to our results, the reason for RH was commonly neurological (n=3), after that hematologic diseases (1%) and carbon monoxide intoxication (0.7%). The prevalence of RH was 3.33% (5/150). The effect of endotracheal/tracheostomy tube, arrhythmia, sepsis, systolic and diastolic blood pressure values (mm Hg), presence of seizures, pneumothorax, and coagulation disorders/coagulopathy on RH prevalence was 2.7%.

However, the study demonstrated that the risk factors of hyperkalemia (odds ratio 17.8; 95% confidence interval (CI)1.3-240, $p<0.05$), cardiopulmonary resuscitation (odds ratio 10.1; 95% CI 1.1-93.5, $p<0.05$), and right heart failure ($p<0.05$) were significantly associated with RH (Table 1).

Details on patients with RH and ophthalmologic findings are shown in Tables 2, 3 and 4.

Discussion

Although there is adequate literature on trends in determining RH, there are few studies in pediatric population and the information in developing world about this subject is uncertain. The majority of studies start from a suggestion of child abuse and the incidence of RH in pediatric population when newborns are excluded is ambiguous. Therefore, this study was performed to define the prevalence, distribution, and extent of RH in critically ill children admitted to PICU excluding newborns and patients with trauma. There were 77 (50.3%) male and 73 (47.7%) female patients. These findings were similar to the literature[12,15]. According to our results, the mean age of patients was 5.2±5.6 (median: 2.4) years and we found that children aged less than 2 years predominated (n=79, 51.7%). Consistent with our findings, median age was 1.5 years[12] and 2 years[10] in two studies. It is complicated to compare age distribution among studies because inclusion criteria are various in each study. RH is a frequent finding in child abuse, especially in the shaken baby syndrome which is a serious problem without obvious sign of physical injury[9,15]. Most studies report that RH is not indicative of a preceding trauma and must not be misinterpreted as child abuse because it may also be associated with CPR, accidental trauma, and various diseases[1,11,16,17].

Retinal hemorrhage is common in non-accidental head injury, particularly in the shaken baby syndrome, with the incidence of 38%-100%[1,18]. In contrast, no RH was found in a study of 108 infants with apparent life-threatening events[19]. We report a 3.33% prevalence of the

TABLE 1. Demographic characteristics of study patients

Variable	(N=150)
Age (years), mean±SD (median)	5.2±5.6 (2.4)
1 month-1 year	50 (32.7)
1-2 years	29 (19)
2-5 years	22 (14.4)
5-10 years	17 (11.1)
10-18 years	32 (20.9)
Gender	
Male, n (%)	77 (50.3)
Female, n (%)	73 (47.7)
Prevailing diagnosis, n (%)	
Infectious diseases	17 (11.3)
Gastroenterological	2 (1.3)
Pulmonary	18 (12)
Metabolic	19 (12.7)
Hematologic-oncologic	4 (2.7)
Neurological	54 (36)
Cardiologic	11 (7.3)
Endocrinologic	1 (0.7)
Nephrological	3 (2)
Poisoning	13 (8.7)
Genetic disorders	6 (4)
Immune disorders	2 (1.3)
Respiratory failure, n (%)	117 (76.5)
Mechanical Ventilation, n (%)	117(76.5)
Endotracheal tube/tracheostomy, n (%)	117 (76.5)
Arrhythmia, n (%)	7 (4.6)
Hyperkalemia, n (%)	3 (2)
Pneumothorax, n (%)	2 (1.3)
Sepsis, n (%)	24 (15.7)
Cardiopulmonary resuscitation, n (%)	45 (29.4)
Hypotension, n (%)	31 (20.39
Hypertension, n (%)	16 (10.5)
Heart failure, n (%)	4 (2.6)
Seizures, n (%)	50 (32.7)
Coagulation disorders, n (%)	23 (15)

TABLE 2. Risk factors for retinal hemorrhage in children (N=150)

Risk factor	Pearson χ^2-test analysis Man Whitney *U* Test	Logistic regression*
Age/age group	p>0.05	1.0 (0.9-1.0)/1.3 (0.7-2.4) (p>0.05)
Gender	p>0.05	0.7 (0.1-4.0) p>0.05
Diagnosis	p>0.05	1.1 (0.6-2.2) p>0.05
Respiratory failure	p>0.05	0 (0) (p>0.05)
Mechanical ventilation	p>0.05	0 (0) (p>0.05)
Endotracheal tube/tracheostomy	p>0.05	0 (0) (p>0.05)
Arrhythmia	p>0.05	5.7 (0.5-60) (p>0.05)
Hyperkalemia	p<0.05	17.8 (1.3-240) (p<0.05)
Pneumothorax	p>0.05	0 (0) (p>0.05)
Cardiopulmonary resuscitation	p<0.05	10.1 (1.1-93.5) (p<0.05)
Sepsis	p>0.05	1.3 (0.1-12.4) (p>0.05)
Hypotension	p>0.05	0.7 (0.1-4.5) (p>0.05)
Hypertension	p>0.05	0.3 (0.04-2.0) (p>0.05)
Heart failure	p<0.05	11.8 (0.9-140.1) (p>0.05)
Seizures	p>0.05	3.1 (0.5-19.3) (p>0.05)
Coagulation disorders	p>0.05	3.9 (0.6-24.9) (p>0.05)

***** Odds ratio and 95% confidence intervals

TABLE 3. Details on patients with retinal hemorrhage and ophthalmologic findings

	Age (months)	Gender	Weight	Diagnosis
Patient 1	120	M	17	Cerebral palsy, motor mental retardation, swallow of tooth
Patient 2	48	M	16	Carbon monoxide intoxication
Patient 3	50	M	12	Epilepsy, pneumonia
Patient 4	192	F	70	Aplastic anemia, sepsis
Patient 5	24	F	12	Febrile convulsion, status epilepticus, post-arrest

TABLE 4. Details on patients with retinal hemorrhage and ophthalmologic findings in critically ill children

	Risk factors	Retinal hemorrhage			Survival
		Severity	Laterality	Layer	
Patient 1	MV, ETT, Arrhythmia, CPR, Seizure	Moderate	Unilateral, left	Intraretinal	Survived
Patient 2	MV, ETT, CPR, hypotension	Mild	Unilateral, right	Preretinal	Survived
Patient 3	MV, ETT, seizure	Mild	Bilateral	Superficial intraretinal	Survived
Patient 4	MV, ETT, CPR, hyperkalemia, coagulation disorder	Mild	Unilateral, right	Preretinal	Survived
Patient 5	MV, ETT, CPR, seizure, coagulation disorder	Mild	Bilateral	Intraretinal	Survived

MV = mechanical ventilation; ETT = endotracheal tube; CPR = cardiopulmonary resuscitation

presence of any RH in critically ill children, with no severe multilayered RHs, conversely to those reported as 15.1% in critically ill pediatric population[12,20]. Gayle *et al.* state that RH occurs in 10% of children presenting no evidence of trauma with any other risk factor for hemorrhage. Some studies suggest that the retinal venous system in infancy is more vulnerable to increased intrathoracic pressure[1,11]. Consistent with our findings, retinal bleeding was mostly mild, not extensive (75%). In addition, RH in PICU was not usually severe, multilayered or extensive. The rate of severe bilateral multilayered RH was 3.8% and was completely in association with severe trauma, sepsis, coagulopathy or a combination of these factors[12,20]. A review has described the association of severe bilateral extensive RH with abusive head trauma[7]. Binenbaum *et al.* prospectively examined fundus of children undergoing lumbar puncture as part of their clinical care and found that only a small proportion of children with non-traumatic elevated intracranial pressure (16%) had RH[21]. In our study, the reason for no case of severe RH might be that our study excluded patients with abusive head trauma, penetrating eye trauma, and all other trauma patients. A literature review suggests that the severity of RH is more valuable in predicting abuse than the presence of RH[8].

In our study, CPR and heart failure were significantly associated with RH. In some studies, RH has been reported as a sequel of CPR[1,10]. Chest compression from any cause raises intrathoracic pressure and this induces RH by directly increasing retinal venous pressure. In addition, simultaneous chest inflation with compression increases the right atrial pressure. Therefore, CPR produces salient pulsatile venous hypertension of the head and neck. Increased intracranial pressure by compression has been shown to cause retinal venous hypertension and RH[1,10]. This might be the reason that in our study heart failure was significantly associated with RH besides CPR.

Hyperkalemia was stated to be a precipitating event for RH in cardiopulmonary arrests requiring chest compression[4]. In our study, hyperkalemia was significantly associated with RH. Studies are limited regarding effects of hyperkalemia on RH and this was a key finding drawing attraction

to electrolyte imbalances that might cause or precipitate RH. Further studies are necessary on this issue as soon as possible.

Like most studies, we found that there was no detectable impact of age, age group, gender, admission diagnosis, respiratory failure, requirement of mechanical ventilation, presence of an endotracheal/tracheostomy tube, arrhythmia, sepsis, hypo/hypertension, seizures, pneumothorax, and coagulopathy on the prevalence of RH. This was all highly correlated with the literature[1,22,23]. However, some studies stated that the presence of coagulation disorders/coagulopathy increased the prevalence of RH as expected[1,3,12]. The reason might be that there were only 23 (15%) patients presenting with coagulation disorders.

It is uncommon that a child with shaking impact injury would attend initially an ophthalmologist and our experience suggests that most pediatric intensivists/emergency physicians have difficulty in evaluating the fundus of a child. Considering diagnostic importance of RH, it seems important for a pediatric intensivist/emergency physician to learn through examination of the fundus and pupil dilatation about visualization of retina in a child when necessary. If there is suspicion of RH, an ophthalmologist's opinion should be required for confirmation and documentation. The challenges ophthalmology faces today must be overcome by developing long-term strategies connected with remembrance of healthcare system values and diagnostic procedures as physicians[24-26]. Any child found to have RH might have an underlying medical condition that requires further investigations.

To our knowledge, our research is an important prospective study estimating the prevalence of RH in a population of critically ill children without any kind of trauma. By this means, we hope to decrease the risk of RH underdiagnosing. The strength of our study was that by excluding patients with trauma we provided an outcome more likely to approach the baseline incidence of RH in all sick children. Limitations of this study may include the absence of a control group of healthy children, and unfortunately, the patients meeting the inclusion criteria could not be enrolled to the study due to refusal of informed consent. Additional studies with larger samples should be carried out to warrant these results.

Conclusion

We report a 3.33% prevalence of the presence of any RH in critically ill children, mostly mild and no severe bilateral multilayered RH. The risk factors of hyperkalemia, cardiopulmonary resuscitation and heart failure were significantly associated with RH. In addition, a study focused on the effects of RH on visual acuity and visual outcome in the future will be helpful for understanding the long-term impact of RH. ■

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SAŽETAK

Krvarenje mrežnice u kritično bolesne djece – prospektivno istraživanje

Tülin Köksal, Şanlıay Şahin, Esra Dağ Şeker, Ganime Ayar, Mutlu Uysal Yazıcı i Alkım Öden Akman

Cilj ovoga opservacijskog istraživanja bio je utvrditi učestalost, raspodjelu i opseg krvarenja mrežnice (KM) u kritično bolesne djece, njihove demografske značajke, klinička obilježja i ishod bolesnika s KM, isključujući bolesnike s traumom. Također smo nastojali opisati utjecaj dobi, spola, dijagnoza kod prijma, čimbenika rizika poput repiracijskog zatajenja, potrebe mehaničke ventilacije, prisutnosti endotrahealne/traheostomske cijevi, kardiopulmonalne reanimacije, aritimije, hiperkalijemije, pneumotoraksa, sepse, srčanog zastoja, hipo/hipertenzije, prisutnosti napadaja, prisutnosti koagulacijskih poremećaja na tu raspodjelu kao sekundardni rezultat. Podatci su prospektivno prikupljani uzastopno od travnja 2013. do travnja 2014. godine. Za vrijeme istraživanja utvrđeno je ukupno 150 bolesnika koji su odgovarali uključnim kriterijima. Omjer muških i ženskih bolesnika bio je 1,05. Nije bilo uočljivog utjecaja dobi, dobne skupine, spola, dijagnoze kod prijma, respiracijskog zatajenja, potrebe mehaničke ventilacije, prisutnosti endotrahealne/traheostomske cijevi, aritmije, sepse, hipo/hipertenzije, prisutnosti napadaja, pneumotoraksa, prisutnosti koagulacijskih poremećaja/koagulopatije na učestalost KM. Istraživanje je pokazalo da su rizični čimbenici poput hiperkalijemije, kardiopulmonalna reanimacija i srčani zastoj značajno povezani s KM. Svako dijete koje ima KM moglo bi patiti od nekog osnovnog medicinskog stanja koje zahtijeva daljnje pretrage. Usto, buduća studija usredotočena na učinke KM na vidnu oštrinu i ishod vida pomoći će u razumijevanju dugoročnog utjecaja KM.

KLJUČNE RIJEČI

Djeca, kritično bolesna; Pedijatrijska jedinica intenzivnog liječenja; Krvarenje mrežnice