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Article

Intracranial Hemorrhage in Childhood Hemophilia Patients

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Abstract: Childhood hemophilia, a hereditary bleeding disorder predominantly affecting males, arises due to mutations in the genes encoding clotting factors VIII or IX. Intracranial hemorrhage represents a significant and life-threatening complication in pediatric patients with hemophilia. The incidence of intracranial hemorrhage in children with hemophilia, although relatively low, is notably higher compared to the general pediatric population. In this study, the objective is to examine patients with hemophilia who have experienced intracranial hemorrhage retrospectively. This study is a multicenter, retrospective analysis using data from three tertiary care centers in a provincial city in Turkey. Data were obtained from the participants' hospital records. The presence of inhibitors in the participants and the prophylaxis used against them were included in the analysis. Trauma history was queried, with types of traumas examined, including traffic accidents, falls, and a traumatic vaginal delivery. The duration and causes of complaints among the participants were investigated. The causes of complaints were categorized as fever, hematoma, convulsions, loss of consciousness, and hemiparesis. The participants' physical examination findings were classified as fever, hematoma, and loss of consciousness. The duration of hospital stays was evaluated. The hemorrhage location was classified into five groups: parenchymal, subdural, scalp, subarachnoid, multiple hemorrhagic foci. The recurrence of bleeding, the need for transfusion, surgical intervention, and mortality were also examined. A significant differences was identified between the participants' survival rates and age variables, transfusion in < 36 month. Nine participants were spontaneous intracranial bleeding, two experienced cranial trauma as a result of traffic accidents, and 25 participants were exposed to head trauma due to falls. Of the remaining individuals, one suffered head trauma from a severe impact, one done cranial trauma following a traumatic vaginal delivery. Fourteen participants required transfusion, and three underwent surgical intervention. According to the results of the statistical analyses, the variables Factor Level, Physical Examination Findings, Transfusion, Recurrent Bleeding, Inhibitor, and Prophylaxis were found to affect survival significantly. No significant relationship was determined between the other analyzed variables and survival. In our study, five of the participants examined have died. Accordingly, the mortality rate identified in our study is 13.1%.

Keywords: childhood hemophilia; intracranial hemorrhage; pediatric population; mortality rate

1. Introduction

Childhood hemophilia, a hereditary bleeding disorder predominantly affecting males, arises due to mutations in the genes encoding clotting factors VIII (Hemophilia A) or IX (Hemophilia B) [1]. This X-linked recessive disorder manifests early in life, often with prolonged bleeding episodes following minor injuries or surgical procedures [2]. In severe cases, spontaneous hemarthroses, or bleeding into joints, are common, leading to significant morbidity due to joint damage and chronic pain [3].

Intracranial hemorrhage (ICH) represents a significant and life-threatening complication in pediatric patients with hemophilia [4]. The pathophysiology of hemophilia, marked by the inability to form stable blood clots, predisposes affected children to spontaneous and trauma-induced bleeding episodes, with intracranial hemorrhage being among the most severe manifestations [5].

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The incidence of ICH in children with hemophilia, although relatively low, is notably higher compared to the general pediatric population. This condition necessitates immediate medical intervention due to its potential to cause irreversible neurological damage or death [6]. The presentation of ICH in these patients can vary, ranging from subtle neurological deficits to acute and catastrophic neurological deterioration [7]. Symptoms may include severe headache, vomiting, altered consciousness, seizures, and focal neurological signs, which warrant prompt imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI) to ascertain the diagnosis [8].

Intracranial hemorrhages in children undergoing prophylaxis are reported to be quite rare. However, in children whose prophylactic treatments are not administered regularly, these life-threatening hemorrhages are more common than previously recognized [9]. Post-hemorrhagic complications may include behavioral disorders, hemiplegia/paresis, and epilepsy. Hemorrhages frequently occur following trauma and must be substantiated through imaging techniques. This condition is considered an emergency due to its high mortality and morbidity risks. In acute hemorrhage, immediate factor therapy should be initiated upon the patient's arrival at the emergency department, with the target factor level being 80-100% [10].

In this study, the objective is to examine patients with hemophilia who have experienced intracranial hemorrhage retrospectively.

2. Material and Method

2.1. Study Population and Participants

The data for this study were obtained from three distinct tertiary healthcare institutions. The study included 38 patients with Hemophilia A and Hemophilia B. Of these participants, 35 had Hemophilia A, and three had Hemophilia B. A total of 40 intracranial hemorrhage episodes occurring in 38 patients were evaluated.

2.2. Study Design

Our study aimed to share our experiences regarding intracranial hemorrhages, considered one of hemophilia's rare yet most significant complications. This study is a multicenter, retrospective analysis using data from three tertiary care centers in a provincial city in Turkey. The demographic characteristics of the participants, specifically the age variable, were examined. All participants were male. Data were obtained from the participants' hospital records. The presence of inhibitors in the participants and the prophylaxis used against them were included in the analysis. Trauma history was queried, with types of traumas examined, including traffic accidents, falls, and a traumatic vaginal delivery. The duration and causes of complaints among the participants were investigated. The causes of complaints were categorized as fever, headache, convulsions, loss of consciousness, and vomiting. The participants' physical examination findings were classified as focal neurological deficit, mental status changes, speech disorder, and optic disc edema. The duration of hospital stays was evaluated. The hemorrhage location was classified into five groups: parenchymal, subdural, scalp, subarachnoid, multiple hemorrhagic foci. The recurrence of bleeding, the need for transfusion, surgical intervention, and mortality were also examined.

2.3. Measurement of Factor Levels

The participants' factor levels were categorized as severe, moderate, and mild. A less than 1% factor level was considered severe, 1% to 5% was considered moderate, and 5% to 45% was considered mild [11].

2.4. Exclusion Criteria

- Participants who refuse to participate in the study,
- Chronic inflammatory,

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- Thrombotic diseases,
- Neoplastic diseases,
- Major surgical interventions in the past three months,
- Experienced major trauma in the past three months.

2.5. Examined Variables

- Age,
- Presence of inhibitors,
- Prophylaxis,
- Trauma history,
- Duration and causes of complaints,
- Physical examination,
- Duration of hospital stays,
- Location of the hemorrhage,
- Transfusion,
- Surgical intervention,
- Mortality.

2.6. Ethics

Ethical approvals were obtained from the institutions where the research was conducted. Participation in the study was based on voluntary consent. Informed consent was obtained from the parents of all participants. The principles of the Declaration of Helsinki conducted all stages of the research.

2.7. Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) software was utilized in the analyses. Descriptive statistics were provided for clinical and demographic characteristics. Chi-square and Mann-Whitney U tests were employed to compare groups. Possible relationships between death and certain variables about participants were examined using bivariate linear regression analysis. In all analyses, a p-value of <0.05 was considered the threshold for statistical significance.

3. Results

The average age of the participants is 37.87 ± 38.16 months. A significant differences was identified between the participants' survival rates and age variables, transfusion in < 36 month . (Table 1).

Table 1. Survival rates and the age variable among the participants.

		< 36 month	> 36 month	P
Transfusion	**Yes**	10	4	**0,03**
	No	11	13	
Recurrent Bleeding	**Yes**	6	2	**0,02**
	No	17	15	
Surgery	**Yes**	6	7	0,8
	No	13	12	
Ex. / Treated	**Exitus**	3	2	**0,03**
	Treated	17	16	

The oldest participant is 24 years old. All participants are male. The factor level is classified as mild in one participants, moderate in two, and severe in 35. Inhibitor development was identified in seven participants. Prophylaxis was administered to 23 participants.

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Among the participants, nine participants were spontaneous intracranial bleeding, two experienced cranial trauma as a result of traffic accidents, and 25 participants were exposed to head trauma due to falls. Of the remaining individuals, one suffered head trauma from a severe impact, one done cranial trauma following a traumatic vaginal delivery.

In four participants, fever complaints were observed; in eight of them, headaches; in ten of them, convulsions; in six of them, loss of consciousness and in ten of them vomiting. It was determined that complaints had persisted for a week or longer in four participants, in thirty-four participants were developed in a few days.

In ten participants, focal neurological deficits; the mental status change was detected in nineteen participants, speech disorders in two of them, and optic disc edema in seven of them.

In evaluating the hospital stay thirteen participants required hospitalization for one week and twenty-five participants required hospitalization for longer.

Hemorrhage in the parenchyma was detected in eleven participants, and multiple hemorrhagic foci were identified in fifteen participants. Subdural hemorrhage in eight participants, scalp hemorrhage in one, and subarachnoid hemorrhage were found in three participants.

Fourteen participants required transfusion, and three underwent surgical intervention.

According to the results of the statistical analyses, the variables Factor Level, Physical Examination Findings, Transfusion, Recurrent Bleeding, Inhibitor, and Prophylaxis were found to affect survival significantly (Table 2). No significant relationship was determined between the other analyzed variables and survival. In our study, five of the participants examined have died. Accordingly, the mortality rate identified in our study is 13.1%.

Table 2. Variables with a relationship to survival.

		Treated	Exitus	P
Factor Level	Mild/Moderate	3	0	**0,01**
	Severe	30	5	
Physical Examination Findings	Focal Neurological Deficit	9	1	**0,02**
	Mental Status Change	15	4	
	Speech Disorder	2	-	
	Optic Disc Edema	7	-	
Hemorrhagic Region	Parenchymal	10	1	0,2
	Subdural	7	1	
	Scalp	1	-	
	Subarachnoid	3	-	
	Multiple Hemorrhagic Foci	12	3	
Transfusion	Yes	11	3	**0,03**
	No	22	2	
Inhibitor	Yes	5	2	**0,02**
	No	28	3	
Recurrent Bleeding	Yes	7	1	**0,01**
	No	28	4	
Prophylaxis	Yes	22	1	**0,03**
	No	11	4	

This model was examined using bivariate linear regression analysis, revealing that the variables of Factor Level, Physical Examination Findings, Transfusion, İnhibitor, Recurrent Bleeding significantly impacted survival.

According to the analysis, the presence of findings such as convulsions and loss of consciousness during admission accompanying the physical examination increases the risk of death approximately 3.5 times (Table 3).

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Table 3. Bivariate linear regression analysis.

	B	S.E.	Wald	df	Sig.	Exp(B)
Factor Level	-3,307	2,312	2,045	1	0,153	,037
Physical Examination Findings	1,258	,698	3,246	1	**0,072**	3,517
Transfusion	3,019	1,694	3,176	1	**0,075**	2,464
Inhibitor	1,011	2,134	1,341	1	**0,085**	2,591
Recurrent Bleeding	3,582	1,259	1,211	1	0,359	1,781
Constant	-2,410	3,058	,621	1	0,431	,090

4. Discussion

The incidence and severity of ICH in hemophilia patients are intrinsically linked to the level of circulating clotting factors. Patients with severe hemophilia are at a disproportionately higher risk due to their near-absent levels of functional clotting factors, leading to an inability to form stable hemostatic plugs following vascular injury effectively. Intracranial hemorrhage is a severe complication in hemophilia patients, leading to disability and, in some cases, death. Although it can occur at any age, it is commonplace in neonates and children. In hemophilic children with intracranial hemorrhage, severe factor deficiency is often identified. In one study, all hemophilic children with intracranial hemorrhage were found to have severe factor deficiency [12]. In our study, severe factor deficiency was detected in 35 out of 38 participants, establishing a frequency of 89%**.**

The initial presentation of intracranial bleeding in children with hemophilia often includes nonspecific symptoms such as persistent headaches and irritability, which may be mistakenly attributed to less severe conditions [13,14]. As the hemorrhage progresses, more overt neurological signs may emerge. These include altered levels of consciousness, ranging from lethargy to coma, reflecting the increasing intracranial pressure and cerebral involvement [15].

The pathophysiology of intracranial hemorrhage in hemophilic children involves the disruption of vascular integrity within the central nervous system. Due to insufficient clotting factors, the hemostatic plug formation is delayed or ineffective, leading to uncontrolled bleeding within the intracranial space. This can result from minor head trauma or occur spontaneously, with the latter being particularly insidious due to the absence of an obvious precipitating event [15]. Studies have determined that fractures such as skull base and upper cervical fractures, which develop as a result of head trauma, frequently lead to ICH. In our study, conditions that lead to cerebral hemorrhage were examined. While 80% of the participants had a history of head trauma, eight participants experienced spontaneous cerebral hemorrhage without any history of trauma [16,17].

Intracranial bleeding, a grave, and potentially fatal complication presents significant challenges in pediatric patients diagnosed with hemophilia [4]. The immature hemostatic mechanisms in children further exacerbate the risk of intracranial bleeding, necessitating prompt and precise medical intervention [16]. During their developmental stages, the cerebrovascular autoregulation system in children leads to turbulent transitional hemodynamics. This increases the likelihood of vascular rupture and predisposes them to ICH. Some studies characterize the relationship between hypoxemia and the development of severe ICH and the immature cerebrovascular autoregulation system [16,17]. However, some studies do not confirm this relationship [18].

In an analysis of related studies, the mortality rate was lower than the one identified in our study, which may be attributed to the high number of participants with severe factor deficiency in our cohort [10]. Our study's findings indicate that the mortality rate is higher among participants under 36 months of age. Consistent with this observation, the need for transfusions, recurrent bleeding, and surgical interventions are also more frequent in individuals within this age group. The results of studies in the literature similarly support this conclusion. In our study, the mortality rate in participants younger than 36 months was approximately 17%, while this value was approximately 12% in participants older than 36 months. The difference between the groups was also statistically significant.

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In our study, the mortality rate is approximately 13%, which is a considerably high value. In a similar study, the mortality rate was determined to be 2.5% [19]. Another study indicated that the mortality rate was about three times this value [20]. Differences in the number of participants or the severity of the cases examined explain these discrepancies. There are studies in the literature that have found a mortality rate similar to our study [21].

The mortality rate among participants with recurrent hemorrhage was 16,6%, significantly higher than the rate identified in participants without recurrent hemorrhage in our study. The frequency of recurrent bleeding detected in similar studies is lower than in our study [22].

Clinically, intracranial bleeding can manifest with a spectrum of neurological symptoms, ranging from subtle behavioral changes and irritability to severe presentations such as seizures, focal neurological deficits, and altered consciousness [23]. The diagnosis is primarily reliant on neuroimaging modalities, with computed tomography (CT) and magnetic resonance imaging (MRI) being pivotal in delineating the extent and precise location of the hemorrhage [24].

In the pediatric period, the severity of hemophilia is the most significant risk factor for ICH. Andersson and colleagues examined patients with severe hemophilia and emphasized the role of prophylaxis in reducing the risk of ICH [20]. Similarly, Bladen and colleagues studied hereditary bleeding disorders in over 1,000 participants and confirmed that ICH episodes in children with hemophilia occur predominantly in those with severe disease. Another study involving 23 patients with hemophilia A and B identified 54 ICH events, asserting [25] that severe disease is a critical factor in the development of ICH [9]. The data obtained from our study corroborate these findings. Similar to the examples given above, in our study the mortality rate was lower in participants who received prophylaxis than in those who did not. Therefore, the mortality rate is higher in participants who received prophylaxis and this finding is statistically significant. In our study, it was evaluated that the higher mortality rate in participants who received prophylaxis was due to their more severe trauma and multifocal hemorrhages.

Consequently, even minor head trauma can precipitate significant hemorrhagic events [26,27]. In pediatric populations, the vulnerability to ICH is accentuated by the increased likelihood of head injuries associated with developmental milestones and physical activities [28]. Furthermore, the immaturity of the pediatric neurological system exacerbates the clinical impact of ICH, often resulting in profound neurological deficits or mortality if not promptly managed [29]. In our study, it was determined that the frequency of spontaneous cerebral hemorrhage in the participants was 21%, and the frequency of bleeding resulting from head trauma was approximately 80%.

Focal neurological deficits, such as hemiparesis or cranial nerve palsies, may develop, signifying localized areas of brain damage [30]. Such deficits often correlate with the specific site of hemorrhage, providing critical diagnostic clues. Additionally, visual disturbances, including blurred vision or loss of vision, can occur due to optic nerve compression or involvement of the visual pathways [31]. Mental status changes were the most commonly observed finding during the participants' physical examinations, while focal neurological deficits were the second most frequently identified symptom. However, some studies have recorded neurological deficits as the most prevalent finding [32]. Another characteristic identified was that mortality was more common in participants with mental status changes. The mortality rate in participants with mental status changes was 21%.

Inhibitors were detected in seven of the participants. Five of the individuals with detected inhibitors exhibited recurrent bleeding. Long-term complications, such as motor deficits and mental retardation, were identified in these cases. Similar studies in the literature support our findings [33].

In a study conducted on 112 hemophilia patients, 88 of whom presented with intracranial hemorrhage, the identified risk factors associated with intracranial hemorrhage included age < 3years, age > 50 years, hemophilia severity, the presence of inhibitors [10]. It was noted that the mortality rate related to intracranial hemorrhage was higher in patients with inhibitors (approximately 50%), and approximately 20% of surviving patients were found to have disabling sequelae. In our study, the frequency of inhibitors was 19%, and the mortality rate among patients with inhibitors was approximately 43%. The data from both studies are mutually supportive. It was determined that the mortality rate was higher in participants who were determined to have bleeding

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from multifocal focus compared to other Hemorrhagic Regions. Here too, the frequency was found to be approximately 20%.

Despite the introduction of new hemophilia medications, the increase in experienced hemophilia centers, and the development of appropriate treatment methods for hemophilia patients, intracranial hemorrhages continue to occur and remain a serious concern today.

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