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Association between Neonatal Phototherapy and Cancer during Childhood

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ABSTRACT

Background: Phototherapy is the most effective and commonly used treatment for neonatal jaundice, which reduces the need to exchange transfusion. Today, phototherapy is widely used even in unnecessary cases; however, clinicians who use phototherapy should be aware of the possible adverse effects of this treatment to avoid unnecessary use of it. Therefore, this study aimed to evaluate the relationship between neonatal phototherapy and childhood cancer.

Methods: This case-control study assessed 500 children up to 14 years of age with every kind of cancer that referred to Children's Medical Center, Tehran, Iran, during 2015-18. Moreover, 500 children without cancer referring to a General Clinic of Children's Medical Center, Tehran, Iran were included in this study as the control group. History of phototherapy and its duration evaluated in these two groups. Furthermore, demographic characteristics, including maternal age during pregnancy, birth weight, gender, smoking by father, type of cancer, age at cancer detection, and history of cancer in relatives were recorded in this study.

Results: The results of a single-variable logistic regression showed that neonatal phototherapy without any other variables was not significantly correlated with childhood cancer. However, phototherapy will increase the risk of cancer by 55% when it is accompanied by the male gender, maternal age >35 years during pregnancy, and smoking by father.

Conclusion: The potential risk of developing cancer with neonatal phototherapy should be considered versus its benefits in reducing the bilirubin.

Keywords: Cancer, Child, Phototherapy

Introduction

Neonatal jaundice is one of the most common and usually benign neonatal problems. Moreover, it is the most common cause of hospitalization in neonates. Approximately, 60% and 80% of the term and premature infants developed jaundice during the first week of life, respectively (1). Jaundice is associated with an increased risk of neurological dysfunction due to bilirubin deposition. This disorder occurs when bilirubin passes through the blood-brain barrier and precipitates mainly in the ganglia basal cells (2). The goal of the therapy is to prevent brain injury by decreasing the serum bilirubin level (3). Phototherapy is the most effective and commonly used treatment for neonatal jaundice, which reduces complications by declining bilirubin levels (3, 4).

Little side effects of phototherapy have been reported so far. Although it is almosta safe treatment, its long-term side effects are required to be investigated, especially in preterm infants(5).Some studies explain the relationship between phototherapy and skin cancer(6). Furthermore, two large epidemiological studies have shown that phototherapy is associated with childhood cancers(7,8).On the otherhand, these relationships have not been proven yet, and some studies are reinforcing this hypothesis(8,9). Phototherapy generates free oxygen radicals that can damage the host cells and lead to the breakdown of the DNA chain (10).The accumulation of DNA damage over time can lead

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to gene changes in the cells and made them mutagenic or carcinogenic(11). Although maximal light absorption by DNA is 245-290 nm wavelengths, DNA damage has been also observed at 460 nm wavelengths(12).Recently, the use of LED bulbs has been increased; however, according to meta-analytic studies, this method had no advantages, compared to previous ones (10).

There is a dearth of research on the potential effect of phototherapy, as a commonly used treatment for neonatal jaundice, on developing cancer during childhood. Moreover, the results obtained from these studies are controversial. Therefore, this study aimed to evaluate the relationship between neonatal phototherapy and childhood cancer.

Methods

This case-control study assessed 500 children up to 14 years of age with every kind of cancer referring to Children's Medical Center, Tehran, Iran, during 2015-18 as the control group. Moreover, 500 children without cancer referring to the General Clinic of Children's Medical Center, Tehran, Iran were included in this study as the control group. The exclusion criteria were: 1) children beyond 14 years of age 2) presence of Down, VonHippel-Lindau, Beckwith-Wiedemann, and Neurofibromatosis syndromes 3) congenital major anomalies, 4) lack of permission by the children's parents, and5)incomplete data.

Demographic characteristics covered such information as age, gender, gestational age, birth weight, maternal age, and carcinogenic factors, including a family history of cancer, paternal smoking, phototherapy, and its duration.

All cancer patients who referred to the Children's Medical Center, Tehran, Iran, during 2015-18 were included in this study. The data were recorded in pre-prepared checklists and analyzed in SPSS software (version 18) through descriptive statistics to describe the data using frequency (qualitative variables), as well as mean and standard deviation (quantitative variables). Furthermore, the chi-square test, t-test, or multivariate analysis tests, such as regression were used to analyze the data.

Considering a 95% confidence interval and test power of 80%, a p-value less than 0.05 was considered statistically significant. This study was conducted based on the ethical principles of the Helsinki declaration, and the study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (ID:1396.3945).

Results

A total of 1000 children were enrolled in this study, including 500 cancer patients (case group) and 500 children without cancer (control group). The most common tumors in the cancer group were acute lymphoblastic leukemia (ALL) and neuroblastoma. The mean ages of the children were 6.8 and 4.3 years in the case and control groups, respectively. Table 1 tabulates other demographic characteristics of the participants.

In total, 33.8% and 19.6% of the fathers in the case and control groups were smokers, respectively, and this difference was significant (P=0.001). Moreover, 31.8% and 37.2% of the case and control groups had parental consanguinity, respectively (P=0.072). Furthermore, the incidence of cancer in close relatives was 25.2% in the case and 30.6% in the control group; however, this difference was not significant (P=0.057). Furthermore, there was a significant difference between the groups regarding the history of neonatal phototherapy (23.6% and 30.2% in the cases and controls, respectively, P=0.019).

According to the results of a single-variable logistic regression, regardless of confounding and other variables, the male gender was a risk factor for cancer. Accordingly, the risk of developing cancers was four times higher in males, compared to females (P= 0.001). For each year, increasing maternal age at pregnancy was increased by 1.05 times the risk of cancer in children. In addition, a history of smoking by the father will increase the risk of cancer in the child by 2 times (Table2).

The results showed that some variables had

Table 1. Demographic characteristics of the participants

	Group Statistics				
	Group	N	Mean	Std. Deviation	P-value
Maternal Age during pregnancy (year)	Case	500	26.74	5.45	0.001
	Control	500	25.38	4.84	
Child age(year)	Case	500	6.86	4.02	0.001
	Control	500	4.39	2.53	
Birth weight (gr)	Case	496	3158.30	519.43	0.001
	Control	500	2852.04	508.06	

Table 2. Risk factors affecting cancer using univariate regression

Group2	Odds Ratio	P>z	[95% Conf. Interval]	
			Lower Limit	Upper Limit
Gender (male)	4.03	0.001	3.08	5.28
Age	1.25	0.001	1.20	1.30
Relative parents	1.27	0.073	0.98	1.65
Mothers'age at pregnancy	1.05	0.001	1.03	1.08
BW	1.00	0.001	1.00	1.00
Paternal smoking	2.09	0.001	1.57	2.79
Abortion	1.09	0.646	0.76	1.56
Stillbirth	1.61	0.073	0.96	2.70
Phototherapy history	0.71	0.019	0.54	0.95
Phototherapy duration	0.83	0.001	0.74	0.92
History of cancer in family	0.76	0.057	0.58	1.01

Table 3. Risk factors of childhood cancerusing logistic correlation

Group2	Odds Ratio	P>z	95% Confidence Interval	
			Lower Limit	Upper Limit
Gender	5.09	0.001	3.80	6.82
Phototherapy history	1.55	0.007	1.13	2.12
Paternal smoking	1.83	0.001	1.33	2.51
Mother's Age during pregnancy	1.08	0.001	1.05	1.11

direct impacts on the risk of cancer. They include male gender, history of neonatal phototherapy, history of paternal smoking, and the mother's age during pregnancy. Birth weight due to the high collinearity was removed in the final analysis.

Aftere liminating such variables as gender, maternal age during pregnancy, and paternal smoking, it was found that phototherapy in the neonatal period increased the risk of cancer by 55%. Moreover, the history of paternal smoking (excluding other variables) showed an increase in the risk of neonatal cancer by 83%. Each year, increasing maternal age, apart from other conditions, enhanced the risk of cancer in a child by 8%. Eventually, the risk of cancers in the male gender was five times higher than females regardless of other variables (Table 3).

Discussion

The results of single-variable logistic regression showed that the history of neonatal phototherapy, regardless of other factors and variables, had no significant relationship with childhood cancer. However, this factor has effects along with other factors, including birth weight, maternal age during pregnancy, and history of smoking by fathers. Moreover, the results of a single-variable logistic regression revealed that the neonatal phototherapy had no significant relationship with acute lymphoblastic leukemia (ALL), Neuroblastoma by using a single-variable logistic regression, too. Phototherapy in the neonatal period increased the risk of cancer by 55% when it is accompanied by gender (i.e., male), history of smoking by father, and maternal age during pregnancy.

In 1979, Speck WT and Rosenkranz HS suggested the potential effects of phototherapy on an increased risk of cancer. In their study, they investigated the mutagenicity of the blue light in the laboratory environment. In addition, they noted that phototherapy had a role in oxidative stress and DNA damage; moreover, it was a factor in the pathology of cancer. Therefore, they recommended that the benefits of phototherapy should be considered concerning its potential harm, especially in prophylactic cases (13).In the same line, Aycicek. et al. investigated 65 neonates between 3-10 days exposed to intensive (n=23) or conventional phototherapy(n=23) for at least 48 h due to neonatal jaundice along with a control group (n=19). Their results showed that both intensive and conventional phototherapy could lead to DNA damage in term neonates who had jaundice; however, there was no correlation between bilirubin levels and damage levels (12).

In a study conducted by Ramyet al., the effects of hyperbilirubinemia and two types of phototherapy (i.e., intensive phototherapy or conventional) were investigated on DNA damage in peripheral blood mononuclear cells in non-hemolytic hyperbilirubinemia term infants. Their results showed no difference between neonates with or without jaundice in terms of DNA damage. Nonetheless, after exposure to phototherapy, this damage significantly increased, compared to the time before exposure. The duration of phototherapy was positively correlated with DNA damage; nevertheless, no correlation was found between the intensity of light and the damage

(14).These studies and other studies on human infants indicated DNA damage, changes in levels of cytokines, and evidence of oxidative stress after phototherapy (15-17). This is a matter of concern since all of these situations are expressed in the pathogenesis of cancers. However, the clinical significance of these changes should still be evaluated.

This study was the first in Iran to investigate the clinical and epidemiological association between neonatal phototherapy and cancer in childhood which had some advantages including a relatively large sample size and the exact diagnosis of the type of cancer.

According to a study conducted in Iran during 2017, phototherapy in jaundiced infants was able not only to induce apoptosis in newborn lymphocytes but also to affect DNA integrity indirectly (18).It is worth mentioning that this study had also some limitations. Considering the cross-sectional nature of the study, a large number of samples were excluded during the research procedure due to the lack of sufficient data. Furthermore, birth weight was removed in the final analysis due to the high collinearity. What confirms this is the high prevalence of phototherapy in low birth weight infants who are more likely to be admitted with different causes and are more likely to have prophylactic phototherapy or even without indication. Moreover, due to the lack of a registry system, there was no access to the exact lab data in these cases. Therefore, multicenter studies with larger sample sizescan also be used to determine this relationship more precisely using the registry records.

Conclusion

Phototherapy can reduce the risk of exchange transfusion; a process that can account for up to 5% of morbidity and up to 1.9% of deaths. However, the risk of developing cancer with neonatal phototherapy should be considered versus its benefits in reducing bilirubin. Therefore, it is necessary to avoid unnecessary and non-indicative phototherapy. It is also recommended to consider a stricter approach in terms of the hospitalization and phototherapy of the neonates with jaundice.

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Conflicts of interest

There are no conflicts of interest regarding the publication of the study.

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