

The relation between neonatal phototherapy and childhood asthma

Heidarzadeh Arani M, Mosaiebi Z, Movahedian AH, Aabedi AR

Assistant professor in asthma and allergy, Kashan University of medical science, Iran

Associate professor in neonatology, Kashan University of medical science, Iran

Associate professor in pediatric cardiology, Kashan University of medical science, Iran

Resident of pediatrics, Kashan University of medical science, Iran

Abstract

Introduction: Asthma is the most common chronic disease in childhood. Many parameters are known as its risk factors. Recently, phototherapy has been recognized as one of the risk factors involved in childhood asthma. Thus, current study has been carried out to identify the relation between neonatal phototherapy and childhood asthma.

Methods & Materials: This is an analytical case-controlled study carried out on asthmatic children with history of neonatal icterus as case group; and non-asthmatic children but with history of neonatal icterus as control group (after matching for age, gender, route of delivery, and birth weight). Among 400 children been studied, 28 subjects in case group and 34 subjects in control group met the inclusion criteria. The subjects, in case and control groups were compared in terms of history of phototherapy and then duration of phototherapy, if they had underwent the same. Statistical analysis was done using Chi-square and t-test statistical methods.

Findings: Among the subjects, 26 cases (92.8%) and 20 controls (58.8%) had history of phototherapy (P-value=0.002). Mean duration of phototherapy in cases was 4.9 days against 3.2 days in control (P-value<0.0001).

Conclusion: Neonatal phototherapy and its duration play a role in childhood asthma. Therefore it is necessary to take the children under phototherapy only in specific cases and also with the least duration.

Keywords: Icterus; Phototherapy; Childhood Asthma.

INTRODUCTION

Asthma is the most common chronic childhood disease, involving five million children less than 18 years of age in US^{1,2}. With regards to existing records, the disease prevalence and severity has increased in the last few years^{3,4}. So, identifying its epidemiologic aspects is of importance to the health system.

One out of 13 school-age children is afflicted with asthma. The disease accounts for the most important cause of physicians' office and emergency rooms referrals, hospitalizations, and also school absenteeism. From 1893 to 1980, the death rate due to asthma has doubled; resulting in 5500 deaths per year. It has been suggested that various perinatal factors such as route of delivery, maternal diseases, birth weight and low gestational age play a role in the incidence of asthma¹.

Recently, phototherapy has been recognized as one of the risk factors for the development of childhood

Address for Correspondence: Kashan University of Medical Sciences, Beheshti Hospital, Tel: +98-361-5552999, Fax: +98-361-5575057, Email: marz heidar@yahoo.com

asthma⁵. Approximately 60% of term and 80% of preterm neonates experience neonatal icterus during the first week of life for the treatment of which, phototherapy or blood exchanges are employed. Various complications such as dehydration, diarrhea, rashes and depletion of vitamins (e.g. Riboflavin) have been reported following phototherapy¹.

In a Swedish study done in (2007), researchers found a direct correlation between phototherapy for neonatal icterus with childhood asthma⁵. Another study from Japan suggests that icterus plays a role in alleviating asthma symptoms⁶.

Phototherapy influences the neonate immune system by directly effecting T-lymphocytes and resulting consequently in disturbance of development of the immune system. In theory, inhibition of T lymphocyte function at the time of immune system development during neonatal period may lead to decreased transformation of the T helper 2 (Th₂) to T helper 1 (Th₁) lymphocytes and thus to increased risk of development of childhood asthma⁷.

As neonatal phototherapy has been postulated as a risk factor for asthma and considering the existing paradoxes and limited data on neonatal icterus and childhood asthma in Iran and other countries, the current study was planned to investigate the relationship between neonatal phototherapy and childhood asthma in Kashan, Iran.

METHODS & MATERIALS

This was an analytical case-controlled study carried out on 28 children with asthma as case group and 34 children without asthma as control group. Diagnostic criteria for childhood asthma were based on clinical manifestations such as dyspnea, cough, and wheezing along with spirometry (in children older than 5 years) carried out by a pediatric asthma and allergy specialist. The subjects were chosen from among 200 children referred to asthma and allergy clinic, Shahid Beheshti Hospital, Kashan. Thirty four children without asthma (control group), were chosen randomly from among the children hospitalized in the pediatric ward after complete group matching with case group. Inclusion criteria included history of neonatal icterus, age between 2 years to 12 years and absence of atopy in both groups and also absence of a history of asthma or

any other chronic respiratory disease in the control group.

Patients who did not fulfill the above-mentioned criteria were excluded from the study. Considering that the prevalence of icterus in boys was higher than in girls, children in both groups were matched for age and sex; and also on the factors proposed by Sherif *et al*⁸, Kiechl-Kohlendorfer *et al*⁹ and Sears *et al*¹⁰ such as, route of delivery (Caesarian section), nutrition (powdered milk), and low birth weight (LBW). In order to distinguish the independent effect of the studied risk factor *i.e.* phototherapy, all children in both groups were matched for these factors.

Children with a history of blood exchanges during their neonatal period were excluded from the study as those neonates with very high serum bilirubin levels who undergo blood exchanges, tend to require shorter periods of phototherapy, as their bilirubin levels drop faster. Also, regarding the role of sepsis in preventing childhood asthma¹¹, children with history of hospitalization due to any reason but icterus were excluded the study.

All the data were gathered from patients by means of holistic questionnaire edited upon research variables. Patient information extracted from data sheets, were analyzed using appropriate abundance tables upon study variables. Gathering the data, they have been analyzed by means of SPSS#13 software along with Kolmogrov-Smirnov test, t test, Leven test, and Chi-Square test.

Table 2. Abundance distribution of icteric children and phototherapy

Phototherapy history groups	Positive (%)	Negative (%)	Total (%)
Case	26 (92.8)	2 (7.2)	28 (100)
Control	20 (58.8)	14 (41.2)	34 (100)
Total	46 (74.2)	16 (25.8)	62 (100)
P-Value	0.002		

Table 1. abundance distribution of studied children upon demographic variables

Variable	Groups	Case	Control	P-Value
Gender	Male	16	19	0.563
	(%)	(57.1)	(55.9)	
	Female	12	15	
	(%)	(42.9)	(44.1)	
Route of delivery	Normal vaginal delivery	15	20	0.798
	(%)	(53.6)	(58.8)	
	Caesarian section	13	14	
	(%)	(46.4)	(41.2)	
LBW	Positive	3	4	0.61
	(%)	(10.7)	(11.8)	
	Negative	25	30	
	(%)	(89.3)	(88.2)	
Age (Mean)		6.33	6.34	0.99
total		28	34	
(%)		(100)	(100)	-

Table 3. Abundance distribution of studied children and duration of phototherapy

Phototherapy duration (days) groups	Number	Mean	Standard deviation	Statistical analysis comparing both groups
Case	26	4.9	1.3	0.001
Control	1.1	3.2	1.1	

FINDINGS

The current study carried out on 28 children in case group and 34 children in control group. Among the study subjects, 57.1% of the cases and 55.9% of controls were male (P-value=0.563). Among cases 46.4% and 41.2% of the controls were born through Caesarian section (P-value=0.798). Also 10.7% of the cases and 11.8% of the controls were LBW (P-value=0.61). No significant difference in age was found between the two groups (P-value=0.99). (Table 1)

In case group 92.8% and in control group 58.8% of children had received phototherapy and the difference was significant (P-value=0.002). (Table 2)

Mean duration of neonatal phototherapy was 4.9 days and 3.2 days in the case and control groups respectively, the difference was statistically significant (P-value<0.001). (Table 3)

CONCLUSION

Asthma is one of the most prevalent diseases worldwide which has an increasing prevalence. Although genetic factors play the most important role in asthma, the increasing prevalence during last two decades cannot be explained by genetic factors alone¹. Various factors, such as perinatal ones, play roles in triggering childhood asthma.

Sherriff *et al* (2001) from Austria, suggested that risk factors of childhood asthma include male gender, birth date from April to December, delivery through caesarian section, low maternal age and consuming powder milk (supplementary milk)⁸. Kiechl-Kohlendorfer *et al* (2000-2005) from Australia, found male gender, civilization, history of neonatal hospitalization, lack of breast feeding, parent smoking after child birth, and LBW as risk factors for asthma⁹. Similarly, a Canadian study by Sears *et al* (1996), concluded that risk factors for childhood asthma include male gender, positive family history, and maternal smoking¹⁰.

Recently, relation of phototherapy in the causation of asthma has been explored. Phototherapy is now used universally in curing mild to moderate neonatal icterus. Apart from acute complications of phototherapy such as diarrhea, skin rashes, electrolyte disturbances, malnutrition and dehydration¹, phototherapy also has some long term complications such as DNA fragmentation and mutation¹¹. Other hazards and complications of phototherapy include potential and long term effects on endocrine system, puberty and DNA repairing mechanisms in the epidermis⁹. On the other hand, phototherapy affects neonate immune system through direct influence on T lymphocytes; and consequently can lead to disturbances of immune system development. In theory, inhibition of T-lymphocyte function at the time of immune system maturation during the neonatal period may lead to decreased Th2 to Th1 lymphocyte transformation and thus to increase in the risks involved in childhood asthma⁷.

In studies carried out in Sweden and other European countries, it was concluded that birth time events such as phototherapy result in an increase risk of autoimmune diabetes^{12, 13}. Therefore, since asthma is also an autoimmune disorder, it is likely that similar findings should hold true.¹⁴

In the current study, it was concluded that history of phototherapy due to neonatal icterus is significantly more frequent in asthmatic children compared with matched controls (92.8% against 58.8%, P-value=0.002). Also mean duration of neonatal phototherapy in asthmatic children with history of phototherapy was significantly more than control group (4.9 in front of 3.2 days, P-

value<0.001). Thus, it seems that phototherapy correlates with childhood asthma.

Similar studies relating to this topic are relatively few; only Aspberg *et al* (2007) in Sweden, pointed the direct correlation between neonatal phototherapy and childhood asthma⁵. Thus, further studies are necessary.

In the above-mentioned study, the effect of neonatal icterus on childhood asthma has not been investigated. Since the prevalence of icterus and phototherapy among asthmatic subjects was higher than in controls, it is not clear whether it is the neonatal icterus of the phototherapy used in the management of the former that leads to childhood asthma.

But in the current study, regarding positive history of icterus in both groups, phototherapy has been established as a potent risk factor in childhood asthma. On the other hand, children in the case group have undergone a longer duration of phototherapy (P-value<0.001). Considering that phototherapy and its duration in the case group were significantly more than that in the control group, it is not clear whether the phototherapy or its duration is the risk factor in childhood asthma. Therefore, newer and further studies are necessary.

Many studies suggest that phototherapy is effective when serum bilirubin level is high and that low serum bilirubin level may just lead to prolongation of treatment duration. On the other hand, in recent years it has been made clear that bilirubin has beneficial antioxidant properties in neonates threatened by oxygen toxicity; and has protective role against diseases triggered due to oxidant factors such as chronic lung disease in premature neonates (BPD), retinopathy of prematurity (ROP), intra ventricular hemorrhage (IVH), and periventricular leucomalecia (PVL)¹⁵⁻¹⁸.

Therefore, it can be inferred from the current and other recent studies, that through avoiding aggressive treatment of high but safe serum bilirubin levels, it is possible to prevent acute and long term complications (e.g. asthma) and also to derive benefit from anti-oxidant traits of bilirubin in diseases induced by oxidant factors. An appropriate solution to decrease the phototherapy duration also needs to be identified.

DISCUSSION

Phototherapy is one of the potent risk factors of childhood asthma and also its duration has a role to play. Phototherapy should be reserved only on selected cases and with the shortest possible duration.

REFERENCES

1. Robert M, Waldo E. Nelson Essentials of pediatrics. 5th ed, 2006: 417-30
2. Richard O. Enuresis. In Michael C, Michael A. Oski's Essential Pediatrics. 12th ed. Lippincott Williams & Wilkins. 2004; **176(3)**: 487-90
3. Anderson HR. Trends in prevalence and severity of childhood asthma. *Brit Med J* 1994; 1600-4
4. Senthilselvan A. Prevalence of physician diagnosed asthma in Saskatchewan 1989 to 1990. *Chest* 1998; **(114)**: 388-92
5. Aspberg S, Dahlquist G, Kahan T, Källén B. Is neonatal phototherapy associated with an increased risk for hospitalized childhood bronchial asthma? *Pediatr Allergy Immunol* 2007; **18(4)**: 313-9. Epub 2007 Mar.
6. Ohnishi T, Yasuda H, Yamaya M, Matsui T, Sasaki H. Transient relief of asthma symptoms during jaundice: a possible beneficial role of bilirubin. *Tohoku J Exp Med* 2003; **199(3)**: 193-6
7. Robert M, Schoenfeld Y. Asthma as a paradigm for autoimmune disease. *Int Arch Allergy Immunol* 2003; **132**: 210-4
8. Sherriff A, Peters TJ, Henderson J, Strachan D. Risk factor associations with wheezing patterns in children followed longitudinally from birth to 3(1/2) years. *Int J Epidemiol*. 2001; **30(6)**: 1473-84.
9. Kiechl-Kohlendorfer U, Horak E, Mueller W, Strobl R, Haberland C, Fink FM, *et al*. Neonatal characteristics and risk of atopic asthma in schoolchildren: results from a large prospective birth-cohort study. *Acta Paediatr*. 2007; **96(11)**: 1606-10.
10. Sears MR, Holdaway MD, Flannery EM, Herbison GP, Silva PA. Parental and neonatal risk factors for atopy, airway hyper-responsiveness, and asthma. *Arch Dis Child*. 1996; **75(5)**: 392-8
11. Feyzullah C, Hasan S, Asiye N. Effect of neonatal sepsis on the development of allergies and asthma in later childhood. *Int Arch Allergy Immunol* 2007; **142**: 145-50
12. Rotem M, Schoenfeld Y. Asthma as a paradigm for autoimmune disease. *Int Arch Allergy Immunol* 2003; **132**: 210-4
13. Dahlquist G, Kallen B. Indications that phototherapy is a risk factor for insulin-dependent diabetes. *Diabetes Care* 2003; **26**: 247-8
14. Hoare C, Wan PO, Williams H. Systematic review of treatment for atopic eczema. *Health Technol Assess* 2000; **4**: 88-92
15. Dani C, Martelli E, Bertini G, *et al*. plasma bilirubin level and oxidative stress in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2003; **88**: F119-23
16. Steven DK, Vreman HJ, Wong RJ, Contag CH. Carbon monoxide and bilirubin production in neonates. *Semin Prenatol* 2001; **25**: 85-93
17. Belanger S, Lavoie JC, Chessex P. Influence of bilirubin on the antioxidant capacity of plasma in newborn infants. *Biol Neonate* 1997; **71**: 233-8
18. Dennery PA, McDonagh AF, Spitz DR, Rodgers PA, and Stevenson DK. Hyperbilirubinemia results in reduced oxidative injury in neonatal Gunn rats exposed to hyperoxia. *Free Radic Biol Med* 1995; **19**: 395-404.