นิพนธ์ต้นฉบับ

Can steroid prevent diphtheritic myocarditis ?

Pisonthi Chongtrakul*
Chotima Patthamanand** Phongphan Nanthapisuth***

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The effect of steroid on Diphtheritic Myocarditis was evaluated by a prospective study, of its early and late administration. Of eighteen children in the study, 9 were given 2 mg/kg/day of prednisolone on the first day of admission, while the other 9 were given this dose after E.C.G. changes or signs of myocarditis had appeared. There were no statistical differences between the two groups in the incidence of E.C.G. change or in the severity of myocarditis, therefore, prednisolone in the above dose neither prevented the occurence of myocarditis nor lessen its severity.

พิสนธิ์ จงตระกูล, โชติมา ปัทมานันท์, ผ่องพรรณ นันทาภิสุทธิ์. คอร์ติโคสเตียรอยด์จะสามารถป้องกันการเกิดกล้ามเนื้อหัวใจอักเสบจากโรคคอตีบได้หรือไม่. จุฬาลงกรณ์เวชสาร 2528 กันยายน; 29 (9) :

ผู้ป่วยเด็กจำนวน 41 คนที่ได้รับการวินิจฉัยว่าเป็นโรคคอตีบ ได้ถูกแบ่งออกเป็น 3 กลุ่มตามความรุนแรงของโรค ผู้ป่วยในกลุ่มที่มีอาการรุนแรงจำนวน 18 รายได้ถูกนำมาศึกษาผลของการให้เพรดนิโซโลน ในขนาด 2 มก. ต่อ กก. ต่อวัน โดยผู้ป่วยในกลุ่มนี้ถูกแบ่งเป็นสองกลุ่ม กลุ่มละ 9 คน โดยกลุ่มแรกคือ กลุ่มศึกษาจะได้รับเพรดนิโซโลนในขนาดข้างต้น ในวันแรกที่รับไว้ในโรงพยาบาล ส่วนผู้ป่วยกลุ่มเปรียบเทียบจะได้รับเพรดนิโซโลนก็ต่อเมื่อตรวจพบว่ามีการเปลี่ยนแปลงของคลื่นหัวใจ หรืออาการแสดงของกล้ามเนื้อหัวใจอักเสบ

ผลการศึกษาพบว่า ในผู้ป่วยทั้งสองกลุ่ม ไม่พบความแตกต่างกันระหว่าง อัตราการเกิดกล้ามเนื้อหัวใจอักเสบโดยดูจากจำนวนผู้ป่วยที่มีอาการแสดงหรือมีคลื่นหัวใจผิดปกติ ดังนั้นเพรดนิโซโลนในขนาดข้างต้นจึงไม่สามารถป้องกันการเกิดกล้ามเนื้อหัวใจอักเสบจากโรคคอตีบในผู้ป่วยที่มีอาการรุนแรงได้ นอกจากนี้ยังไม่พบความแตกต่างกันระหว่าง เวลาที่เริ่มมีการเปลี่ยนแปลงของคลื่นหัวใจ (onset of ECG changes), ระยะเวลาที่คลื่นหัวใจเปลี่ยนแปลง (duration of ECG changes), ปริมาณของเอ็นซัยม์ LDH ที่เปลี่ยนแปลงไป ในผู้ป่วยทั้งสองกลุ่ม ดังนั้นเพรดนิโซโลนในขนาดข้างต้นจึงไม่สามารถลดความรุนแรงของการอักเสบของกล้ามเนื้อหัวใจจากโรคคอตีบ

* ภาควิชาเภสัชวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

** ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

*** ภาควิชาจุลชีววิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

The effectiveness of Steroid has recently been claimed in the prevention of Diphtheric Myocarditis,[1,2] a common and frequently fatal complication of Diphtheria.[3,4,5]

This study was conducted during a small outbreak of Diphtheria in 1982, in order to assess steroid's effect on diphtheria and the occurence of its serious complication of myocarditis.

Material and Method

This was a prospective study in which patients with clinical diagnosis of Diphtheria were admitted into a Diphtheria Ward at the Department of Paediatrics, Chulalongkorn Hospital, from May 1982 to July 1983, and were grouped into severe, moderate and mild cases according to the criteria listed on table 1.

Table 1 Criteria for grading severity of diphtheria

Severe Cases	:	Having at least 3 of these criteria 1. Age less than 4 years.[1,5,6] 2. No or incomplete immunization.[1,5] 3. Received specific treatment later than 3 days from onset of symptoms.[1,5,7] 4. Extensive involvement of pharyngotonsillar area with patches.[1,6] 5. Bullneck.[1,2] 6. Airway obstruction, which required tracheostomy.[1,6]
Moderate Cases	:	Having at least 3 of these criteria 1. Age more than 4 years. 2. Incomplete immunization. 3. Received specific treatment not later than 3 days from onset of symptoms. 4. Moderate involvement of pharyngotonsillar area with patches. 5. Bullneck. (mild degree) 6. Airway obstruction which did not require tracheostomy.
Mild Cases	:	All cases which did not fit into the Severe or Moderate groups and having these criteria 1. Age more than 4 years. 2. Received specific treatment not later than 3 days from onset of symptoms. 3. Mild involvement of pharyngotonsillar area with patches. 4. No bullneck on the day of admission. 5. No airway obstruction.

Only severe cases were included in this study and randomly assigned to the Early Steroid Treatment Group (study group) and the Late Steroid Treatment Group (control).

To the Early Group prednisolone 2 mg/kg/day (orally or intra-muscularly depending on the clinical status), was given from the first day of admission for a total of 14 days in order to cover the second week period when myocarditis frequently occurs.[6] The same dose of prednisolone was given in the Late Group if and when changes appeared on the serial E.C.G.

A single dose of diphtheria antitoxin 100,000 to 120,000 units, and Penicillin G Sodium 50,000 to 100,000 units/kg intravenous 6 hourly for 7 to 10 days were given to each patient.

Clinical signs of myocarditis were followed and recorded daily, and when in doubt ECG and LDH were immediately requested. Routine E.C.G. were performed daily on every patient until changes were detected when LDH would be ordered and E.C.G. continued every other or every day according to the severity of the changes and of the clinical state.

In the Early Treatment Group, prednisolone would be tapered off at the end of the second week if no E.C.G. change occured. Otherwise, prednisolone was continued until the E.C.G. returned to normal. In the Control Group, prednisolone was given only if E.C.G. changes were detected.

All suspected myocarditis patients were treated supportively with restriction of activities and avoidance of fluid and sodium load. Digitalis was given when congestive heart failure developed. No other forms of therapy, eg. cardiac pacing were given.

The non-cultured-proved cases, of Corynaebacterium diphtheria were excluded from the study when results arrived. All patients were asked to return for follow-up but very few complied.

Results

Forty-one patients were admitted but only 29 were culture-positive for Corynaebacterium diphtheria. Of these, 18 were grouped as severe, 5 as moderate and 6 as mild cases. (Only the culture-proved and severe cases were included in the study.) Ages ranged between 6 months and 14 years. The male/female ratio was 1:1.4, but was 1:1.6 in the severe group where ages ranged from 13 months to 14 years, and 88.9 % of patients had no history of immunization against diphtheria.

There were significant differences in the number of E.C.G. changes in the three groups, 72.2% in the severe, 20.0% and 16.7% in the moderate and mild groups respectively, with an overall change of 51.7%.

Myocarditis was diagnosed by tachycardia, bradycardia, muffled heart sound, arrhythmia and congestive heart failure, together with E.C.G. changes and LDH elevation. All patients with myocarditis recovered completely with the E.C.G. returned to normal. There was no mortality in either groups. (table 2)

Table 2 Summary of data on diphtheria patients.

Items	Severe cases		Moderate cases		Mild cases		Total cases	
	No.	%	No.	%	No.	%	No.	%
Number of patients	18	62.07	5	17.24	6	20.69	29	100
Male : female	1:1.6		1:1.5		1:1		1:1.4	
Age Range (year)	1 3/12-14		1 6/12-7		6/12-12		6/12-14	
Culture positive	18		5		6		29	100
Bull neck	9	50.00	1	20.00	1	16.67	11	37.93
History of immunization								
none	16	88.89	5	100.00	5	83.33	26	89.66
incomplete	2	11.11	0	.00	1	16.67	3	10.33
ECG change	13	72.22	1	20.00	1	16.67	15	51.72
Enzyme change (LDH)	13	72.22	1	20.00	0	0.00	14	48.27
Required tracheostomy	11	61.11	0	.00	0	.00	11	37.93
Complication								
palatal palsy	2	9.09	0	.00	0	.00	2	
6th nerve palsy	1	4.55	0	.00	0	.00	1	
kidney involvement	2	9.09	0	.00	0	.00	2	
myocarditis	13	72.22	0	.00	0	.00	13	44.83
death	0	.00	0	.00	0	.00	0	

Although randomly assigned, patients in the Early and Late treatment groups were comparable in age, sex, immunization status, duration of illness prior to treatment, extent of patch, incidence of bullneck and tracheostomy performed. (table 3)

Table 3 Characteristic of population between study group and control group

Items	Study group	Control group
Age range	5.59 ± 3.52 Years*	5.73 ± 4.25 Years
No immunization	8 / 9	8 / 9
Sex	Male:Female 4:5	Male:Female 3:6
Duration of illness prior to R_x	3.27 ± 2.35 Days	3.26 ± 1.87 Days
Extensive patch	7 / 9	7 / 9
Bullneck	4 / 9	5 / 9
Tracheostomy	6 / 9	5 / 9

* mean ± s.d.

A further comparison revealed that there were 77.78% with E.C.G. changes in the Early group against 66.67% in the Late ($p > 0.05$), with comparable onsets (7.10 ± 2.34 days against 6.76 ± 2.15 days, $P > 0.05$) and comparable durations (10.56 ± 2.28 days against 9.59 ± 2.11 days, $P > 0.05$)

LDH was elevated in all cases with ECG changes, with a mean of 112.71 ± 18.31 units and 113.50 ± 15.32 units respectively ($P > 0.05$). (Table 4)

Table 4 Summary of ecg change and ldh change between study group and control group

Items	Study group	Control group	
Ecg change	7 / 9	6 / 9	Ns*
Onset of ecg change	7.10 ± 2.34 Days	6.76 ± 2.15 Days	Ns
Duration of ecg change	10.56 ± 2.28 Days	9.59 ± 2.11 Days	Ns
Level of ldh	112.71 ± 18.31 Unit	113.50 ± 15.32 Unit	Ns

*Ns = non-significant

Table 5 describes the pattern of ECG changes together with the corresponding levels of LDH elevation.

Table 5 Summary of type of ECG change and level of LDH change between study group and control group

Study group		Control group	
Type of ECG change	LDH	Type of ECG change	LDH
1. IBBB	150	1. Occasional arrest, IBBB low voltage	140
2. Sinus tachycardia	119	2. First degree AV block	120
3. RBBB, LT. ant. hemiblock AV dissociation, PVC	115	3. RAD, RBBB	116
4. ST-elevation	105	4. Occasional PVC, LAD PR irregularity	112
5. Non-specific STT change	104	5. Sinus tachycardia	100
6. Flattened-wave	100	6. First degree AV block	93
7. Abnormal T-wave change	96		
Average of LDH change	112.71 ± 18.31	Average of LDH change	113.50 ± 15.32

Discussion

Diphtheria is now a rare disease in a fully immunized community, but is still a health problem in some parts of the world including Thailand.

Diphtheria death rate has been declining due to the decrease in the incidence of reported cases, but the risk of death reported for persons with diphtheria (CFR, case-fatality ratio) has not changed drastically.[5] Hoyne and Welford in 1934 reported 11 per cent for case-fatality ratio[6] while Munford et al, 40 years later reported 10 per cent.[5]

Myocarditis is a common and most fatal complication of diphtheria and accounted for 70 per cent of fatal cases.[3] The incidence of ECG changes, and the incidence of myocarditis in our study are comparable to those of various reports. (Table 6)

Table 6 Comparison between previous reports with the studied group in respect to cardiovascular complication from diphtheria.

	Previous reports	Studied group
	per cent	per cent
ECG changes in all cases	20 - 43[1]	44.8
in severe cases	65.5 - 85[3]	72.2
Incidence of myocarditis	10.6 - 34.6[4]	44.8

(1) Reference 2, 21, 22, 23, 24
(2) Reference 9, 25
(3) Reference 6

The mortality rate of diphtheria is influenced by several factors. Higher mortality rate is found among younger age group[1,5,6], non-immunized subject[1,5], a delay in administration of antitoxin and supportive measure[1,5,7], the site and extent of diphtheric membrane[1,6] and the clinical picture of bullneck[2]. All of these factors were used in the basic criteria for the grading of severity in our study. (Table 1)

Mortality is also higher among persons involved in a small outbreak[5], persons from whom toxigenic Corynebacterium diphtheriae was isolated[5], persons with myocarditis, persons in whom myocarditis occured early in the course of illness and persons with specific patterns of ECG changes e.g. AV dissociation or complete heart block.[8]

As mentioned above, Case-fatality ratio (CFR) of diphtheria remained constant for over half a century. Munford et al[5] suggested two factors which are amenable to correction, which will reduce the CFR. One is to improve the coverage of immunization and the other is to recognize the disease early. One direct method is to reduce the mortality rate from myocarditis or to prevent its occurence.

There have been many improvements to lessen the mortality rate of diphtheric myocarditis. Absolute and prolonged bed rest has been accepted uniformly.

Wesselhoeft[9] recommended the routine use of ECG on diphtheria wards to ensure a prompt and better recognition of diphtheritic myocarditis.

During the year 1920 and 1940, the use of digitalis in the presence of diphtheritic myocarditis and also of a conduction disturbance was felt to be contra-indicated by many observers.[10,11,12,13,14,15] Engle[8] concluded an opposite opinion and stated that digitalis had no untoward effect but had a prompt and definite improvement in her patients. In her series of 554 diphtheria patients, 45 per cent had myocarditis and mortality rate from myocarditis was only 4 per cent.

Chesler[16] recommended that serial SGOT estimations with daily ECG was of value in the early diagnosis of diphtheritic myocarditis.

Matisonn et al.[4] were the first to successfully use the electrical pacing technique in the management of one case of severe diphtheria complicated by complete heart block and respiratory paralysis.

Less has been achieved in the area of preventing the occurence of diphtheric myocarditis. Gore[3] re-emphasized the importance of administration of antitoxin early and in adequate quantity as a measure to prevent myocarditis.

Steroid as an anti-inflammatory drug to be used in the treatment of diphtheric myocarditis or in its prevention was mentioned in the last two decades by some investigators in dilemma.[1,2,17,18,19,20]

In both groups of our patients, we could not demonstrate any statistic difference between the number of patients with ECG change, the onset of ECG change, the duration of ECG change, the number of patients with elevation of LDH and the mean unit of LDH elevation. We also could not demonstrate any difference between the cases assumed to have myocarditis on clinical grounds e.g. the cases with ECG change associated with elevation of LDH. Therefore, we conclude that prednisolone in the dosage of 2 mg./kg./day neither prevent the occurence of diphtheritic myocarditis nor lessen the severity of cardiovascular complication of diptheria. (Table 4)

We do not recommend the routine use of steroid as a preventive measure in diptheritic myocarditis.

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จุฬาลงกรณ์เวชสารได้รับต้นฉบับเมื่อวันที่ 2 เดือน มกราคม พ.ศ. 2528