ORIGINAL ARTICLE

ROLE OF METHYLPREDNISOLONE IN EARLY PREDICTED DIPHTHERIC CARDIOMYOPATHY IN CHILDREN: IS THIS A SOLUTION?

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Background: Diphtheria remains an important cause of paediatric mortality in developing countries. The mortality rate is still 10% and has changed little over the past 20 years with particular reference to developed world. The objective of this study is to examine clinical spectrum of diphtheric cardiomyopathy and by using tools (serum markers, ECG, Echocardiography) to predict the cardiomyopathy and role of steroids in these predicted patients. **Methods**: For this cohort study, 67 patients having diphtheria presenting for the first time in a 3-year period were enrolled after obtaining informed verbal consent from the guardian of each child. Demographical profile, vaccination status, clinical spectrum, ECG interpretation and echocardiographic findings were recorded that predicted the occurrence of diphtheric cardiomyopathy and used intravenous methylprednisolone pulses in these predicted patients to look for their outcome regarding change in severity or the fate in the form of mortality. **Results:** Among the 67 enrolled children (M: F 2.3:1) with age ranging from 24 to 172 months (median 106 months), 56.7% subjects presented with diphtheria were non-vaccinated. 37.3% had a cardiac involvement in the form of diphtheria cardiomyopathy or arrhythmia.7.5% patient expired on follow up. Presence of septal paradoxes on echo had association with the cardiac involvement (OR 10.1: 95% CI 1.2-84.6; *p*=0.0005). IV methyl prednisolone was given in all 37.3% (n=25) patients predicted as diphtheric cardiomyopathy (Asymptomatic) and 88 %(n=22) had a favourable outcome with no morbidity and mortality. 12% (n=3) were expired and they presented with shock and VT as their first presentation (symptomatic). **Conclusion:** Early prediction by alone or in combination of ECG and echocardiographic markers and early use of IV methyl prednisolone in these predicted patients before symptoms, can reduce the mortality related to diphtheric cardiomyopathy and can decrease the burden of the disease in the community. Further randomized controlled trials with a larger sample size are required to unambiguously delineate the prognostic value of steroids in early predicted diphtheric cardiomyopathy.

Keywords: Diphtheria; Cardiomyopathy; Methylprednisolone; Steroids

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INTRODUCTION

Diphtheria remains an important cause of paediatric mortality in developing countries. The mortality rate is still 10% and has changed little over the past 20 years with particular reference to developed world.[1] A resurgence of diphtheria has been observed in developing nations, are largely attributed to waning vaccine immunity and social taboos leading to poor immunization coverage in children especially above 5 years of age. Acute mortality is due to toxin-mediated diphtheritic cardiomyopathy, arrhythmia, suffocation by the pseudo-membrane, disseminated intravascular coagulation, and renal failure.[2–5] The incidence of diphtheritic cardiomyopathy following diphtheria is 10–20%, and some Indian studies reported the occurrence of myocarditis is 16-66% and the associated mortality is ~50%. Myocarditis in diphtheria is reported to be the sole independent predictor of death with an adjusted Odds ratio 25, (95% confidence interval (CI) 3.4-210.3).[5] Clinical signs of diphtheritic cardiomyopathy become apparent by the end of week 2 of infection but, in severe cases, may be a presenting feature.[6] Severe conduction abnormalities including tachyarrhythmia or brady-arrhythmias or complete heart block are reported in ~50% of patients presented with diphtheria cardiomyopathy and reported to be uniformly fatal for children.[7,8]

Due to this high fatality of diphtheria cardiomyopathy or myocarditis people used many drugs like steroids, carnitine and pulses of methyl prednisolone so that they can combat this condition and they concluded as no role or very little role in most series.[9–11] But in almost all series they give the steroids or other drugs after the appearance of either symptoms or full-blown symptoms. There were many studies that predict the occurrence of diphtheria

myocarditis either by clinical features or by electrocardiography.[12,13] We have recently observed on the prognostic and predictor utility of combined echocardiographic and electrocardiography and have shown that, in some cases of diphtheritic cardiomyopathy, intervention with temporary cardiac pacemaker or off label use of IV methylprednisolone may improve the outcome. The ability to predict from simple and readily available measures whether myocarditis will develop or not and prompt management in those predicted patients can change the fate and prognosis of these children.

We aimed to examine clinical spectrum of diphtheria cardiomyopathy and by using tools (serum markers, ECG, Echocardiography) to predict the cardiomyopathy and to use the intravenous methylprednisolone pulses in these predicted patients and to look for their outcome regarding change in severity or the fate in the form of mortality. This will not only decrease chances of life-threatening complications but also minimize cost used to treat them. It will also help us to decrease psychosocial trauma to family.

MATERIAL AND METHODS

This cohort study was conducted at the Department of Cardiology, The Children Hospital and paediatric medicine department DHQ/Allied hospital Faisalabad, Pakistan, over a period of 3years from 1st January 2018 till 31st December 2020. These are tertiary care centers in the province of Punjab with a population of over 120 million [14'15] where we get referral from other tertiary care hospitals in the region as well both for diagnostic and management point of view. Institutional Review Board of the hospital approved the study protocol. All patients presenting to the hospital for the first time and diagnosed as diphtheria were evaluated for inclusion in the study. After obtaining informed consent from patient's parents, evaluation was performed with confirmation of diagnosis through clinical and laboratory (throat swab, serial ECG's and echocardiography) The demographic profile, residence, vaccination status, clinical spectrum, ECG interpretation and echocardiographic findings were recorded on a specially designed questionnaire proforma by the author (UR,RN) from direct caregivers including mother, father or the guardian and ECG and echocardiographic interpretation by a consultant paediatric cardiologist. The diagnosis of diphtheria was made using either one or both of the criteria, i.e., clinically either if the patient had a febrile illness with a characteristic adherent pseudo-membrane visible in the nasopharynx or if the patient presented later (after pseudo-membrane clearance) with a history of recent severe sore throat and signs of cardiomyopathy or if throat culture proven for the Corynebacterium diphtheriae.[12] Diphtheric cardiomyopathy was defined either as Symptomatic diphtheritic cardiomyopathy, the patients who developed symptoms of, and examination findings consistent with, heart failure and abnormal findings on 12-lead electrocardiography or echocardiography or Asymptomatic diphtheritic cardiomyopathy, includes children with no symptoms of heart failure, but with either clinically detected rhythm disturbances or abnormal findings on 12-lead electrocardiography or LV dysfunction on echocardiography, according to contemporary standards of paediatric cardiology.[16] Diphtheria severity score system was defined as: "mild," local symptoms only; "moderate," patient is systemically unwell with a "toxic" facial appearance; "severe," patient is bed-bound, is unable to drink, has difficulty breathing, or has alteration in mental status.[12] Patients having growth of other bacteria on throat culture even suspected clinically as diphtheria were excluded from the study. Several variables were compared among the survivors and non-survivors to define the predictors of outcome. Outcome was defined as fatal outcome as mortality and favourable outcome as either no cardiomyopathy or developed mild dysfunction on echocardiography only and discharged safely after 2 weeks. Children were considered adequately immunized if they had received three or more doses of diphtheria toxoid containing vaccine by age 2 years.[5]

Data was entered in SPSS version 20 and analyzed using its statistical package. Frequency was calculated for qualitative variables including gender, vaccination status, and cardiomyopathy. Data was presented as mean, SD and median. Between groups comparison was done using Chi-square test for categorical data and Students' t-test and Mann Whitney U test for parametric and non-parametric data respectively Univariant and multivariant analysis were performed to determine significance and to identify the predictors having a significant association with cardiomyopathy and mortality. Odd's ratio with 95% CI was computed for the significant variables. All variables found to be significant on univariate analysis (p<0.05).

RESULTS

Sixty-seven subjects presented with diphtheria were recruited in the study in a 3-year period. There were 47 (70.1%) boys and 20 (29.9%) girls with boys to girl's ratio of 2:1. Median age at the time of presentation was 106 months (range 24–172 months). Median day of presentation to a tertiary care hospital was 3 days (range 1–9 days). Nearly 58.2% patients belong to rural areas. Thirty-eight (56.7%) subjects

presented with diphtheria were non-vaccinated for diphtheria vaccine and 18 (26.9%) were completely vaccinated and 11 (16.4%) were partially vaccinated. None of the subject in this cohort was given a booster vaccine at 5-year of age. 70.1% patients had a faucial diphtheria during initial presentation. 28.4% (n=19) had a neck swelling initially at presentation and 11.9% presented with stridor. All the patients who presented with stridor at initial clinical manifestation need a tracheostomy at subsequent days due to overt or impending upper airways obstruction. Majority (83.6%) of children presented with mild severity of the disease. Only 1.5% patients presented with severe disease and toxic look. (Table-1)

Table-1: Clinical spectrum of 67 patients with Diphtheria

Age (months) median ± SD (range)	106±32.08 (24–172)
Gender (boys: girls)	2: 1
Area (rural) n (%)	39 (58.2)
Site of involvement, n (%)	
Faucial	47 (70.1)
Pharyngolaryngeal	14 (20.9)
Laryngeal	6 (9.0)
Immunisation status, n (%)	
Unimmunised	38 (56.7)
Partially immunised	11 (16.4)
Adequately immunised	18(26.9)
Culture positive, n (%)	17 (25.4)
Clinical features, n (%)	
Fever	60 (89.5)
Neck swelling	19 (28.4)
Stridor	8 (11.9)
Tracheostomy at admission	8 (11.9)
Severity score	
Mild	56 (83.6)
Moderate	10 (14.9)
Severe (toxic shock)	1 (1.5)
Complications, n (%)	
Airway compromise	11 (16.4)
Myocarditis	25 (37.3)
polyneuropathy	4 (5.9)
Mortality	5 (7.5)

In all the affected cases 25.4% patients had a positive throat culture for the Corynebacterium diphtheriae. Both the electrocardiography (ECG) and echocardiography were different at initial presentation and subsequent follow up. 76.1% (n=51) had a normal ECG at initial presentation (65.7% at subsequent ECGs) 4 (6.0%) had a right bundle branch block (RBBB), 3% had a 1st degree heart block (10.4% on subsequent ECGs), 1.5% had complete heart block (3% on subsequent ECGs), 1.5% had VT (4.5% on subsequent ECGs). 73.1% (n=49) had a normal echocardiography at presentation, 23.9% (n=16) had septal paradoxes at initial echocardiography and 3% (n=2) had a LV systolic dysfunction (22.4% on subsequent echocardiography).

There were many predictors that predict the subsequent cardiac involvement and ultimately the outcome of the patients. Septal paradoxes was an important marker in the prediction of the cardiomyopathy in patients with diphtheria. Septal paradoxes had 76% sensitivity and 100% specificity with a positive predictive value (PPV) of 100%. Nasopharyngeal membrane had a PPV of 40.4% (p=0.42). Neck swelling had a PPV of 57.9% (p=0.02). Moderate severity score of diphtheria disease had a PPV of 90% and severe disease had a PPV of 100%. Tracheostomy at presentation having a PPV of 100% (p=0.001). Some parameters had a very strong positive predictor value regarding outcome of the disease in the form of death. Ventricular tachycardia (VT) at presentation or on subsequent ECG had a PPV of 94% and complete heart block had a PPV of 82%.

25 (37.3%) had a cardiac involvement in the form of diphtheria cardiomyopathy or arrhythmia. The mean interval between onset of respiratory symptoms and myocarditis was 5.9±2.4 days (range 2–11 days). Total 5 (7.5%) patients expired during course of illness during study period. Three doses of intravenous methyl prednisolone pulses (30mg/kg/dose) were given to all the patients predicted on echocardiography (Septal paradoxes on initial or subsequent echo) or ECG (RBBB, ST segment changes, VT) or present with the severe disease in the index hospital, on the same day as the initial investigation being done. All patients received continuous cardiac monitoring during therapy. Total 17 patients (16 on initial echo and 1 on subsequent echo) who were having septal paradoxes were given 3 doses of IV methyl prednisolone on admission (median 1day, range 1–3). Out of these 8 patients developed mild LV dysfunction on echocardiography on subsequent days (median 5days, range 3–8 days), 5 patients did not develop any cardiac symptoms later on ,3 patients develop only ST segment changes in later course of illness and no LV dysfunction were recorded on subsequent echocardiography. All these 16 patients were discharged after total stay of 2 weeks (Mild LV dysfunction patients were treated with Milrinone infusion and diuretics and patients with ST changes were managed conservatively). Out of these 17 patients 1 patient presented at admission with sever LV dysfunction and in shock and also having septal paradoxes but expired on 6th day of admission despite all the management. Methyl prednisolone was given in 8 more patients and out of these 8 children 4 patients have RBBB and 2 patients had ST segment changes. These patients completely recovered during course of illness and discharged. 2 patients were presented with arrhythmia on 5th and 7th

day of illness and presented with VT and despite all drugs and anti-arrhythmic drugs expired within 2 days. Remaining 42 (62.7%) were neither had echocardiographic or ECG or clinical predictor for development of cardiomyopathy and were not given methyl prednisolone and all remained normal and discharged after 2 weeks. (Table-2) The reaming 2 patients who were expired, 1 patient had a RBBB on initial ECG (in the initial part of study) and were missed and we did not give methyl prednisolone to that patient and he developed brady-tachyarrhythmia on 7th days of illness and expired. The other patient presented with complete heart block on 8th day of illness and despite of temporary pacemaker could not survive.

Out of 25 patients with myocarditis 5 (20%) died (Odd's ratio 14.3, 95% CI 3.1–68.5, p=0.0001). Presence of arrhythmia was associated with the highest mortality (OR 18.1; 95% CI 2.7–73.9; p=0.0001). Presence of septal paradoxes on echo had association with the cardiac involvement (OR 10.1: 95% CI 1.2–84.6; p=0.0005)

Table-2: Clinical characteristics of all 25 patients in which methyl prednisolone were used

Patient	Age (months)	Sex	Throat culture	Severity score	Septal paradoxes	ECG	LVEF (%)	Outcome
1	48	M	Negative	Mild	Yes	Normal	63	Discharged
2	132	M	Negative	Moderate	No	RBBB	66	Discharged
3	120	M	Negative	Mild	Yes	Normal	54	Discharged
4	130	M	Negative	Mild	Yes	Normal	51	Discharged
5	118	M	Negative	Mild	Yes	Normal	68	Discharged
6	116	F	Negative	Mild	No	RBBB	71	Discharged
7	120	M	Negative	Mild	No	ST changes	63	Discharged
8	72	F	Positive	Moderate	No	VT	47	Expired
9	48	M	Negative	Mild	No	VT	52	Expired
10	84	F	Negative	Mild	Yes	Normal	61	Discharged
11	72	F	Negative	Mild	Yes	Normal	65	Discharged
12	111	M	Positive	Moderate	Yes	Normal	49	Discharged
13	84	M	Positive	moderate	Yes	Normal	52	Discharged
14	129	M	Negative	Mild	Yes	Normal	71	Discharged
15	136	M	Negative	Mild	Yes	Normal	63	Discharged
16	154	M	Positive	Moderate	Yes	Normal	54	Discharged
17	120	F	Positive	Moderate	Yes	Normal	48	Discharged
18	50	M	Negative	Moderate	Yes	Normal	61	Discharged
19	102	M	Negative	Severe	Yes	Normal	26	Expired
20	157	M	Negative	Mild	Yes	Normal	55	Discharged
21	98	M	Negative	Moderate	Yes	Normal	56	Discharged
22	130	M	Negative	Mild	No	ST changes	69	Discharged
23	112	F	Negative	Mild	No	RBBB	64	Discharged
24	84	M	Positive	Mild	Yes	Normal	66	Discharged
25	96	F	Negative	Mild	No	RBBB	74	Discharged

DISCUSSION

Diphtheria, caused by toxigenic strains of Corynebacterium diphtheriae, is an ancient disease with a significant high incidence and mortality that has always been characterized by epidemic waves of occurrence and is more common in winter in Pakistan. There are sporadic cases of diphtheria and cardiomyopathy associated with diphtheria in the developed world[17] but it's still a significant cause of mortality in developing world like Pakistan[5,18].

In this study, we demonstrated the early predictors of diphtheria cardiomyopathy aiming at early detection and pick up of the disease and response of methyl prednisolone on these patients with reference to the outcome of the disease in the form of mortality or morbidity. There was male predominance in our study and it is comparable with the literature.[13,18] The Male: Female is 2.3:1 with 70.1% were boys which is comparable to regional literature as well.[18] Median age at the time of presentation was 106 months (range 24–172 months) and other studies also had a range of presentation 62–120 months.[5,13,19] In this study and the related literature the cluster of diphtheria among age group of 5–10y is possibly due to lack of booster dose (DT). Patients less than 5 year are possibly rare because of immunization effect and also maternal antibodies in the younger infants. So, with advancing age due to possible modifying response of antibodies due to lack of booster dose is likely reason for common presentation of diphtheria at this age group. 56.7% subjects presented with diphtheria were non-vaccinated for diphtheria vaccine and 26.9% were completely vaccinated which is comparable to the regional data[4] in which 56.3% were non immunized. Although immunized and partially immunized children were also presented with diphtheria but their number is less and likely diminished efficacy of

administered vaccine at early age group is the reason of this presentation. It is possibly the reason of immunization status that the majority 58.2% children belong to rural areas of Pakistan.

The diphtheria cardiomyopathy usually associated with exotoxins mediated myocardial injury produced by these microorganisms.[19] The incidence of diphtheritic cardiomyopathy following diphtheria is 10–20%, and some Indian studies reported the occurrence of myocarditis is 16–66% and the associated mortality is ~50%.5,19 Our study showed 37.3% had a cardiac involvement in the form of diphtheria cardiomyopathy or arrhythmia. The mean interval between onset of respiratory symptoms and myocarditis was 5.9±2.4 days (range 2–11 days). Majority of the patients with myocarditis were asymptomatic, had only ECG changes, SGOT elevation, and early changes in the echocardiography and had a favourable outcome. Out of 25 patients having diphtheria cardiomyopathy there was 20% expired during the course of treatment. Overall mortality among diphtheria patients was 7.4% which is comparable to the local and regional data[13,18] where it was 8.9% and 5% but the 20% expiry among diphtheria cardiomyopathy is significantly low as compare to study by Jayashree M, Shruthi N *et al*[5] where the frequency was above70%. So, we proposed that if methylprednisolone was given in asymptomatic patients on the basis of prediction of diphtheric cardiomyopathy than the outcome in the form of mortality in diphtheric cardiomyopathy can be significantly reduced. So here there is contrast observation in previous studies[11,12] where they have given steroids in symptomatic patients when full blown disease occurs and they documented that there is no role of steroids in combating mortality. This expiry rate was irrespective of the anti-diphtheritic serum (ADS) administration because almost all the patient got the ADS at admission. It was observed that almost all patients developed cardiac involvement within first week of onset of respiratory symptoms and patients who had bull neck and extensive faucial patches had more incidence of cardiac involvement and this is comparable to the literature as well.[5,20] Occurrence of diphtheria and cardiomyopathy related to diphtheria is also a seasonal trend and more common in winter particular from October to January in Pakistan and this is comparable to regional data[21], so this also depicts the seasonal trend of diphtheria cardiomyopathy.

There are many predictors of the diphtheria cardiomyopathy like nasopharyngeal membrane (PPV=40.4%), neck swelling (PPV=57.9%) immunization status (PPV=11.2%) but multivariate regression analysis found all of them non-significant as a predictor of diphtheria cardiomyopathy similar to regional data [5]. Among predictors the presence of septal paradoxes in initial echocardiography had a PPV of 100% (p=0.001) severity score had a PPV 100% (p=0.001). So, by doing serial echocardiography in the early course of disease we can easily predict that patient will develop the cardiac involvement or not and this is the time period where you can intervene and may change the outcome of the disease and reduce both mortality and morbidity. Serial ECGs and presence of RBBB and ST segment changes initially was also a good predictor of diphtheria cardiomyopathy in combination with echocardiography findings.

We had given 3 doses of intravenous methyl prednisolone (30 mg/kg/day) to all these predicted patients. Previous study that was conducted by Varghese MJ *et al*[22], given the high dose steroids or immunoglobulin after the full-blown symptoms of the disease and they found that there was no significant role of these drugs in diphtheria cardiomyopathy either it was a LV dysfunction or arrhythmia. Other studies done by Thisyakorn U *et al*[23] and Mason JW *et al*[24] also depicted that the role of steroids were controversial and they also given the drugs that already developed the LV dysfunction or arrhythmia. In contrary to that in our study we gave the drug in those 25 patients who were predicted on ECG or echocardiographic findings. In those patients after given the methyl prednisolone either mild symptom occurred or some patients only develop mild LV dysfunction or only mild ECG changes. Out of these patients 22 patients were discharged with no residual effect in majority of children. So, early administration of high dose corticosteroids before the development of complete symptoms of cardiomyopathy can change the fate of these children if they were predicted early. All these results were irrespective of the administration anti-diphtheritic serum (ADS) because almost all the patient got the ADS at admission. Three patients expired in our study despite giving methyl prednisolone and this was similar to other studies[22–24] where two patients presented with full blown disease as they presented with ventricular tachycardia (VT) to begin with and one patient presented with severe disease and sever LV dysfunction and in toxic shock to begin with. In these patients we also tried the methyl prednisolone along with other supportive medication but they could not survive. The patients presented with ventricular tachycardia presented at 5th and 7th day of onset of illness which was a significant delay in presentation (usual presentation median day 3) and they already developed the arrhythmia. Although there was mild LV dysfunction in both patients but uncontrolled VT was the reason of death of these two kids. One patient presented in toxic shock on 9th day

of illness to our setup and despite giving steroid expired on the next day as he already developed the sever LV dysfunction. All the remaining 42 (62.7%) were not predicted to develop the cardiomyopathy and on subsequent follow up neither of them developed the LV dysfunction or arrhythmia and all were discharged after 2 weeks. Four patients developed diphtheric neuropathy and developed problem in walking and dysphagia and managed conservatively and supportive medicine were given and recovered in 6–8 weeks follow up without residual deficit.

So, the off-label use of corticosteroids in early predicted patients can alter the fatal outcome of diphtheria cardiomyopathy. In experimental animals, glucocorticoid administration has been reported to improve muscle responses to stimulation of nerve segments demyelinated by diphtheria toxin or other inflammatory cases, probably by diminishing conduction block and also small role in fulminant myocarditis.[25–27] Conduction system disturbances in patients with diphtheric myocarditis are markers of severe myocardial damage and are uniformly fatal despite ventricular pacing, so by preventing conduction abnormalities or arrhythmia, which is the leading cause of death in diphtheria cardiomyopathy, by early administration of corticosteroids can alter the outcome but further randomized controlled trials with a larger sample size are required to unambiguously delineate the clinical effect of corticosteroids the treatment of diphtheric cardiomyopathy in children.

There was an inherent limitation of collection of data from two or three tertiary care hospital settings in the study and it only included the patients who did reach to such facilities and may missed some patients who are sick enough and either treated locally or unable to reach the tertiary care hospitals. High-quality, large-scale RCTs with a good size control group (Placebo administration) should be careful designed to determine the well-defined role of corticosteroid treatment for diphtheric cardiomyopathy. By doing this we may be able to change the mortality or morbidity related to this grave disease in developing countries.

CONCLUSION

Diphtheria is still a public health problem in many developing countries and remains the major cause of morbidity and mortality due to lack of implementation of extended program of immunization (EPI) and also the booster dose of diphtheria in our setup. Diphtheria with its worst complications like diphtheria cardiomyopathy is still highly prevalent in this region of the world and major cause of mortality among diphtheria patients. Early prediction by alone or in combination of ECG and echocardiographic markers and early use of IV methyl prednisolone in these predicted patients before symptoms, can reduce the mortality related to diphtheric cardiomyopathy and can decrease the burden of the disease in the community.

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AUTHORS' CONTRIBUTION

UR: Conceptualization, literature search, Study design, Data collection and interpretation, Write up. RN: Literature search, study design, proof reading. SUS: Study design, data analysis, proof reading. FIB: Study design, Proof reading. ZF: Study design, data analysis

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