HIGH-DOSE INTRAVENOUS DEXAMETHASONE IN THE MANAGEMENT OF DIARRHEAL PATIENTS WITH ENTERIC FEVER AND ENCEPHALOPATHY

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Abstract. We conducted a retrospective chart analysis of diarrheal patients with enteric fever and encephalopathy (among survivors and non-survivors) to examine the role of high-dose, intravenous dexamethasone as an adjunct to appropriate antimicrobial therapy in their management. We studied all patients admitted to the Special Care Ward (SCW) of Dhaka Hospital between October 2006 and October 2007 with a diagnosis of encephalopathy in association with enteric fever. Twenty-three cases were identified with three mortalities. All bacterial isolates (*Salmonella* Typhi and *Salmonella* Paratyphi) were multi-drug resistant. Survivors were significantly more likely to have received high dose dexamethasone (100% *vs* 00%; $p < 0.001$) and had hypoglycemia less often (6% *vs* 67%; $p = 0.045$) compared to those who died. The results suggest high dose intravenous dexamethasone, as an adjunct to appropriate antimicrobial therapy, substantially reduces mortality among diarrheal patients presenting with enteric encephalopathy.

INTRODUCTION

Enteric fever is endemic in many developing countries (Choo *et al,* 1988), and encephalopathy (enteric encephalopathy) is a common feature of severe enteric fever, manifested as altered consciousness, such as disorientation, confusion, delirium (Nag *et al*, 1975; Punjabi *et al*, 1988; Ozen *et al*, 1993; Mandal, 1996; Dutta *et al*, 2001). The reported incidences of enteric encephalopathy vary between 10% and 30% (Baker, 1981). In the absence of prompt, appropriate treatment the case fatality from enteric encephalopathy is high, with cases fatality rates reported as high as 56% (Hoffman *et al*, 1984; Dutta *et al,* 2001). The classic clinical pattern of enteric fever has changed over time, and the emergence of multi-drug resistance (MDR) enteric fever, associated with higher case-fatality, has complicated the management of severe illness (Koul *et al,* 1991; Sharma and Gathwala, 1993; Keusch, 1998; Dutta *et al,* 2001). Steroids have been used alone in the management of enteric fever (Smadel *et al,* 1951; Koul *et al,* 1991) without convincing therapeutic benefits (Eskes, 1965). However, the use of conventional low dose corticosteroid therapy in enteric encephalopathy along with effective antimicrobial therapy has been reported to produce clinical benefits (Zellweger and Idriss, 1960; Midha and

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Singh, 1975); high dose intravenous dexamethasone has been reported to substantially reduce case mortality as well as morbidity in enteric encephalopathy (Hoffman *et al*, 1984; Punjabi *et al*, 1988). In our clinical seting, it is not unusual to encounter patients with enteric encephalopathy. Based on the findings of an earlier study (Hoffman *et al*, 1984) our hospital has adopted the use of intravenous dexamethasone in the treatment of enteric encephalopathy. However, there is lack of data regarding the role of high dose dexamethasone in the management of diarrheal patients with enteric encephalopathy, which prompted us to conduct this analysis. We did not consider a randomized, double blind study due to the results of the earlier study and because it is a standard practice in our hospital. We conducted a retrospective chart analysis to assess diarrheal patients with enteric encephalopathy treated with high dose dexamethasone and appropriate antibiotic therapy.

MATERIALS AND METHODS

Patient enrollment

The study participants were patients admitted to the Special Care Ward (SCW) of Dhaka Hospital, ICDDR, B; Dhaka, Bangladesh between October 2006 and October 2007. Most critically ill patients attending the hospital, over 1,200 per year, are treated on this ward. The hospital provides treatment for 110,000 diarrheal patients with or without associated complications and with or without other health problems per year. The majority of patients came from a poor socio-economic background from urban and suburban Dhaka, the capital city of Bangladesh. A clinical diagnosis of enteric encephalopathy was made based on isolation of *Salmonella* Typhi or *Salmonella* Paratyphi from blood or fecal cultures, and or a positive Widal test and using the Glasgow Coma Scale (GCS).

Study design

This was a retrospective analysis of data from patient records. We identified 23 patients meeting the criteria as a case: diarrheal patient with enteric fever and features of encephalopathy. Twenty patients recovered and three died. We defined enteric fever as a patient with culture proven enteric fever, as defined by isolation of *S.* Typhi or *S.* Paratyphi from a blood or fecal culture and/or a positive Widal test. A Widal test was deemed positive when the antibody titer against somatic antigen (O) was ≥1:160 or when there was a rising titer. A diagnosis of encephalopathy was made when a patient with enteric fever had a GCS score ≤14. Dexamethasone was administered at a dose of 3 mg/kg initially followed by 1 mg/kg every 6 hours for the next 48 hours (Hoffman *et al*, 1984; Punjabi *et al*, 1988). Dehydration was assessed following modified WHO guidelines, and when present, was corrected using either oral rehydration salts (ORS) solution or intravenous rehydration fluids as appropriate (Alam and Ashraf, 2003). We analyzed the clinical and laboratory characteristics of these patients and assessed the role of dexamethasone and other features among survivors and fatalities.

Statistical methods

We developed and pre-tested case report forms (CRF) before finalizing them for data acquisition. All data were entered into a personal computer (PC) and edited before analysis using SPSS for Windows (version 10.2; SPSS, Chicago) and Epi Info (version 6.0, USD, Stone Mountain, GA). Differences in proportions were compared by the χ^2 test and differences in means were compared by Student's *t*-test or Mann-Whitney test, as appropriate. A probability of 0.05 was considered statistically significant. Strength of association was determined by calculating

relative risk (RR) and their 95% confidence intervals (CI). Age, sex, type and duration of diarrhea, dehydration on admission, extent and duration of fever (≥38ºC), radial pulse, coated tongue, palpable liver, severe sepsis [presence of any two of the followings: tachypnea, tachycardia, temperature instability (hypo- or hyperthermia measured by rectal temperature), abnormal WBC count (>11,000/mm^3 , <4,000/mm^3 or, band to neutrophil ratio of ≥0.1) and hypotension in the absence of clinical dehydration or after correction of dehydration plus signs of poor peripheral perfusion (absent peripheral pulses)] (Goldstein *et al*, 2005), colitis (defined as abdominal distension associated with pain, rebound tenderness and reduced or absent bowel sounds associated with distended or dilated bowel loops on plain abdominal radiograph), lobar pneumonia (presence of lobar consolidation on chest X-ray), hypoglycemia (random blood glucose ≤3 mmol/l by bedside rapid finger blood glucose test), positive blood, stool or rectal swab culture, Widal test result, receiving intravenous (IV) fluid and antimicrobials, GCS score (motor response: obeys simple commands = 6, attempts to remove source of painful stimuli to head or trunk = 5, attempts to withdraw from source of pain = 4, flexes arm at elbow and wrist in response to nail bed pressure = 3, extends arms at elbow and wrist in response to nail bed pressure = 2, no motor response to painful stimuli = 1; verbal response: oriented = 5, disoriented = 4, random speech = 3, mumbling = 2, no speech = 1; eye opening: eyes open =4, open to speech = 3, open to pain = 2, no opening = 1), high dose dexamethasone, white blood cell count (WBC), serum electrolytes, serum creatinine, and socio-economic status (poor if monthly income <5,000 taka, USD 70) were analyzed in a univariate model. Logistic regression analysis could not be performed as some variables did not meet its requirements.

Ethical approval

Informed consent could not be obtained due to the retrospective study. Analysis of data was carried out anonymously.

RESULTS

Among the 23 patients 13 (57%) were female. The mean ± SD age of the patients was 17.5 ± 5.3 years. The median (range) duration of diarrhea was 30 (3-240) hours. Seven patients (30%) presented with dehydration (on admission) (Table 1). All patients presented with fever with a pre-admission median (range) duration of 7 days (3-20 days) and a mean ± SD temperature of 39.4% ± 1.2ºC (Table 1). The mean ± SD radial pulse was 114/minute ± 29. Eight (40%), 3 (13%), 3 (13%), and 2 (11%) had a coated tongue, palpable liver, lobar consolidation on X-ray, and colitis, respectively (Table 1). The median (range) peripheral blood white cell count (WBC) was $4.5x10^9$ ($2.0x10^9$-$12.3 x10^9$)/l with a mean ± SD lymphocyte count of 24 ± 10.5% (Table 1). The mean ± SD serum sodium, potassium, and median (IQR) creatinine were 128.0 ± 7.3 mmol/l, 3.0 ± 0.88 mmol/l, and 126 (111, 138) micromoles/l, respectively (Table 1).

Among the survivors, one developed aphasia that did not resolve during hospitalization. All of the three (13%) patients who died were female. The mean ± SD GCS score was 12 ± 2 among both the survivors and the mortalities. All the survivors received high dose dexamethasone while none of the fatalities did (100% *vs* 00%; $p < 0.001$); the survivors were less likely to have hypoglycemia (6% *vs* 67%; $p = 0.045$). Blood cultures in 12 of the survivors (52%) were positive for *S.* Typhi and in 4 were positive for *S.* Paratyphi; 2 of the fatalities (67% of the fatalities) were positive for *S.* Paratyphi. Of the 4 other survivors, *S.* Typhi and *S.* Paratyphi

Table 1
Clinical and laboratory characteristics of diarrheal patients with enteric encephalopathy.

Characteristic	*N* =23 (%)
Female	13 (57)
Age (months) (Mean ± SD)	17.5 ± 5.3
Poor socio-economic status (monthly income <5,000 taka)	14 (70)
Type of diarrhea	
Acute watery diarrhea	22 (96)
Invasive diarrhea	1 (4)
Duration of diarrhea prior to admission (hours) (Median, IQR)	30 (5, 108)
Dehydrating diarrhea (some / severe)	7 (30)
Fever (≥ 38ºC)	23 (100)
Temperature (ºC) (Mean ± SD)	39.4 ± 1.2
Duration of fever prior to admission (hours) (Median, range)	7 (3, 20)
Radial pulse (beat / minute) (Mean ± SD)	114 ± 29
Coated tongue	8 / 20 (40)
Palpable liver	3 (13)
Colitis	2 / 19 (11)
Lobar pneumonia	3 (13)
WBC (/ l of blood) (Median, range)	4.5 x10^9 (2.0 x 10^9-12.3 x10^9)
Lymphocyte (%) (Mean ± SD)	24 ± 10.5
Serum sodium (mmol / l) (Mean ± SD)	128.0 ± 7.3
Serum potassium (mmol / l) (Mean ± SD)	3.0 ± 0.88
Serum creatinine (micromoles / l) (Median, IQR)	126 (111, 138)
IV fluid	9 (43)
Total IV fluid received (Median, IQR)	1,900 (1,250, 4,950)
Steroid received (Inj. dexamethasone)	20 (87)
Death	3 (13)

N, number of patients; IQR, inter-quartile range; ºC, degrees Celsius; / l, per liter

were isolated from rectal swab cultures in 3 patients and 1 patient, respectively, and all four had a positive Widal test (Table 2). The blood and rectal swab cultures of the remaining fatality were negative but the Widal test was positive (antibody titer against Typhi "O" antigen was 1:320) (Table 2). All blood and rectal swab culture isolates were resistant, by disc diffusion method, to chloramphenicol, ampicillin and trimethoprim-sulphamethoxazole with intermediate susceptibility to ciprofloxacin. Twenty-two patients (96%) (20 survivors and 2 fatalities) were treated with ceftriaxone. One patient (fatality) was treated with ciprofloxacin (administered parenterally) (Table 2). The duration of antimicrobial therapy was 14 days. The age distribution, type and duration of diarrhea, presence of dehydration, temperature, duration of fever, radial pulse, lobar pneumonia, severe sepsis, WBC count, lymphocyte count, serum sodium, potassium and creatinine levels, and receiving of intravenous rehydration fluid did not differ between the survivors and the fatalities (Table 2).

DISCUSSION

Our study was not a randomized, con-

Table 2
Comparison of characteristics among the survivors and fatalities in the study patients.

Characteristic	Survivors *N* (20) (%)	Fatalities *N* (3) (%)	RR (95% CI)	*p*-value
Female	10 (50)	3 (100)	Unidentified	0.23
Age (mean ± SD)	16.8 ± 5.2	21.7 ± 4.9	Not applicable	0.223
GCS score (Mean ± SD)	12 ± 2	12 ± 2	Not applicable	-
Type of diarrhea				
Acute watery diarrhea	19 (95)	3 (100)	-	-
Invasive diarrhea				
Duration of diarrhea (median, range)	48 (3, 240)	24 (24, 24)	-	-
Dehydrating diarrhea (some/severe)	6 (30)	1 (33)	1.11 (0.2-6.3)	1.0
Temperature (ºC)	39.5 ± 1.1	38.5 ± 1.4	Not applicable	0.176
Duration of fever (median, range)	7 (3, 20)	7 (6,12)	Not applicable	0.830
Radial pulse (beats/minute) (Mean ± SD)	120 ± 13	130 ± 78	Not applicable	0.599
Colitis	2 (10)	0 (0)	-	-
Lobar pneumonia	2 (10)	1 (33)	3.3 (0.4-26.5)	0.356
Severe sepsis	2 (10)	1 (33)	3.3 (0.42-26.45)	0.356
Hypoglycemia (RBS <3.0 mmol/l)	1/17 (6)	2 (67)	11.33 (1.44-89.19)	0.045
WBC (/l of blood) (median, range)	$4.3x10^9$	$5.5x10^9$	Not applicable	0.669
($2.0x10^9$, $12.3x10^9$)	($3.0x10^9$, $9.0x10^9$)			
Lymphocytes (%) (Mean ± SD)	23 ± 11	28 ± 10	Not applicable	0.471
Serum sodium (mmol/l) (Mean ± SD)	127.1 ± 6.7	132.2 ± 10.1	Not applicable	0.285
Serum potassium (mmol/l) (Mean ± SD)	2.9 ± 0.8	3.7 ± 1.1	Not applicable	0.168
Serum creatinine (micromole/l) (Median, IQR)	133.0 (104.5, 135.0)	111.0 (111.0, 111.0)	Not applicable	0.286
Growth on blood culture				
Salmonella Typhi	12 (60)	0 (0)	-	-
Salmonella Paratyphi	4 (20)	2 (67)		
No growth	4 (20)	1 (33)		
Growth on rectal swab culture				
Salmonella Typhi	3/17 (17)	0 (0)	-	-
Salmonella Paratyphi	1/17 (6)	0 (0)		
No growth	13 (77)	2/2 (100)		
Widal test (positive)	5/5 (100)	3/3 (100)	-	-
Total IV fluid received (ml) (Median, IQR)	1,500 (1,200, 1,800)	2,050 (1,050, 6,200)	Not applicable	0.485
Antimicrobial therapy				
Inj. ceftriaxone	20 (100)	2 (67)		
Inj. ciprofloxacin	0 (0)	1 (33)	Unidentified	0.130
High dose dexamethasone	20 (100)	00 (00)	Unidentified	<0.001

RR, relative risk; CI, confidence interval; RBS, random blood sugar

trol clinical trial and had the limitations of retrospective chart analysis. Yet, the differences in the case-fatality rates among patients receiving the high dose dexamethasone therapy (*n*=20) and those who did not (*n*=3) (0% *vs* 100%) achieved statistical significance. Violation of standard hospital practice of using high-dose dexamethasone occurred in all three fatalities because they all died before the cultures and Widal test

results were available. The blood cultures of two of the fatalities grew *S.* Paratyphi. The third patient had a Widal test suggestive of enteric fever but a rectal swab culture was not performed on this patient.

The mechanism of action of dexamethasone in enteric encephalopathy is not known. Endotoxins released by *S.* Typhi and *S.* Paratyphi stimulate macrophages to produce monokines, arachidonic acid and its metabolites, and free oxygen species that are probably responsible for the toxic effects, particularly in those with enteric encephalopathy (Nag *et al,* 1975; Johnston *et al,* 1978; Clark *et al,* 1981). It is possible dexamethasone either reduces these levels or counteracts the physiological effects of these products or both, and acts as an antioxidant resulting in reduced fatalities (Hoffman *et al,* 1984). Cerebellar edema and venous congestion of brain cells are often evident in enteric encephalopathy (Chand and Singh, 1988) and high dose dexamethasone may play a role in substantially reducing these (Girgis *et al,* 1993), although this theory has been challenged by another publication (Trevett, 1994). The similar GCS scores (12) among the survivors and the fatalities suggests both groups of patients had similar involvement of the CNS. Our findings are similar to those observed among non-diarrheal patients with enteric encephalopathy (Hoffman *et al,* 1984; Punjabi *et al,* 1988).

Hypoglycemia was common among our fatalities and is not uncommon in enteric fever (Singh and Singh, 2001). We did not find any published data regarding hypoglycemia in patients with enteric encephalopathy. All three fatalities in our study were females. We do not have a ready explanation for this observation. This may reflect differences in care seeking behavior among females in our society where they often conceal their illness from family members and are less likely to attend health care facilities until seriously ill. This is supported by the fact they all died before their laboratory test results were available. The total male to female ratio in our study was 1.3:1, which supports our theory stated above. There was a slight female predominance (57%) in the study population, a higher incidence (Choo *et al,* 1988) of enteric encephalopathy and a higher case fatality rate (Butler *et al,* 1991).

All clinical isolates (*S.* Typhi and *S.* Paratyphi) were resistant to chloramphenicol, ampicillin and trimethoprim-sulphamethoxazole, were intermediately susceptible to ciprofloxacin, and full susceptibility to ceftriaxone and cefexime as determined by disc diffusion method. All the patients were multi-drug resistant (MDR) cases of enteric fever and were treated with parenteral ceftriaxone, except for the patient who received parenteral ciprofloxacin and had a fatal outcome, but no significant association between antimicrobial type and morbidity was observed. An association between enteric fever caused by MDR strains and encephalopathy has been reported (Koul *et al,* 1991; Kabra *et al,* 2000; Mahmud *et al,* 2008).

We observed a coated tongue in two-thirds of our patients and hepatomegaly in 13% of them. A coated tongue is thought by some to be a classical feature of typhoid fever and hepatomegaly has been reported more common in patients with MDR typhoid fever (Girgis *et al,* 1993; Dutta *et al,* 2001). We did not observe relative bradycardia, leukopenia or lymphocytosis in either group of patients. These findings may represent changing clinical patterns of enteric fever (Hoffman *et al,* 1984; Choo *et al,* 1988; Koul *et al,* 1991; Sharma and Gathwala, 1993; Keusch, 1998; Dutta *et al,* 2001). Two of our patients, both among the survivors, developed toxic colitis, a serious complication of enteric fever (Girgis *et al,* 1993) and recovered without surgical intervention. Thirteen percent of our patients had radiological lo-

bar consolidation similar to an earlier report (Dutta *et al*, 2001).

Similar to earlier reports (Bobin *et al*, 1993), we found no influence of age on case fatality. All of our patients were adolescents similar to a previous report (Ugwu *et al*, 2005). We observed no differences in peak body temperature or duration of fever between groups. The consistent finding of persistent high fever may represent a consequence of the products of macrophage stimulation by the released of endotoxin from the pathogens (*S*. Typhi and *S*. Paratyphi) (Nag *et al*, 1975; Johnston *et al*, 1978; Clark *et al*, 1981). The presence of persistent high fever in patients with enteric encephalopathy has been reported earlier (Girgis *et al*, 1993, Jain *et al*, 1986). Development of encephalopathy during the first week of enteric fever is considered to carry a grave prognosis (Dutta *et al*, 2001). None of our patients receiving high dose dexamethasone died, suggesting the beneficial role of dexamethasone in preventing deaths.

We found no association between intravenous fluid administration and case fatality, suggesting the judicious use of intravenous fluid for a specific indication (dehydration or sepsis) does not cause problems, such as over hydration or pulmonary edema. All our patients had diarrhea, 30% had dehydrating diarrhea with vomiting, and 11% had severe colitis as an indication for administration of intravenous fluid.

We did not observe any differences in serum sodium or potassium levels between the groups, but the general finding of hyponatremia and hypokalemia in the study population may be due to the fact that nearly all (96%) had diarrhea and half (50%) had vomiting. A tendency to have reduced serum electrolytes with enteric encephalopathy, consequent to disturbances in central osmoregulation, has been suggested (Zellweger and Idriss, 1960). Our observations are similar to a number of previous studies (Marmion, 1952; Watson, 1954; Zellweger and Idriss, 1960).

We found no differences in the duration of diarrhea, dehydration, severe sepsis, and serum creatinine levels between the survivors and the fatalities, indicating similar clinical severity between the groups, similar to previous studied (Hoffman *et al*, 1984, Punjabi *et al*, 1988).

We observed a serious residual complication in one patient who developed aphasia that persisted until discharge; we are not sure about the long-term outcome of this complication in the absence of a follow-up assessment. We did not perform an EEG or CT scan of the brain to document the changes associated with encephalopathy in our patient as has been reported previously (Midha and Singh, 1975; Bansal *et al*, 1995; Adehossi *et al*, 2003).

There were other limitations of our study in addition to small sample size. We had no routine follow-up of the patients after discharge from the hospital, although they were advised to report back in the event of encountering a problem. None of the patients returned for follow-up. We did not perform CSF studies in any of our patients except for those presenting with other features of meningitis (neck rigidity, positive Kerning's sign, positive Brudzneski's sign, positive Babinski sign, unconscious) since in the presence of features of encephalopathy in diagnosed cases of enteric fever we assumed them to be due to enteric encephalopathy. CSF studies performed in four patients were normal (clear CSF fluid with normal pressure, normal biochemistry results, a leukocyte count less than 5/mm^3 on a centrifuged sample and no organisms seen on Gram stain or culture). At health facilities with available resources to perform CSF studies, they should be performed irrespective of the presence or absence of meningeal signs.

In conclusion, mild hyponatremia and hypokalemia are frequent findings in diarrheal patients presenting with enteric encephalopathy. Diarrheal patients with MDR enteric fever associated with abnormal mental status have better survival when dexamethasone is administered in high doses in addition to an effective antimicrobial therapy. We observed a fatal outcome in all three cases who did not receive high-dose dexamethasone therapy. We also observed hypoglycemia as a common finding with enteric encephalopathy and its presence has been associated with a higher case fatality rate. Although our study was not a randomized, controlled clinical trial, it seems reasonable to believe that high dose dexamethasone therapy as adjunct to appropriate antimicrobial therapy is life-saving for diarrheal patients with enteric encephalopathy, as has been reported in patients without diarrheal illness. Our data highlights the importance of excluding hypoglycemia and electrolyte abnormalities and their early detection and aggressive management as a potentially life-saving therapeutic modality.

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