The impact of empirical hydrocortisone therapy on clinical outcomes in dengue fever: a retrospective chart review

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Background: The role of steroids in dengue infection (DI) remains uncertain.

Methods: A retrospective chart review was conducted on patients $\geq$18 y of age diagnosed with DI based on positivity for dengue non-structural antigen 1 or immunoglobulin M between October 2017 and November 2018.

Results: Hydrocortisone was administered to 106 of 406 patients. DI with warning signs occurred in nine patients (9.5%) in the steroid cohort and eight patients (2.5%) in the non-steroid group. The incidence of severe DI, bleeding and admission duration were similar between the groups.

Conclusions: Our study shows no significant benefit of empirical steroids in DI.

Keywords: dengue, corticosteroids, clinical outcomes

Introduction

Immune dysregulation has been proposed as a mechanism for severe complications related to dengue infection (DI). Steroids have been used in DI based on single-arm studies suggesting a benefit, as well as physician experience.[1] However, the data supporting the use of steroids in DI is conflicting and there is a lack of high-quality trials supporting this practice.[2]

We present a retrospective comparison of clinical outcomes of patients with DI who received steroids compared with those treated conventionally.

Methods

We performed a retrospective chart review of patients admitted with DI between October 2017 and November 2018 at Nawaloka Hospital Sri Lanka (NH). Patients $\geq$18 y of age with DI confirmed by a positive non-structural antigen 1 (NS1) and/or dengue immunoglobulin M (IgM) test were included. Clinical, laboratory and radiologic data were collected. We reviewed 417 clinical charts from patients with DI, among which 406 (97.4%) were selected for inclusion. The remaining charts were excluded due to unclear documentation of clinical information. The Kolmogorov–Smirnov test demonstrated that our data were normally distributed. Computed *t*-test, analysis of variance and χ^2 tests were used to assess the statistical significance of differences between patient groups. Statistical analyses were performed using SPSS version 16 (IBM, Armonk, NY, USA) and p-values <0.05 were considered significant.

Results

We included 406 patients with a mean age of 37.3 y (standard deviation 14.25; median 36.5 y [interquartile range 30–41]). There were no significant differences in the vital signs or baseline investigations on admission between the groups (Supplementary Table 1). Intravenous hydrocortisone was administered to 106 patients (26.1%) and all patients received standard supportive care. The median dose of hydrocortisone was 100 mg three times per day for a median of 4 d starting from day 1 of admission. The initial dose of steroid was given at a median of day 3 of fever.

DI with warning signs occurred in nine patients (9.5%) in the hydrocortisone group and eight patients (2.5%) in the non-hydrocortisone group (χ^2 test; p = 0.004). There was also no

Table 1. Comparison of the incidence of shock, need for intensive care unit (ICU) stay and unplanned outpatient follow-up between the hydrocortisone and non-hydrocortisone groups

Category	Intravenous hydrocortisone administered (N = 106), n (%)	Intravenous hydrocortisone not administered (N = 300), n (%)	p-Value
Patients diagnosed with shock	4 (3.7)	11 (3.6)	$\chi^2 = 0.0025$ degrees of freedom = 1 0.96[a]
Patients without shock	102 (96.3)	289 (96.4)	
Number of deaths	0	1 (0.3)	NA
Requirement for ICU stay	8 (7.5)	14 (4.6)	0.25[b]
Number of patients reviewed within 1 week as outpatient after discharge[c]	78 (73.5)	121 (40.3)	0.001[b]
Common reasons for follow-up (n/N = 78/121)			
Body weakness and body pain	21 (26.9)	55 (45.4)	0.008[b]
Loss of appetite	12 (15.4)	37 (30.6)	0.015[b]
Upper respiratory tract infection	14 (17.9)	10 (8.3)	0.04[b]
Urinary tract infections	13 (16.6)	8 (6.6)	0.02[b]
Gastroesophageal reflux disease and acute gastroenteritis	18 (23.1)	11 (9.1)	0.006[b]

[a]χ^2 test.
[b]Comparison of proportions: Z-test.
[c]Unplanned outpatient visits.

significant difference in the incidence of thrombocytopaenia below 50×10^9/l or transaminitis over twice the upper limit of normal. The incidence of clinically significant bleeding, severe DI, shock or the need for intensive care was similar between the groups. One death occurred in the non-hydrocortisone group. The average length of hospital stay was also similar between the groups. Gastroesophageal reflux disease (GORD) and urinary tract infections following discharge were more common in the hydrocortisone group. This resulted in more unplanned outpatient visits (73.5%) compared with the non-steroid group (40.3%; Z-test; p = 0.001). Table 1 summarises the incidence of selected complications in each group.

There was a significant difference in the platelet count on day 5 (79×10^9/l in the hydrocortisone group vs 62×10^9/l in the non-hydrocortisone cohort; t-test; p = 0.043) and day 6 (74×10^9/l vs 53×10^9/l; t-test; p = 0.010) of fever (Supplementary Figure 1A). There were no significant differences in the other haematologic parameters (Supplementary Figure 1B–D) or liver function tests (Supplementary Figure 2) between the groups.

Discussion

Our data suggest that empirical steroid therapy does not confer a clinically significant benefit in unselected patients with DI. This is in keeping with findings from previous randomised studies.[3] We also demonstrate that steroid-related complications such as GORD and infection are a concern in this setting. The incidence of DI with warning signs was greater in the steroid group; however, given that the absolute numbers were small (nine and eight patients in each cohort, respectively), these data are not conclusive. Steroids have not been proven to be beneficial in dengue-related thrombocytopaenia.[3] We demonstrated a superior platelet count on days 5 and 6 for steroid-treated patients. However, this difference was not clinically relevant, as the nadir platelet count in both cohorts was $>50\times10^9$/l, and clinically significant bleeding would not be expected at this level of thrombocytopaenia.

Administration of methylprednisolone in patients with DI who develop hypotension and third spacing resulted in a reduced duration of fever and faster haematologic recovery in a retrospective study.[4] These findings suggest that steroids may be beneficial in selected patients with severe DI. There is also evidence suggesting early administration of steroids (within 120 h of the onset of fever) maybe beneficial.[5] Although the majority of patients in our study received steroids within this time frame, they were not selected for steroid therapy based on clinical severity.

Our study was a retrospective, single-centre analysis, hence our findings need confirmation in independent cohorts. We

postulate that patients with DI who benefit from steroids are those with more prominent immune dysregulation. The discovery of biomarkers to identify patients with DI who may benefit from steroids should be a priority for future research. Prospective randomised trials investigating the utility of steroids in DI are called for.

Supplementary data

Supplementary data are available at *Transactions* online.

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