Adjunctive Corticosteroid Therapy in 149 Grade II (Non-Shock) Adult DHF Patients: An Analysis during January 2008-February 2010

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Background: *It is well known that immunopathogenesis play an important role in the development of severe complications in DHF. Since 2006, the authors have experience in giving immunomodulators to save life of many severe complicated adult DHF patients. This experience stimulates our interest on the benefit of adjunctive corticosteroid therapy in adult grade II DHF patients.*
Objective: *To find out whether there are some benefits of giving adjunctive corticosteroid therapy in adult grade II DHF patients.*
Design of the study: *Retrospective analysis during January 2008-February 2010.*
Material and Method: *One hundred and forty nine adult grade II DHF patients were admitted at Vichaiyut Hospital. They were divided into 3 groups according to the different therapy designed by the responsible clinicians. Group 1 consisted of 59 cases who received full dose-short course of intravenous dexamethasone (4 milligram every 6 hours for 2-3 days). Group 2 consisted of 61 cases who received intermittent 4 milligrams intravenous dexamethasone only at febrile episode and group 3-29 cases did not received corticosteroid. All the patients were investigated similarly. Age, sex, symptoms and signs including daily hematologic studies (Hct, Wbc, differential count, platelet count) were recorded. Serum SGOT, SGPT, bilirubin, alkaline phosphatase and albumin BUN, creatinine were performed on admission and repeated as indicated. The parameter to measure the benefit of adjunctive corticosteroid included 1) severity of thrombocytopenia, 2) liver impairment, 3) the days of illness as determined by fever and 4) the length of the hospital days.*
Results: *The clinical severity of all the three groups were quite similar. There was no benefit of using adjunctive corticosteroid therapy in term of changing the severity of thrombocytopenia and liver impairment. However, the days of illness and the length of hospital days were shorter at 4.6 days and 3.7 days respectively in the group who received full dose, continuous-short course of dexamethasone intravenously. This is statistically significant when compared to the other two groups who had the longer total days of fever at 5.8 days and 6.03 days and the longer length of hospital days at 5.19 days and 4.5 days respectively ($p < 0.05$).*
Conclusion: *Adjunctive corticosteroid by given full dose, continuous short course in grade II adult DHF reduced the course of illness (days of fever) and the length of hospital days. These findings indicated the benefit of using adjunctive corticosteroid therapy in grade II adult DHF patients.*

Keywords: *Adult DHF grade II, Full dose with short course of adjunctive corticosteroid therapy, Reduction of days of fever, Length of hospital days*

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Dengue hemorrhagic fever (DHF), an important disease of Thailand as well as the South East Asia Countries is characterized by high acute febrile onset accompanied with rash, petechia sports, myalgia and gastrointestinal disturbance. Before 1960, the mortality rate of DHF was very high, the most important serious complications of the disease consisted of shock, which if not well corrected in time, severe bleeding secondary to severe thrombocytopenia and disseminated intravascular coagulation (DIC) leaded to the multiorgan failure and death[1,2]. With the better understanding of the pathophysiology of DHF the fatal outcome has been improved. Many lines of

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evidences indicated that immunopathogenesis play a big role on the development of severe complications namely shock, bleeding and multiorgan failure[3]. In 1975, the three adult DHF patients having DIC in whom 2 died and one survived were first reported in Thailand[4]. Recently, we have reported one adult female DHF patient who developed hemophagocytic syndrome during convalescent stage of the disease. She presented with progressive cytopenia and multi-organ failure and was successfully treated by pulse methyl prednisolone and intravenous immunoglobulin G (IVIgG)[5]. During the last ten years, the incidence of adult DHF was increased rapidly[6-8]. Along with the increased incidence of adult DHF, the unusual complications of multiorgan failure and the benefit of using corticosteroid therapy was reported[8]. Since immunopathogenesis of DHF is quite well known at the present time, corticosteroid therapy was tried in many aspects concerning the benefit of survival of the severe cases, the improvement in duration and degree of thrombocytopenia. However, there were no definite answers on the benefit of corticosteroid therapy[9-11]. It is still be a controversial subject at the present time.

Rational of study

Since 2006, the authors have experience of using high dose corticosteroid plus methyl prednisolone and high dose intravenous immunoglobulin G therapy to save life of many adult severe complicated multi-organ failure DHF patients[5,8,12]. From this experience, it raises the question on the benefit of adjunctive corticosteroid therapy in mild to moderate severe complicated group II adult DHF patients. The authors therefore have use adjunctive continuous intravenous high dose-short course corticosteroid therapy in 59 grade II adult DHF patients. During the same period, there were the other 2 groups of patients who were treated differently according to the other clinician's judgment. The first group consisted of 61 patients who received intermittent intravenous dexamethasone only at febrile episode. The second group of 29 patients did not receive corticosteroid. The authors therefore use these two groups as control, comparing with the outcome of our 59 patients.

Material and Method

This work is approved by the ethic committee of Vichaiyut hospital and Vichaiyut Medical Center. Associated Professor Doctor Prapote Clongsusuek who is the director of this institute, acting as a chairman of ethic committee.

Period of the retrospective study

January 2008 to February 2010.

Patients

One hundred and forty nine grade II proven adult DHF were divided into 3 groups according to treatment modality defined by responsible clinicians.

Group I 59 patients received full dose of dexamethasone 4 mg intravenously every 6 hours continuously for 2-3 days.

Group II 61 patients received intermittent intravenous dexamethasone 4 milligram only at episode of fever.

Group III 29 patients did not received corticosteroid therapy.

Investigations

History and physical examinations were completely taken in every patient. DHF was confirmed by positive N_1SAg, dengue IgM antibody or positive PCR for dengue virus. Complete blood count was performed daily in every case. Liver function tests consisted of SGOT, SGPT, GGT, albumin, globulin, alkaline phosphatase and bilirubin were done on admission and at interval afterwards. Other blood tests including blood urea nitrogen and creatinine were performed on admission and were repeated as indicated.

End points to measure the benefit of adjunctive corticosteroid therapy

1. Reduction in severity of thrombocytopenia.
2. Changes in severity of hepatic impairment.
3. The length of illness as measured by the days of fever.
4. Length of hospital days.

Data analysis

Data are presented as the mean (range) for continuous variables or as a number (percentage) of patients for categorical variables.

Test different among the three groups of grade II DHF patients of continuous variables were performed using ANOVA or Kruskal Wallis test and multiple comparison by Bonferroni adjustment.

A p-value of less than 0.05 was considered to be significant difference.

Results

The clinical presentations of the patients were quite similar in all 3 groups. Mean age was between

36.7, 31.1 and 33.3 years respectively. Male ware predominant in all 3 groups (ratio 33:26, 31:30, 17:12 respectively). Symptoms and signs namely GI dysfunction, myalgia, headache, upper respiratory tract infection, mild bleeding, abdominal pain, hepatomegaly, with mild rising of SGOT/SGPT were quite similar in all 3 groups. It should be noted that the incidence of GI dysfunction was most frequently found in 57.6, 59 and 65.5 percents respectively. Table 1 showed the end points of laboratory findings to see the benefit of adjunctive corticosteroid therapy. It was found that there was no difference in term of the severity of thrombocytopenia and liver impairment as indicated by maximum SGOT and SGPT in the 3 groups. However, it should be noted that SGPT of over 500 units were more common in group II (6 cases) compared to 2 cases in group I and none in group III.

In the group I who received continuous short course high dose dexamethasone, the number of patients who were admitted on the 1st, 2nd, 3rd, 4th and 5th day of fever were 5, 8, 18, 14 and 8 cases respectively. The effectiveness of dexamethasone I.V. on the fever was shown. The fever came down within one day in 43 cases (73%). Among these 43 cases, 35 cases had high fever within 4 days of illness.

Table 2 showed the benefit of adjunctive corticosteroid therapy in adult grade II DHF patients. It showed that in the group I who received full dose continuous-short course of intravenous dexamethasone had significant shorter total day of fever (4.6 days) and the length of hospital days (3.71 days) as compared to group 2 and group 3 the total days of fever were longer at 5.8 days and 6.03 days and the length of hospital days were 5.19 day and 4.58 days respectively ($p < 0.05$).

Discussion

The benefit of using adjunctive corticosteroid therapy mostly in DHF children has long been a subject of controversy. In mild to moderate DHF children many studies did not show the benefit in using adjunctive corticosteroid therapy. In the present study the authors use additional different parameter to evaluate the benefit of adjunctive corticosteroid therapy. In the present study, the authors found that there was no benefit in term of improving thrombocytopenia or severe hepatitis. These finding agrees with previous study[9]. However, the authors have demonstrated other important benefit that is the shortening of the day of fever and the length of hospital days. These findings supported the result of

Table 1. Degree of thrombocytopenia and hepatic dysfunctions compared among the three groups of 149 adult grade II DHF patients

Findings mean (range)	Gr. 1 $(59)^+$	Gr. 2 $(61)^+$	Gr. 3 $(29)^+$
Lowest platelets/mm^3 x $10^3/mm^3$	53.9 (8-200)	51.9 (3-174)	55.5 (9-135)
Maximum SGOT units	177.8 (19-1,037)	180.9 (15-830)	173.1 (23-654)
Maximum SGPT units	153.3 (15-569)	171.4 (13-815)	108.5 (17-433)
SGPT > 500 units (cases)	2	6	0

$(\ )^+$ = number of cases
Gr. 1 = received continuous-short course of I.V. dexamethasone
Gr. 2 = received intermittent I.V. dexamethasone only at febrile episode
Gr. 3 = no corticosteroid

Table 2. Outcome of adjunctive corticosteroid Rx in grade II adult DHF patients

Findings	Group 1 59 cases	Group 2 61 cases	Group 3 29 cases
Total day of fever, mean (range)	4.60* (2-8)	5.80 (3-8)	6.03 (4-9)
Length of hospital days, mean (range)	3.71* (1-7)	5.19 (2-9)	4.58 (2-8)

* $p < 0.05$ by ANOVA and multiple comparison: Bonferroni
Group 1 = received continuous-short course of I.V. dexamethasone
Group 2 = received intermittent I.V. dexamethasone only at febrile episode
Group 3 = no corticosteroid

previous study by Punygupta in 2009[8]. These findings are benefit for the patients. None of our cases had complications from using full dose-short course corticosteroid. The benefit of using continuous short course I.V. dexamethasone as adjunctive therapy in adult DHF patients should be brought to the consideration. The further prospective study should be performed in order to confirm the result of this study and to gain more knowledge of the conjunctive corticosteroid therapy in non-shock adult DHF patients.

Potential conflicts of interest

None.

References

1. Nimmannitya S. Clinical spectrum and management of dengue haemorrhagic fever. Southeast Asian J Trop Med Public Health 1987; 18: 392-7.
2. Srichaikul T, Nimmannitya S. Haematology in dengue and dengue haemorrhagic fever. Baillieres Best Pract Res Clin Haematol 2000; 13: 261-76.
3. Halstead SB. Dengue: hematologic aspects. Semin Hematol 1982; 19: 116-31.
4. Srichaikul T, Punyagupta S, Nitiyanant P, Alkarawong K. Disseminated intravascular coagulation in adult Dengue haemorrhagic fever: Report of three cases. Southeast Asian J Trop Med Public Health 1975; 6: 106-14.
5. Srichaikul T, Punyagupta S, Kanchanapoom T, Chanokovat C, Likittanasombat K, Leelasiri A. Hemophagocytic syndrome in Dengue hemorrhagic fever with severe multiorgan complications. J Med Assoc Thai 2008; 91: 104-9.
6. Rongrungruang Y, Leelarasamee A. Characteristics and outcomes of adult patients with symptomatic dengue virus infections. J Infect Dis Antimicrob Agents 2001; 18: 19-23.
7. Ungchusak K. Situation and trend of dengue virus infection in Thailand. In: Pancharoen C, Kulwichit W, Tantawichien T, Thisyakorn U, editors. Text book of dengue hemorrhagic fever. Bangkok: Pantagon Advertising; 2003: 11-4.
8. Punyagupta S. Dengue hemorrhagic fever in adults, an emerging problem in Thailand: a retrospective study of 75 adult dengue infection in 2007. J Infect Dis Antimicrob Agents 2009; 26: 1-5.
9. Prasad KPR, Alahakoon DGS, Gunawardane JN. Effect of prednisolone during defervescence in dengue haemorrhagic fever: an open label controlled study. Galle Med J 2008; 13: 18-21.
10. Rajapakse S, Ranasinghe C, Rodrigo C. Corticosteroid therapy in dengue infection-opinions of junior doctors. J Glob Infect Dis 2010; 2: 199-200.
11. Aberdein J, Singer M. Clinical review: a systematic review of corticosteroid use in infections. Crit Care 2006; 10: 203.
12. Srichaikul T. Dengue hemorrhagic fever in adult, an unusual severe complications, an urgent problem need serious attention and proper management. Thai J Hematol Transfus Med 2010; 20: 303-8.

ผลการศึกษาการใช้ adjunctive corticosteroid รักษาผู้ป่วยผู้ใหญ่ไข้เลือดออก grade II 149 คน: วิเคราะห์ระหว่าง เดือนมกราคม พ.ศ. 2551 ถึง กุมภาพันธ์ พ.ศ. 2553

ถนอมศรี ศรีชัยกุล, สมพนธ์ บุณยคุปต์, ลัดดา สรคุณพิพิธกุล, อุมาพร อุดมทรัพยากุล

ภูมิหลัง: จากประสบการณ์ของผู้นิพนธ์พบว่า ผู้ป่วยไข้เลือดออกผู้ใหญ่ซึ่งมีภาวะแทรกซ้อนหนัก มี multiorgan failure และ hemophagocytic syndrome สามารถรอดชีวิตได้โดยการรักษาด้วย corticosteroid ขนาดสูง และ intravenous immunoglobulin G ทำให้ต้องการศึกษาการใช้ corticosteroid ร่วมรักษาผู้ป่วยผู้ใหญ่ไข้เลือดออก grade II จะได้ประโยชน์มากขึ้นหรือไม่

วัตถุประสงค์: เพื่อศึกษาว่าการใช้ dexamethasone ฉีดเข้าทางหลอดเลือดดำในขนาด 4 มิลลิกรัมทุก 6 ชั่วโมง เป็นเวลา 2-3 วัน จะช่วยให้ได้ประโยชน์มากขึ้นกับผู้ป่วย ผู้ใหญ่ไข้เลือดออก grade II หรือไม่

วัสดุและวิธีการ: เป็นการศึกษาย้อนหลังในผู้ป่วยไข้เลือดออกผู้ใหญ่ grade II 149 คน ระหว่างมกราคม พ.ศ. 2551 ถึงกุมภาพันธ์ พ.ศ. 2553 โดยแบ่งผู้ป่วยเป็น 3 กลุ่ม ตามการรักษาที่แตกต่างกันตามความต้องการแพทย์ผู้รักษา กลุ่มที่ 1 มี 59 คน ได้รับ dexamethasone 4 มิลลิกรัมทุก 6 ชั่วโมง เป็นเวลาต่อเนื่อง 2-3 วัน กลุ่มที่ 2 มี 61 คน ได้รับ dexamethasone 4 มิลลิกรัม เข้าหลอดเลือดดำเฉพาะเวลามีไข้ และกลุ่มที่ 3 มี 29 คน ไม่ได้รับ corticosteroid ผู้ป่วยทั้ง 149 ราย ได้รับการตรวจร่างกาย ซักประวัติ บันทึก เพศ อายุ และ investigations ทางเลือด, ตับ และ ไต เหมือนกัน ปรากฏว่ามีความหนักเบาในอาการของโรค เพศ อายุ คล้ายคลึงกันทั้ง 3 กลุ่ม

การวัดผลโดยใช้ปัจจัย 4 อย่าง คือ 1) ความรุนแรงของเกล็ดเลือดต่ำ 2) ความรุนแรงของภาวะตับเสียหน้าที่ 3) ระยะเวลาที่เป็นโรควัดด้วยจำนวนวันที่มีไข้ 4) ระยะเวลาที่อยู่ในโรงพยาบาล

ผลการศึกษา: ปรากฏว่าการใช้ corticosteroid ร่วมรักษาผู้ป่วยไข้เลือดออกผู้ใหญ่ไม่ทำให้ความรุนแรงของภาวะเกล็ดเลือดต่ำและตับเสียหน้าที่เปลี่ยนแปลง อย่างไรก็ตาม ระยะเวลาที่เป็นโรคไข้เลือดออกวัดโดยจำนวนวันที่มีไข้สูงและมีอาการ และระยะเวลาที่อยู่ในโรงพยาบาลสั้นลงอย่างชัดเจนคือ 4.6 วัน และ 3.7 วัน ตามลำดับ ในขณะที่กลุ่มที่ 2 และกลุ่มที่ 3 มีระยะเวลาที่มีไข้สูงนานกว่าคือ 5.8 วัน และ 6.01 วัน และระยะเวลาที่อยู่ในโรงพยาบาลนานกว่าคือ 5.19 วัน และ 4.5 วัน ตามลำดับ ($p < 0.05$)

สรุป: การใช้ dexamethasone ขนาดสูงในระยะสั้น ฉีดเข้าหลอดเลือดดำในผู้ป่วยผู้ใหญ่ไข้เลือดออก grade II ช่วยทำให้ระยะเวลาของโรคและระยะเวลาที่อยู่ในโรงพยาบาลสั้นลง ซึ่งเป็นประโยชน์ต่อผู้ป่วย