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*International Journal of Current Research*
*Vol. 9, Issue, 10, pp.59368-59372, October, 2017*

**INTERNATIONAL JOURNAL OF CURRENT RESEARCH**

**ISSN: 0975-833X**

## RESEARCH ARTICLE

# EFFECT OF THE METHYLPREDNISOLONE IN THE PROGRESSION OF DENGUE WITH WARNING SIGNS. A CLINICAL TRIAL

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**ARTICLE INFO**

*Article History:*
Received 10th July, 2017
Received in revised form
11th August, 2017
Accepted 18th September, 2017
Published online 31st October, 2017

*Key words:*

Dengue, Methylprednisolone, Mexico.

**ABSTRACT**

**Aims and Objective:**The impact of dengue on the communities affected largely depends on the presence of complicated cases requiring hospitalization and special care. The aim of this study was to evaluate the effect of a rapid intravenous infusion of methylprednisolone (MPDN) on mortality, complications, days of hospital stay, and recovery from thrombocytopenia in patients with type B dengue according WHO criteria (with warning signs) during an epidemic outbreak in Colima, Mexico.

**Materials and Methods:** A random controlled clinical trial was conducted in which 10 patients received MPDN and 20 controls received saline solution as a placebo.

**Results:** The mean hospital stay was 1.2 fewer days in the group treated with MPDN than in the control group ($p<0.02$), the recovery speed of pulse pressure was faster in the MPDN group ($p = 0.03$), and there were no differences in the platelet recovery rate or inthe appearance of complications or deaths.

**Conclusions:** MPDN can be useful in the management of patients with dengue with warning signs and possibly in patients with severe forms reducing the hospital stay without undesirable effects.

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**Citation*:* Dr. Francisco Espinoza- Gómez, José Conrado Aréchiga Ramírez, José Hugo Sánchez Gómez, Dr. Oscar Alberto Newton Sánchez, Dr. Iván Delgado Enciso, Dr. Alejandro Uriel Lopez Lemus and Dr. Fabián Rojas-Larios. 2017**. "Effect of the methylprednisolone in the progression of dengue with warning signs. A clinical trial", *International Journal of Current Research*, 9, (10), 59368-59372.

## INTRODUCTION

Dengue is the viral vector-borne disease with the greatest social impact that is largely derived from the high attack rates during epidemics. There is an abrupt increase in demand in relation to hospital services and days of disability (Shepard, *et al,* 2011), but perhaps thegreatest damage caused by the diseaseis that resulting from its complicated cases and deaths. Even though the frequency of these severe forms and mortality attributable to dengue is very low, the direct and indirect economic costs and the DALYs lost represent a social burden that could lead topolitical conflicts and uncertainty in the governability of the affected regions (Mendoza- Cano*, et al*, 2017). This is why, apart from the implementation of preventive measures, such as vector mosquito control (especially *Aedesaegypti*L), the optimization of the medical management of patients with dengue is the object of continuous review and updating.

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Although there is not yet a specific medical treatment regimen for the disease, there are numerous venues of research for antiviral agents (Vere Hodge, 2015), algorithms for managing the cases in endemic zones, such as the DENCO guidelines (WHO, 2009), regimens for fluid replacement (Wills, *et al* 2005), and optimization in the use of blood products, such as platelets and blood. In this framework, a line that has received special attention for many years is the use of anti-inflammatory agents, particularly steroids, which could alter the outcome of complicated cases of dengue (Min, *et al*, 1975). Considering that the pathophysiology of severe dengue is largely attributable to the triggering of inflammatory cascades, whether through the mechanism of increased antigenic uptake (Morens, 1994) in subjectspreviously sensitized to different serotypes than the one affecting the individual, or through the direct effect of certain strains of the virus that directly stimulate the massive release of kinins and other mediators of systemic inflammation (Avirutnan, 2006). The fact that medications, such as corticoids, block these processes at various levels is a reasonable justification forthe continued exploration of their efficacy on the progression of dengue. A

critical point is the time at which the medication is applied, given that it should be administered at a stage in which there are warning signs (phase B of the DENCO guidelines), and not necessarily indicators of severity, or phase C, which is when these medications have been tested (Premaratna, *et al*. 2011). Another critical point is the type of corticoid used and the length of time it is administered. In this respect, the regimen proposed for the management of septic shock, as well as in cases of acute dengue myocarditis with MPDN in short regimes (Hopkins, 1974, Premaratna, *et al*. 2012) could be an interesting alternative management for severe dengue. Recent systematic reviews have concluded that the use of corticosteroids, particularly methylprednisolone, offers no advantages in relation to the progression of severe cases of dengue, and that given its potential complications, this management should be proscribed until more information is available. They point out that there are very few adequately randomized clinical trials, and its use has been limited to the management of critical-stage patients (Panpanich, *et al,* 2006).

In view of the fact that it is not easy to have a sufficient number of patients with confirmed dengue with warning signsover a short period of time, the present trial was conducted during the 2009-2010 epidemic outbreak in the city of Colima, capital of the State of Colima, Mexico, that affected approximately 7,300 persons with an incidence rate of 14:1,000 persons per month. Of those patients, a total of 137 were hospitalized in the Hospital Regional Universitario de Colima during that period, due to the presence of signs of alarm or frank severe dengue described in the DENCO 2009 guidelines (WHO, 2009). The majority of them were hospitalized for drastic reductions in their platelet counts, others had vomiting and abdominal pain, bleeding, reduction of pulse pressure, and some with marked shock. Among all these patients therewere3 fatal cases due to multiple organ failure.

## MATERIALS AND METHODS

A randomized, double-blind clinical trial was conducted that included 10 patients randomly assigned to the treatment group and 10 to the control group. Another 10 patients did not agree to fully participate in the study, but only to receive saline solutions, and they were included as the non-blinded control group. The selected patients were between the ages of 16 and 75 years, without manifested comorbidity (diabetes mellitus, chronic hepatic injury, nephropathies, HIV/AIDS, active alcoholism, cancer) or have contraindication for the use of steroids. All the selected patients underwent initial rapid NS1 test through immunochromatography, later confirmed by IgM with ELISA test, or RT-PCRin those with less than 6 days of evolution (Ayers, *et al*, 2006). All were hospitalized for dengue with warning signs diagnosed by medical personnel not connected with the project. Patients that were admitted with severe dengue (phase C) were excluded. None of the patients abandoned the study. The study was performed during July 2009 to November 2010.

The dependent variable was divided into the following components: a) death; b) days of hospital stay; c) speed of recovery from thrombocytopenia or increased platelet index, defined as the difference in the platelet total from two consecutive days, divided into 24 hours from the maximum platelet descent and expressed as platelets per hour, or better: the nadir of the platelet count; d) development of severe complications; e) speed of pulse pressure recovery in patients that had low blood pressure, expressed in days; and f) blood product requirements (platelets or red blood cells). The independent or intervention variable was the intravenous application of methylprednisolone (MPDN) or intravenous placebo: the control group received an infusion of 250 ml saline solution at 0.9%, simulating the methylprednisolone infusion, for the days the patients were hospitalized. The experimental group received an infusion of MPDN (Solumedrol, labs. Upjohn®) at a dose of 1 mg/kg in 250 ml of saline solution at 0.9% every 24 hours for the days the patients were hospitalized.None of the researchers, patients, or nursesknew what treatment was being administereduntil the end of the study when the envelopes were opened;only the group that had signed statements of consent to receive intravenous fluids, but not medication, knew they were being given saline solution.

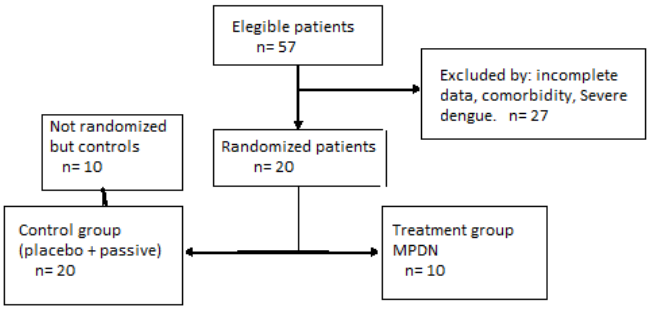



**Figure 1. Diagram that shows the flux in the management of patients**

The confusion variables included sex, age, and time of clinical symptom progression. Ethnicity and socioeconomic level were not considered, given that the population attended to at the hospital is primarily made up of Mexican mestizos with a lower middle socioeconomic level.In order to test hypothesis we compared means of continuous variables after analysis of normal distribution throughout Kolmogorov Smirnoff tests (platelet counts, blood pressure, days of hospital stay). No nominal comparisons were made because there were no deaths or severe complications in any group. No intention to treat was calculated since we have not desertions.Randomization numbers and statistical analysis were done with the SSPS.2 program. The project was submitted to the bioethics committees of the Hospital Regional Universitario de Colima (ref HRU 2009/01/03) and signed statements of informed consent were obtained from the 32 patients that participated in the study.

## RESULTS

Table 1 shows the demographic characteristics of the patients included the study. There were a total of 30 patients, 10 of them in the treatment group and 20 in the control group. Ten of the patients in the control group accepted to be non-randomized controls. The reason for hospital discharge was the total recovery of symptoms, of platelet counts and blood pressure. The patients in the treatment group had 1.2 fewer days in the hospital than those in the control group. The difference was small, but statistically significant. With respect to the speed of recovery from the thrombocytopenia, graph 3 shows that there were no significant differences between the groups.

**Table 1. Demographic variables in both groups**

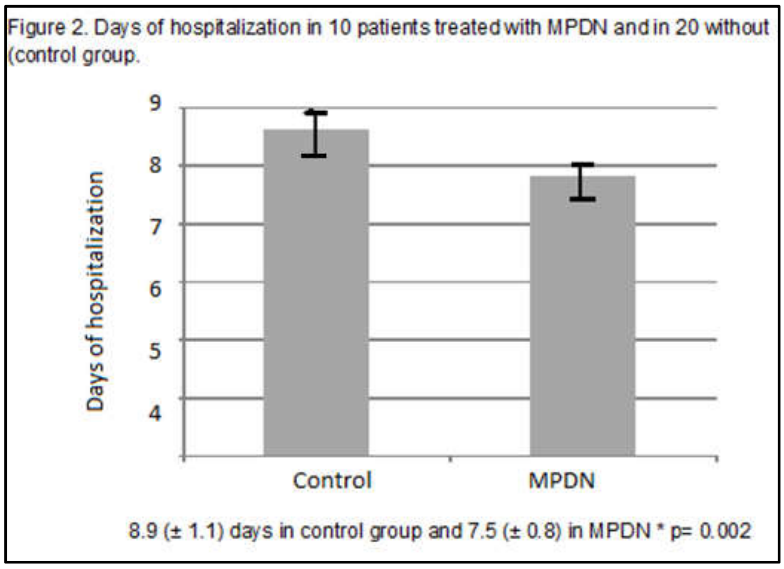
| Variable | Grup 1: control n=20. | Grupo 2: experimental n=12. | p value* |
|---|---|---|---|
| Age | 28.4 ± 13 | 27.5 ± 9.3 | 0.85 |
| Male | 12 | 5 | 0.35 |
| Female | 8 | 7 | |
| IgG positive | 8 | 7 | 0.67 |
| Time of evolution (days) | 6.2 ± 1.5 | 5.8 ± 1.2 | 0.7 |

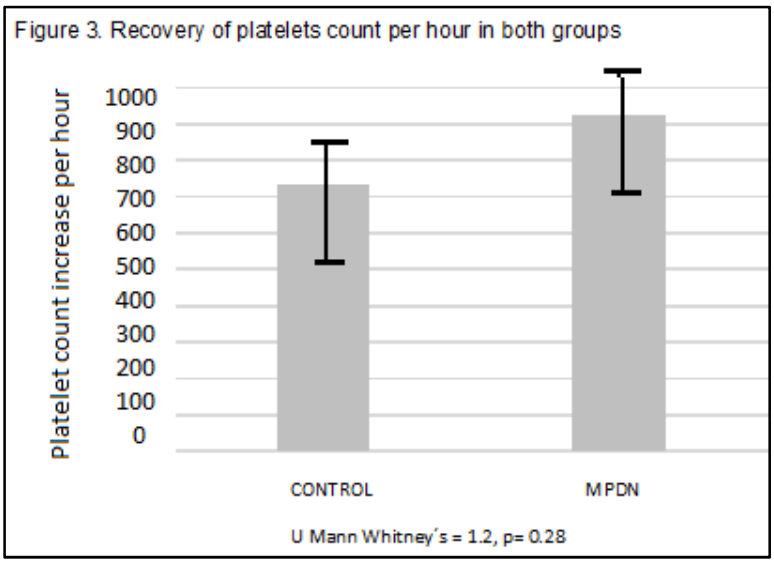
* U Mann Whitney for continuous numeric scales; $\square^2$ test for dichotomic nominal variables.

**Table 2.Clinical characteristics at admission and discharge of both groups. All the patients were classified as having dengue with warning signs (type B)**

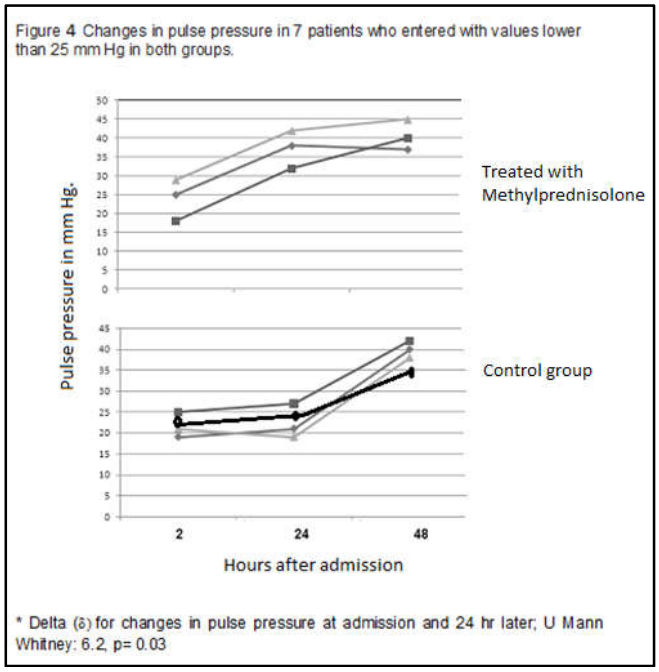
| Variable | Control Group n= 20 | | MPDN Group n= 10 | | *p** value |
|---|---|---|---|---|---|
| | Admittance | Discharge | Admittance | Discharge | |
| Abdominal pain | 5 | 1 | 5 | 0 | 0.72 |
| Vomit | 3 | 0 | 4 | 0 | 1 |
| Bleeding | 4 | 0 | 3 | 0 | 0.89 |
| Sensory alteration | 2 | 0 | 1 | 0 | 0.92 |
| Liver injury | 2 | 0 | 2 | 1 | 1 |
| Platelet count ($mm^3$) | 56,000 | 76,000 | 45,000 | 70,000 | 0.74 |
| Hematocrit (%) | 46 | 35 | 43 | 38 | 0.87 |
| Total Neutrophils | 5,200 | 8,200 | 4,300 | 9,000 | 0.65 |
| Median arterial pressure (mmHg) | 92.2 | 94.5 | 90.7 | 92.3 | 0.75 |
| Hospital stay (days) | 8,9 | | 7.5 | | 0.002 |
| Platelets transfusion | 0 | | 0 | | 1 |
| Red blood cell transfusion | 1 | | 1 | | 0.97 |

* U Mann Whitney´s test was done for continuous variables and $\square^2$ for dichotomic nominal variables. Since the multivariate analysis showed no significant associations, only the variable hospital stay was considered significant.



The changes in pulse pressure observed during the first 48 hours after admission in 7 patients with pulse pressure ≤20 mm Hg (considered as predictor of shock in dengue patients, according Ranjit, *et al,* 2007), thispulse pressure had an immediate recovery after the first 24 hours after receiving the MPDNcompared with those in the control group, although in the next hours both groups recovered the pulse pressure up to 30 mm Hg after 48 hs as can be appreciated in Fig. 4.




In regard to the development or worsening of clinical symptoms, there were no cases in any group of progressive liver failure, bleeding, encephalopathy, or cardiopulmonary failure and there were no deaths registered in any of the groups. In general, all the patients wereable to continue with at-home management. It should be underlined that during the study period there were 6 other patients not included in the trial that developed severe forms and required intensive care; 3 of them died: one from fulminating liver injury and two from multiple organ failure. One patient that had sudden onset of acute respiratory distress syndrome (ARDS), with severe hypoxemia and a Kirby index of 124, received a regimen of MPDN and the acute respiratory symptoms were resolved in 24 h, with a total clinical, gasometric, and radiologic recovery in 8 days.

## DISCUSSION

First, it could be emphasized that the brief use of moderate doses of MPDN in patients with dengue with warning signs did not produce undesirable effects in relation to the control group, even though a longer follow-up would have to be conducted to see whether they presented with late complications such as hyperglycemia, hypokalemia, orsuperinfections. These findings coincide with previous reports that the use of corticosteroids in dengue does not appear to be as harmful as has been hypothesized for years (Premaratna, *et al*. 2012). In the present study the use of MPDN reduced hospital stay by a mean of one day, which does not seem to be a big difference, but if it is translated into a large-scale reproducible effect, it would imply considerable savings, especially in times of epidemics, when the demand for hospital beds is overwhelming.

The effect on the platelet curve was not as prominent as expected, but as the new DENCO2009 guidelines point out this parameter is becoming less essential in the decision to shorten or prolong hospital stay (WHO, 2009). The 7 patients that had reduced pulse pressure as a warning sign had hemodynamic recovery upon their release, but those treated with MPDN had a faster recovery than those in the control group. Although this finding was modestly statistically significant due to the small number of observations, it leads to the hypothesis that the use of steroids in phase B or C of dengue could shorten the time of low blood pressure, which, in turn, could prevent many of the severe complications than usually present with sudden onset in this disease. This would explain why the patient with ARDS that received MPDN had a rapid recovery. For many years steroids were indicated as part of the management of septic shock (Hopkins, 1974), but this fell into disuse due to the potential appearance of more complications and immunosuppression in the patient. However, in the case of dengue, in which bacterial invasion is not the direct causal event, but rather the inflammatory changes and endothelial alterations triggered by the virus or by kinins, it would seem recommendable to resume the use of fast acting steroids immediately before fatal complications develop, obviously under strict supervision inintensive care units. The perspective of the present analysis, as mentioned at the end of the study,is to continue studying more patients in both groups and to include more severe cases, such as those with bleeding, liver failure, encephalopathy, or cardiopulmonary failure. This trial should also be considered in children; they normally have an immunologic response different from that of adults. And of course, the entire concept is one of coadjuvant treatmentto current management, with volume replacement and the rational use of platelets in cases in which they are strictly necessary.

**Acknowledgements**

This project received financial support from the Ramón ÁlvarezBuylla Fund of theUniversidad de Colima. The authors wish to thank the Internal Medicine Department and the Nursing personnel of theHospital Regional Universitario de Colimafor their support. The authors declare that they have no conflict of interest with the pharmaceutical industry or any other institution.

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