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14. ABSTRACT

Dengue viral infection is prevalent throughout tropical and sub-tropical regions of the world. Disease presentation ranges from self-limited fever to life-threatening dengue hemorrhagic fever. This study assessed the use of near infrared spectroscopy (NIRS) measurements of muscle oxygen saturation (SmO2), muscle pH, and continuous arterial waveforms to predict which subjects would develop severe disease. Children ages 6 months to 15 years of age admitted to the hospital with suspected dengue were enrolled. Children were monitored daily for a variety of laboratory values and assessments of volume status in addition to waveform monitoring and NIRS. Results demonstrate that a cardiac reserve index calculated from arterial waveforms and to a less demonstrable extent, muscle pH and Sm02 correlated with fluid status and fluid resuscitation efforts. Further algorithm analysis, evolution of measurement technique and study of these tools in adults may provide useful information in the management of patients diagnosed with dengue virus infection.

15. SUBJECT TERMS

Dengue, severe dengue, dengue hemorrhagic fever, near-infrared spectroscopy, nexfin, compensatory reserve index, CRI, NIRS, arterial waveforms, non-invasive monitoring, shock

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Introduction

The funded work was a subset of assessments evaluated within a clinical trial that enrolled children between 6 months of age and less than 18 years of age admitted to the dengue unit of a Bangkok, Thailand, hospital with a suspected dengue infection. The purpose of the study was to determine the clinical, immunologic and virologic correlates that identify children who do not develop clinical evidence of shock; to characterize the pathophysiology of severe dengue illness before, during and after and acute shock; and to identify and quantify clinically useful markers of dengue disease outcome. In order to achieve these objectives, multiple physical exam signs and laboratory values were assessed including those funded by this grant, specifically, blood pressure and arterial wave forms measured by the Nexfin device to provide data for a Compensatory Reserve Index (CRI) and hematocrit, muscle pH and muscle oxygenation as measured by Near-Infrared Spectroscopy (NIRS).

Keywords

Dengue, severe dengue, dengue hemorrhagic fever, near-infrared spectroscopy, nexfin, compensatory reserve index, CRI, NIRS, arterial waveforms, non-invasive monitoring, shock, muscle pH, muscle oxygenation, heart rate variability

Overall Project Summary

'Clean' arterial waveforms have been successfully collected for retrospective analysis with the Compensatory Reserve Index (CRI) algorithm developed by the US Army Institute of Surgical Research (USAISR). Data have been analyzed from 107 additional patients over 5 consecutive days of hospital care (new method of data collection for this second iteration).

The preliminary analysis of CRI calculated from arterial waveforms of 4 DHF patients indicated that the algorithm provides a non-invasive method to continuously assess hemodynamic status and effectiveness of care in dengue patients.

Preparations are well underway for additional patient enrollment in the next iteration of our work, to be initiated at Kamphaeng Phet Provincial Hospital in Kamphaeng Phet, Thailand. This additional enrollment will have the benefit of adding adult patients to the current pediatric patient pool.

Dr. Jennifer Friedman (Brown University), the current statistical resource for the project and her post doc Sangshin Park have begun analysis of the latest set of dengue data Unfortunately, for this set of data (2012) only 28% of the NIRS data was collected on Fever Day -1, compared to 47% of the 2010 data set. Despite the larger n for the 2012 data set, it doesn't appear that we have the power to further our analysis of the prediction of hypovolemia and shock. We have data in response to treatment, so we are considering exploring the use of NIRS to assess the possibility of detecting fluid overload.

Arterial waveform analysis continues to be conducted by Vic at the Institute for Surgical Research by Victor Convertino. Near-infrared data from 2012 is being analyzed and results will be published when available.

Key Research Accomplishments

The CRI algorithm has been demonstrated to provide a non-invasive method to continuously assess hemodynamic status and effectiveness of care in dengue patients.

Infrared spectroscopy muscle pH and oxygenation measurement tract consistently with patient volume status and fluid resuscitation.

Conclusion

Use of the Nexfin device has demonstrated that it can be used to provide a non-invasive method to continuously assess hemodynamic status and effectiveness of care in dengue patients. Heart rate and heart rate variability however did not differ significantly between subjects with dengue fever and those with dengue hemorrhagic fever. In future work we will continue to evaluate the use of pulse wave forms to predict shock and will assess other instruments to measure arterial wave forms, i.e. pulsoximetry instead of blood pressure, and the further integration of data from vital signs into an increasing subtle and more accurate index.

Near Near-Infrared Spectroscopy (NIRS) assessment of muscle pH and muscle oxygenation correlated well with volume status and fluid resuscitation. An accurate hematocrit assessment algorithm however has not been demonstrated. Use of this measurement and further algorithm adjustment will continue.

Publications, Abstracts, and Presentations

Heart rate variability in patients being treated for dengue viral infection: new insights from mathematical correction of heart rate. Carter R 3rd, Hinojosa-Laborde C, Convertino VA. Front Physiol. 2014 Feb 25;5:46.

Preliminary evaluation of near infrared spectroscopy as
a method to detect plasma leakage inchildren with dengue hemorrhagic fever. Soller B, Srikiatkachorn A, Zou F, Rothman AL, Yoon IK, Gibbons RV, Kalayanarooj S, Thomas SJ, Green S.
BMC Infect Dis. 2014 Jul 17;14:396. doi: 10.1186/1471-2334-14-396

A manuscript entitled “Noninvasive Method for Fluid Resuscitation Monitoring in Dengue Hemorrhagic Fever: A Preliminary Report” is being submitted to the journal of Clinical Infectious Diseases.

A manuscript describing Heart Rate Variability in dengue virus infection is currently in development using additional patient data.

Inventions, Patents and Licenses

None.

Reportable Outcomes

Compensatory Reserve Index

Three laboratory Phase I clinical trials have been completed to support a 510(k) application for FDA approval of the first prototype Pulse Oximeter with the CRI algorithm and capability for real-time continuous collection of photoplethymographic (PPG) analog signals. An FDA-cleared marketable device is anticipated within the next year.

NIRS

NIRS is a noninvasive technique which can be used to assess tissue oxygenation in muscle tissue.
We are currently finalizing the design of the CareGuide 4100 which will use a lower cost disposable. The disposable used with the 3100 was too expensive for use in the dengue project. Instead, we placed the optics and electronics boards into a different case so we could supply lower cost disposables for the project. Going forward, we are creating a version of the 4100 that will be powered with line current and can use the same disposables as the CareGuide 4100 product. The new systems will display the results on an android tablet. The product for the dengue study will also benefit from the updated software which will eliminate the cumbersome calibration steps required prior to each patient use. This is expected to improve compliance when the sensor becomes detached during the night, since it will no longer require a specially trained research nurse to restart the system.

Other Achievements

None.

References

None.

Appendices

None.