Near-infrared spectroscopy technique to evaluate the effects of drugs in treating traumatic brain edema

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Abstract. The aim of this study was to evaluate the effects of several drugs in treating traumatic brain edema (TBE) following traumatic brain injury (TBI) using near-infrared spectroscopy (NIRs) technology. Rats with TBE models were given hypertonic saline (HS), mannitol and mannitol+HS respectively for different groups. Light scattering properties of rat’s local cortex was measured by NIRs within the wavelength range from 700 to 850 nm. TBE models were built in rats’ left brains. The scattering properties of the right and left target corresponding to the position of normal and TBE tissue were measured and recorded in vivo and real-time by a bifurcated needle probe. The brain water contents (BWC) were measured by the wet and dry weight method after injury and treatment hours 1, 6, 24, 72 and 120. A marked linear relationship was observed between reduced scattering coefficient ($\mu_s'$) and BWC. By recording $\mu_s'$ of rats’ brains, the entire progressions of effects of several drugs were observed. The result may suggest that the NIRs techniques have a potential for assessing effects in vivo and real-time on treatment of the brain injury.

1. Introduction

Trauma is the commonest cause of death in young people (aged <45 years) worldwide, and up to half the deaths are caused by traumatic brain injury (TBI) in the United States [1]. Traumatic brain edema (TBE) following TBI is defined as increased liquid content in brain substance. TBE leading to an expansion of brain volume has a crucial impact on morbidity and mortality as it increases intracranial pressure (ICP), impairs cerebral perfusion and oxygenation, and contributes to additional ischemic injuries. Dehydration therapy is the major way to the TBE treatment. Mannitol, a preferred dehydration agent, has been extensively used in clinical therapy. However, numerous studies on the
mannitol agent have recently revealed some adverse effects after repeating doses, including renal failure [2-8] and edema rebound phenomena[9-12]. Instead of mannitol, hypertonic saline (HS) solutions have been increasingly used as an attractive alternative in basic science and clinical studies [13-21]. Different administration routes, concentrations (2% to 23.4% NaCl) and doses were investigated in these studies. Therefore, it is necessary to establish an in vivo monitoring method to determine the therapeutic efficacy, and thus, to guide the treatment protocols in clinic.

Near infrared technique features some advantages in that it provides a relatively high temporal resolution, it is cheap to build, and is easily maintained. It has been used widely in the differentiation tissue types in recent years [22, 23]. It is known that near-infrared (NIR) light in the 700-850 nm wavelength range is special to tissues as light scattering is more prominent than light absorption. There is a significant difference in light-scattering properties between normal tissues and injured tissues due to their differences in anatomical substructure [24, 25]. In our previous work, a linear correlation between $\mu_s'$ and water content in rat brain tissues was found [26], which implied that $\mu_s'$ may serve as an indicator for the brain water content. In this study, an effort was made to develop NIR technology as an alternate method for monitor of brain trauma.

The aim of this study is to establish an innovative method to real time evaluate the therapeutic efficacy of dehydration agents treatments. The functional near infrared spectroscopy (fNIRs) was used to real time monitor the changes of reduced scattering coefficient $\mu_s'$ in rat brain tissues. Acute regional brain trauma was induced in Sprague-Dawley rats (SD) by Feeney’s apparatus. The effect of mannitol+ hypertonic saline (HS) treatment monitored by fNIRs was compared to that of commonly used mannitol agent and HS agent.

2. Materials and methods

2.1. Instruments and Methods

The fNIRs experimental system[26, 27] for optical parameter measurement consisted of a halogen light source (HL-2000, Ocean Optics Inc. Dunedin, FL), a bifurcated needle probe (600 μm o.d. with two single mode fibers of 100 μm), a USB optical spectrometer (USB2000, Ocean Optics Inc.) with wavelength grating from 340-1020nm, a rat brain stereotactic instrument (Jiangwan type1), a stepper power driver (MID-7604 National Instruments), a step motor and controller (PCI-7344) and a computer. Absorption coefficient ($\mu_a$), reducing scattering coefficient ($\mu_s'$), oxygen saturation(SO$_2$), oxygenated hemoglobin (HbO$_2$), deoxygenated hemoglobin (Hb), oxygenated hemoglobin total (HbTotal), cerebral blood flow (CBF) and cerebral blood volume (CBV) of tissue are continuously recorded with this fNIRs equipment [28, 29]. In brief, the wide band light was delivered by the deliver fiber inside the probe to the surface of the tissue, and the reflected spectrum was collected by another fiber inside the probe. The slope of the spectrum within 700–850nm was obtained by a fitting method. The reduced scattering coefficient ($\mu_s'$) was calculated based on the empirical equations, which were deduced by extensive simulation experiment of the NIRs system [29]. Comparing the $\mu_s'$ measurement of NIRs to that of Oximeter, the $\mu_s'$ on 690nm wavelength by NIRs for the specific probe (0.2mm diameter) was proven to be more accurate. The empirical equation of $\mu_s'$ on 690nm is displayed as the following, which was used in this study.
\[ \mu'_{690} = 4.5203 \exp(-0.3241 \times \text{slope}) \] (1)

2.2. Experimental animals

One hundred Sprague-Dawley rats (half male and half female, weight about 230-280g, the Medical Animal Center of Southeast University, Nanjing, P.R.China) were randomly divided into 5 groups \((n=20\) for each group). Control group was normal rats for control experiment. Traumatic group was traumatic model without treatment. Treatment group (TGroup) 1, 2 and 3 were traumatic models with different treatment of 2g/kg mannitol for TGroup 1, 7.5% HS for TGroup 2 and 1g/kg mannitol+7.5% HS for Tgroup 3 after trauma, respectively, as listed in Table 1. Each group was divided into five subgroups \((n=4)\) for brain water contents measurement at different time points of 1 hour \((h)\), 6h, 24h, 72h and 120h, as shown in Table 1. The traumatic model rats were achieved by hitting the left epidural in a preset windows by Feeney's free-falling body against devices [30] (30g heavy falling from the height of 20cm above the rat brain to produce an impact of 600g \(\times\) cm), causing a focal cerebral contusion in the left parietal lobe. Apnea for a few seconds indicated the success of inducing a brain injury model. On right sides, a burr hole were performed with 1 mm dental drill, but were not traumatic. Rats in the control group only had a bone window drilled at the same position (left and right sides), but were not injured. All rats were kept in their habitual environment until the day of the experiment. All experiments were carried out in compliance with the Animal Management Rules of the Ministry of Health of the People's Republic of China (document no. 55, 2001), and the guidelines for the Care and Use of Laboratory Animals of Southeast University Medical Center.

Table 1. Protocol of animal model \((n=100)\).

| Groups                | Subgroups                                      |
|-----------------------|------------------------------------------------|
| Control group         | Time                                           |
|                       | 1h    6h  24h  72h  120h                       |
| Traumatic group       | Control, not injured                           |
| Treatment group 1 (TGroup 1) | Traumatic model with 2g/kg mannitol treatment |
| Treatment group 2 (TGroup 2) | Traumatic model with 7.5% HS treatment       |
| Treatment group 3 (TGroup 3) | Traumatic model with 1g/kg mannitol +7.5% HS treatment |

2.3. Near-infrared Spectroscopy (NIRS) monitoring in real-time

All rats were kept in their habitual environment until the day of the experiment. The subject rats were anesthetized with 1% Nembutal (40mg/kg) and mounted into the stereotactic frame in a flat-skull position. After the skull was exposed, the dual-fiber probe was installed on stereotaxic frame [28, 29]. The step motor drove the fiber probe deep into the skull at an interval of 0.7mm until it reached the surface of the dura mater. The reduced scattering coefficient \((\mu_s')\) of the cortex was continuously monitored and recorded \((2Hz\) in frequency, \(10min)\) by fNIRs system. After 10min of data acquisition, a pause was given for tail vein injection, viz. 2g/kg mannitol for TGroup 1, 7.5% HS for TGroup 2, 1g/kg mannitol +7.5% HS for TGroup 3 and saline for the control group. Then measurements were
resumed until the end of the dehydration process (about 4-5 hours). Data on both the injured (left) and contralateral (right) sides were obtained. In addition, rats in each subgroup were monitored by fNIRs at different time points (1h, 6h, 24h, 72h and 120h). Control group was monitored following the same procedures on the ipsilateral and contralateral sides, respectively.

2.4. Measurement of brain water content

At the end of the designated monitoring time points (1h, 6h, 24h, 72h and 120h), all rats were sacrificed by decapitation under deep pentobarbital anesthesia. And the brains were removed immediately. Cortex tissue (about 1 mm3 in volume) was removed around the injury focus and the corresponding position in the contralateral side; The dissected cortex tissue was firstly placed on the electronic analytical balance to measure the wet weight (WW) and then placed in an oven at 100°C for 72h until the weight was constant (a difference of less than 0.2mg in twice weighting) to measure the dry weight (DW). Brain water content was calculated according to the following equation:

\[
\left(\frac{\text{WW} - \text{DW}}{\text{WW}}\right) \times 100\%.
\]

2.5. Statistical analysis

All statistical analysis on the data of \(\mu_s'\) and brain water contents were analyzed by SPSS statistical software package (SPSS 13.0 for Windows) and a t-test was performed. Group data were presented as mean ± S.D. A value of \(P < 0.05\) was considered statistically significant. The correlation of \(\mu_s'\) and brain water contents were analyzed by linear forward regression.

3. Results

3.1. Rat cortex reduced scattering coefficient \(\mu_s'\) (cm\(^{-1}\)) at different time points

![Figure 1. \(\mu_s'\)–versus–time curves.](image)

Rats reduced scattering coefficient \(\mu_s'\) values were recorded at different time points. The time profiles were illustrated in Figure 1. For the rats in traumatic group (with traumatic model, but without treatment), rat cortex reduced scattering coefficient \(\mu_s'\) values in the traumatic side increased at about 60 minutes after injury and significant difference was observed at about 6 hours after injury compared to control group \((p<0.01)\), the \(\mu_s'\) values were 3.95 cm\(^{-1}\) higher than that at 72 hours after
injury, the $\mu_s'$ values achieved a peak value of 18.12 cm$^{-1}$, which was higher than control group ($p<0.01$): 120 hours after injury, the $\mu_s'$ values dropped slightly but were higher than control group ($p<0.01$).

The cortex $\mu_s'$ values of each treatment group at 1 hour, 24 hours, 72 hours after injury were significantly lower than traumatic group ($p<0.01$) at 1 hour, 24 hours, 72 hours after injury.

$\mu_s'$ values of traumatic group and all treatment groups were higher on traumatic side than that on contralateral side, as shown clearly in Figure 1.

3.2. The brain water content

Table 2 shows the changes of brain water content (BWC) in different groups at different time points. BWC around the injury focus of traumatic group and all treatment groups increased compared with that of control group at about 60 minutes after injury. But no statistically significant differences were observed. BWC of traumatic group and all treatment groups was significantly higher than that of control group at about 6 hours after injury ($p<0.01$). Then BWC of traumatic group increased rapidly and reached peak edema (82.43±0.81%) at 72 hours after injury ($p<0.01$). In traumatic group, edema at about 120 hours after injury was lower than that at 72 hours after injury. BWC of traumatic group was still significantly higher than that of control group ($p<0.01$) at about 120 hours after injury. BWC of contralateral side in traumatic group was also slightly increased from 1 to 120 hours after injury. But only at the peak of edema (24 hours to 72 hours after injury), the significant differences ($p<0.01$) compared with control group were observed. The increased rate of BWC on contralateral side of traumatic group was far less than that on traumatic side. BWC on contralateral side of traumatic group returned to normal at 120 hours after injury.

Table 2. Rat brain water content at different time in different groups (mean ± S.D., n=5).

| Times | Control | Traumatic | TGroup 1 | TGroup 2 | TGroup 3 |
|-------|---------|-----------|----------|----------|---------|
|       | Ipsilateral side | Contralateral side | Ipsilateral side | Contralateral side | Ipsilateral side |
| 1h    | 77.61±0.37 | 77.60±0.32 | 78.08±0.53 | 78.72±0.49 | 77.16±0.44 |
| 6h    | 77.49±0.41 | 77.62±0.39 | 79.25±0.56 | 78.10±0.58 | 78.61±0.53 |
| 24h   | 77.56±0.47 | 77.43±0.36 | 81.00±0.57 | 78.42±0.43 | 80.12±0.61 |
| 72h   | 77.39±0.53 | 77.47±0.41 | 82.10±0.59 | 79.20±0.66 | 79.20±0.66 |
| 120h  | 77.46±0.40 | 77.52±0.36 | 82.43±0.81 | 79.42±0.79 | 79.22±0.57 |

* $p<0.05$, ** $p<0.01$: traumatic group and TGroup 1,2,3 vs. control group; $\dagger p<0.01$: TGroup 1,2,3 vs. traumatic group; $\ddagger p<0.05$, $\ddagger\ddagger p<0.01$: traumatic side vs. contralateral side; $\ddagger p<0.01$: TGroup 1 vs. TGroup 2; $^\dagger p<0.01$: TGroup 3 vs. TGroup 1 or 2

There was no significant difference on traumatic side between BWC of TGroup 1, 3 and BWC of traumatic group at 1 hour after injury. BWC on traumatic side of TGroup 2 were significantly lower than that of traumatic group ($p<0.01$). There was no difference on traumatic side between BWC of all treatment groups and traumatic group at 6 hours after injury. At the peak of edema (24 hours to 72 hours after injury), traumatic side BWC of all treatment groups was significantly lower than that of traumatic group ($p<0.01$). BWC of TGroup 1 was significantly different (higher) from traumatic group ($p<0.01$) at 120 hours after injury. BWC of TGroup 2 was higher than that of traumatic group at 120 hours after injury. But no statistically significant differences were observed. For the rats of TGroup 3, no statistically significant
differences were observed compared with TGroup 1, 2 at any time point except 120 hours after injury.

Contralateral side BWC of all treatment groups was significantly lower than that of traumatic group at 1h, 24h, 72h and 120h after injury.

3.3. Linear regression analysis

As shown in figure 2, two parameters, the average reduced scattering coefficient ($\mu'_s$) of rats’ local cerebral cortex and BWC of this region at different observation points, were analyzed by linear regression. We obtained the fundamental equations of functions as following,

$$\mu'_s = 1.5494 \times (\text{BWC} \times 100) - 110.54 \quad (2)$$

$R^2 = 0.8709, p<0.001$, a marked linear relationship was observed between the two parameters, which is similar to previous literature [27].

3.4. The reduced scattering coefficient ($\mu'_s$) measured by fNIRs

In order to compare the treatment efficacy in different treatment groups, the $\mu'_s$ values on traumatic sides on the representative rats in TGroup 1,2 and 3 were plotted, respectively, as shown in Figure 3. Curves 1, 2 and 3 represented the $\mu'_s$ value of TGroup 1 rat, TGroup 2 rat and TGroup 3 rat on traumatic side, respectively. A noticeable downward trend were observed on Curves 1, 2 and 3 just 20, 14 and 30 minutes after the dehydrating agent injection ($p<0.05$); the $\mu'_s$ value on both the treatment groups reached a relative steady phase at 60 minutes, 40 minutes and 70 minutes after injection of mannitol, HS and mannitol + HS, respectively. The steady state maintained about 2.5 hours. Finally, Curves 1, 2 and 3 rose back to pre-injection levels at about 5 hours post-injection, as shown in Figure 3. The recovery rate for TGroup 2 (HS treatment) is slower than that of mannitol and mannitol + HS. The time profile formed a “U-shape” curve.

The time profiles of $\mu'_s$ on treatment groups and control group were compared in Figure 4. Rat brain cortex $\mu'_s$ values of control group had no significant change before and after the administration of saline (curve 1). The $\mu'_s$ values in TGroup 1, 2 and 3 decreased after administration of different dehydrating agent. Compared to control group, the significant differences of $\mu'_s$ values occurred at about 20 minutes for TGroup 1, at about 14 minutes for TGroup 2 and about 30 minutes for TGroup 3, respectively ($p<0.05$).
60 minutes after administration of mannitol, $\mu_s'$ reached a relative steady status with a maximum reduction of 2.89% (curve 2). At 36 minutes after administration of HS, the $\mu_s'$ reached a relative steady phase with maximum decline of 3.43% (curve 3). At 70 minutes after administration of mannitol + HS they reached the relative steady phase with the maximum decline of 2.78% (curve 4).

**Figure 3.** In vivo and real-time $\mu_s'$ Determined by NIR system on the rats of treatment groups.

**Figure 4.** Comparison of $\mu_s'$ changes on different group rats of control group and TGroup1,2,3.

4. Discussion

In previous studies on brain trauma, typical means of evaluating edema following brain injury include the dry/wet weight method and the special proportion calculation method [31]. These methods displayed many disadvantages, such as sacrifice of animals, error in weight measurement and so on. To avoid these shortcoming, a special bifurcated needle-shaped functional near infrared probe was used in this study to in vivo and real-time measure the reduced scattering coefficient ($\mu_s'$) in rats’ local cerebral cortex.

The $\mu_s'$ values in traumatic side of TGroup1, 2 and 3 were significantly lower than that of traumatic group at about 1 hour after injury, ($p < 0.01$), whereas no significant difference in BWC was observed during the same period. This result indicated that $\mu_s'$ values were more sensitive to change of brain edema than BWC. Brain edema could be predicted earlier by using $\mu_s'$ values.

Usually, the edema is observed to reach the peak 24~72 hours after injury. For rats in TGroups 1,2 and 3, the maximum decrease of $\mu_s'$ values in traumatic side occured at 72 hours after injury (about 25.2% ~25.7%). And the $\mu_s'$ values in contralateral side of TGroups 1, 2, 3 rats showed the same decrease percent (about 20%). The result may suggest that HS and mannitol with equal osmotic gradient had the same capability of dehydration on both traumatic and contralateral side. There was not the synergistic effect between mannitol and HS. During the same period, the decrease percent of BWC was much smaller than that of $\mu_s'$ values, indicating that $\mu_s'$ values are more sensitive to edema than the BWC.

The regression equation, the equation (2), showed a marked linear relationship between $\mu_s'$ values and brain water content. The good correlation between $\mu_s'$ and BWC implied that $\mu_s'$ values may serve as an indicator for edema assessment. The dynamic changes of $\mu_s'$ value after the administration of dehydrating agent could be in vivo continuously monitored and recorded which avoid the complicated procedures of BWC measurement.
After analyzing the $\mu_s$ data, we found that the therapeutic efficacy of different dehydration treatments on brain edema can be assessed from these parameters, including the onset time, the maximum reduction percent of $\mu_s$ values, the time required to achieve the maximum effectiveness and efficacy, as shown in Table 3. The onset time of TGroup 3 was longer than that of TGroup 1 and 2. The maximum reduction percent of $\mu_s$ values of TGroup 3 was 2.78%, which is similar to TGroup 1 and lower than that of TGroup 2. The time required to achieve the maximum effectiveness and efficacy in TGroup 3 was 70 minutes, which was substantially larger than that in TGroup 2 (36 minutes) and larger than TGroup 1 (60 minutes). The results may indicate that the therapeutic efficacy of mannitol + HS was not superior to that of mannitol or HS alone.

Table 3. $\mu_s$ values of treatment groups.

| Group   | The onset time (min) | The time required to achieve the relative steady phase (min) | The maximum reduction percent of $\mu_s$ (%) |
|---------|----------------------|-------------------------------------------------------------|--------------------------------------------|
| TGroup 1| 20                   | 60                                                          | 2.89                                       |
| TGroup 2| 14                   | 36                                                          | 3.44                                       |
| TGroup 3| 30                   | 70                                                          | 2.78                                       |

5. Conclusion

This study demonstrated that fNIRs has the ability to in vivo and in real-time monitor the development of traumatic brain edema following injury and the treatment effect of dehydrating agents. Rats’ cortical $\mu_s$ values measured by fNIRs are a reliable parameter for assessing brain edema and drug treatment. The occurrence and development of cerebral edema could be detected earlier with the sensitive indicator $\mu_s$ values.

By recording the changes of $\mu_s$ value, the entire progress of dehydration therapy was disclosed. According to the experimental data, the following conclusions can be obtained: there was not the synergistic effect between mannitol and HS; the therapeutic efficacy of mannitol + HS was not superior to that of mannitol or HS alone.

The result demonstrated that the fNIRs technique has a potential for in vivo and real-time assessing the efficacy of treatment on the brain injury. Based on this study, developing an in vivo non-invasive optical monitoring method on traumatic brain edema will be our future direction.

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