Intraoperative Indocyanine Green–Based Cortical Perfusion Assessment in Patients Suffering from Severe Traumatic Brain Injury

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OBJECTIVES: **The pathophysiology of traumatic brain injury (TBI) largely involves the brains vascular structural integrity. We analyzed the value of an intraoperative cortical indocyanine green (ICG) angiography in patients with severe TBI and acute subdural hematoma who underwent decompressive craniectomy.**

METHODS: **ICG-derived fluorescence curves of cortex and cerebral vessels were recorded by the use of software integrated into a surgical microscope in 10 patients. The maximum intensity, rise time (RT), time to peak, and residual fluorescence intensity (FI) were estimated from cortical arteries, the parenchyma, and veins.**

RESULTS: **ICG-derived fluorescence parameters were correlated with the short-term outcome 3 months after discharge. Five patients had a favorable and 5 an unfavorable outcome. Patients with a favorable outcome showed a significant longer RT in the arteries and a trend towards a significant longer RT in the veins. Overall mean residual FI was 47.5 $\pm$ 6.8% for the arteries, 45.0 $\pm$ 7% for the parenchyma and 57.6 $\pm$ 6% for the veins. The residual FI of the parenchyma and the veins was significantly greater in patients with an unfavorable clinical outcome.**

CONCLUSIONS: **Patients with an unfavorable clinical outcome showed an altered shape of the ICG-derived fluorescence curve, a shorter increase of the ICG-derived fluorescence intensity in the cortical arteries, and significantly greater residual fluorescence intensity. These observations are likely a correlate of an increased intracranial pressure, a capillary leak, and venous congestion. Intraoperative quantification of the ICG-derived fluorescence might help to appreciate the clinical outcome in patients with severe TBI.**

INTRODUCTION

With an incidence of 100–300/100,000 cases per year, traumatic brain injury (TBI) is a major cause of mortality and morbidity, especially in young adults.[1,2] More than one-third of patients suffering a severe TBI die due to the brain component of their (commonly polytrauma) injury, and approximately 60% have an unfavorable outcome.[3] These are only some of the factors constituting the huge individual, social, and economic impact of TBI.

The pathophysiology of TBI is probably a cascade of damages: the primary injury involves the direct impact on the brain with immediate disruption of the cerebral, neuronal, and vascular structural integrity. This leads to local and systemic sequelae known as secondary brain injury, including dysfunction of the blood–brain-barrier, disruption of the neurovascular interplay, ischemia and hypoxia, inflammation, oxidation, accumulation of

Key words
- Cerebral blood flow
- Cerebral perfusion
- Decompressive craniectomy
- ICG
- Indocyanine green
- Traumatic brain injury

Abbreviations and Acronyms
aSDH: Acute subdural hematoma
AU: Arbitrary units
CT: Computed tomography
CTP: Computed tomography perfusion
DC: Decompressive craniectomy
FI: Fluorescence intensity
GOS: Glasgow Outcome Scale
ICG: Indocyanine green
ICP: Intracranial pressure
mRS: Modified Rankin Scale
ROI: Region of interest
RT: Rise time
TBI: Traumatic brain injury
TTP: Time to peak

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excitotoxic metabolites, cellular calcium accumulation, and induction of necrosis and apoptosis.[4-7] In particular, disruption of the blood–brain barrier and cellular swelling leads to a cerebral edema and—together with primary injuries of the brain—to an increase of the intracranial pressure (ICP).[7-9] Increased ICP alone induces cerebral ischemia, affects the venous outflow, and further compromises the integrity of the blood–brain barrier, thereby further promoting cerebral edema.

Nonsurgical treatment approaches involve the pharmacological treatment of increases ICP (e.g., by hyperosmolar solutions), reduction of the neuronal activity, improvement of the venous outflow (e.g., by body position), and maintenance of an adequate cerebral perfusion.[10-14] Surgery is a second key approach in the treatment of increased ICP.[15-17] Immediate evacuation of epi- or subdural hematomas prevents cerebral herniation and improves outcome. Decompressive craniectomy (DC) in patients suffering from acute subdural hematoma (aSDH), contusions, or intractable intracranial hypertension is a standard approach to reduce increased ICP.[18,19]

During DC, intraoperative evaluation of TBI-induced pathophysiological changes (beyond ICP measurement) routinely was not possible, and prediction of the outcome was "little more than prophecies."[3] Recently, intraoperative quantification of indocyanine green (ICG)-based fluorescence angiography was considered to be useful for intraoperative monitoring of regional cerebral blood flow. In our present retrospective study, we analyzed the value of an intraoperative cortical ICG angiography in patients with TBI who underwent DC. Multiple ICG parameters were measured and quantified; these results were correlated with short-term clinical outcome.

MATERIALS AND METHODS

This retrospective, uncontrolled single center analysis was approved by the local research ethics committee (internal study number: 5525).

Inclusion Criteria

ICG-derived fluorescence pattern quantification was performed in patients with severe TBI in whom DC had to be performed. All patients included fulfilled the following criteria: 1) severe TBI with aSDH; 2) DC; and 3) intraoperative estimation of ICG-induced fluorescence with the FLOW 800 tool of the surgical microscope (Carl Zeiss Meditec AG, Oberkochen, Germany). Exclusion criteria were indication for DC other than TBI with aSDH, conservative treatment or surgical treatment other than DC (e.g., burr hole craniotomy), hyperthyreosis, renal insufficiency, or allergy against ICG.

Surgery

Standard DC consisted of an approximately 10 by 12-cm fronto-parieto-temporal craniectomy and duroplasty. Temporal trepanation was extended down to the lateral skull-base. ICG-derived fluorescence estimation was performed immediately after decompression, opening of the dura, and hematoma evacuation. A ventricular catheter was inserted in all patients for ICP monitoring and treatment after ICG measurement. At the end of surgery, patients were transferred to the intensive care unit, and sedation was continued for at least 3 days or until ICP values stabilized to a noncritical level (20 mm Hg). Sequential computed tomography (CT) scans were performed during that phase of disease to check mid-line shift and exclude additional pathologies requiring surgical intervention.

Clinical outcome was assessed at the time of patient transfer to a rehabilitation center and 3 months after discharge. At each assessment, the Glasgow outcome scale (GOS) and the modified Rankin Scale (mRS) were calculated[20-24]: outcome was dichotomized in favorable outcome (GOS 4 and 5; mRS 0–3) and an unfavorable outcome (GOS 1–3; mRS 4–6).

ICG Methodology and Data Recording by the FLOW 800 Tool

ICG-based fluorescence angiography procedure, data recording, and emulation were performed as previously described.[25] In brief, a 5-mg ICG bolus (ICG Pulsion; Pulsion Medical Systems, Munich, Germany) was administered intravenously, and ICG-derived fluorescence was recorded by a surgical microscope equipped with an infrared fluorescence detection and analysis tool (OPMI Pentero microscope with the FLOW 800 tool; Carl Zeiss Meditec AG, Oberkochen, Germany). The ICG signal was detected from the cortical surface of the frontal, temporal, and parietal lobe with the Sylvian fissure as the center with constant angle (about 90°) and a constant distance between the microscope and cortex (about 30 cm). The surgical microscope was not moved during the recording period of at least 45 seconds.

Data Processing

Intraoperatively, the FLOW 800 tool compiles 2-dimensional visual maps of the cortical structures according to maximal fluorescence intensities (FIs) or time to half-maximal fluorescence, respectively. After surgery, FI course over time of the cortical arteries, veins, and parenchyma was further analyzed in freely definable regions of interest (ROIs). To do this, a ROI was placed in the index artery and veins and 10 representative regions of the cortical parenchyma. An index artery or vein was defined as the vessel with the first appearance of ICG-derived fluorescence, respectively. For each ROI, the following parameters were defined as previously described[25]: maximum FI in average fluorescence units, the time to peak (TTP), defined as the time interval between the first appearance of ICG-derived fluorescence and the maximal FI; the rise time (RT) as the interval between 10% and 90% of the maximum signal; and the cerebral blood flow index (maximum FI/RT).

The residual FI was defined as the residual baseline fluorescence after the first inverse parabolic fluorescence and a secondary, smaller fluorescence peak indicating recirculation of the ICG. Residual FI was expressed relative to the maximum FI (**Figure 1**). Definition of the ICG-derived fluorescence parameters in the present study and in previous studies refers to the fluorescence in only one vascular compartment (artery, parenchyma, and capillaries or vein). Therefore, these parameters defer from time-associated brain parameters as derived from the computed tomography perfusion (CTP), which uses different definitions and usually refers to multiple vascular compartments.[26-28]

Statistical Analysis

Descriptive statistics including mean and standard error of mean were calculated for all continuous variables. Data are presented as