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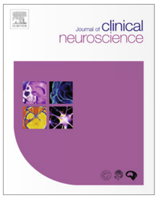

Clinical Study

Bedside saccadometry as an objective and quantitative measure of hemisphere-specific neurological function in patients undergoing cranial surgery

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ABSTRACT

Cranial surgery continues to carry a significant risk of neurological complications. New bedside tools that can objectively and quantitatively evaluate cerebral function may allow for earlier detection of such complications, more rapid initiation of therapy, and improved patient outcomes. We assessed the potential of saccadic eye movements as a measure of cerebral function in patients undergoing cranial surgery peri-operatively. Visually evoked saccades were measured in 20 patients before (−12 hours) and after (+2 and +5 days) undergoing cranial surgery. Hemisphere specific saccadic latencies were measured using a simple step-task and saccadic latency distributions were compared using the Kolmogorov–Smirnov test. Saccadic latency values were incorporated into an empirically validated mathematical model (Linear Approach to Threshold with Ergodic Rate [LATER] model) for further analysis (using Wilcoxon signed rank test). Thirteen males and seven females took part in our study (mean age 55 ± 4.9 years). Following cranial surgery, saccades initiated by the cerebral hemisphere on the operated side demonstrated significant deteriorations in function after 2 days ($p < 0.01$) that normalised after 5 days. Analysis using the LATER model confirmed these findings, highlighting decreased cerebral information processing as a potential mechanism for noted changes ($p < 0.05$). No patients suffered clinical complications after surgery. To conclude, bedside saccadometry can demonstrate hemisphere-specific changes after surgery in the absence of clinical symptoms. The LATER model confirms these findings and offers a mechanistic explanation for this change. Further work will be necessary to assess the practical validity of these changes in relation to clinical complications after surgery.

1. Introduction

Although the outcome of patients undergoing cranial surgery has improved over the past few decades, these operations continue to carry a significant risk of morbidity and mortality [1,2]. Early detection of the onset of complications is critical in avoiding permanent residual neurological damage as it encourages early intervention [3]. The Glasgow Coma Scale (GCS), conceived by Teasdale and Jennet in 1974, is the cornerstone bedside test for assessing conscious state in neurosurgical patients [4,5]. Since its inception, the GCS has been invaluable in communicating levels of consciousness in peri-operative patients; however it was not designed with the intent to detect early complications in the neurosurgical patient. Furthermore, the GCS is an ordinal scale. Thus although the GCS is a useful tool in expressing impaired neurological states on a numerical scale, in no way does the GCS actually quantify general cerebral function [5]. In terms of patient care this means that the detection of early neurological deterioration before obvious clinical manifestations is not achievable. We feel that there is a role for an adjunctive assessing tool that can objectively and quantitatively evaluate cerebral function in neurosurgical patients through a simple, reliable, and rapidly performed bedside test that allows comparison between brain hemispheres.

Neuropsychological tests have been utilised in an attempt to improve assessments of cognitive function peri-operatively, however, they are also limited for several reasons [6,7]. They may require specialist training and can be time consuming, lasting as long as 100 minutes [6]. Extended assessment periods may not be tolerated by the elderly population, and can delay surgical

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intervention at critical time periods. In addition, they are not applicable to the entire population, excluding individuals without a strong command of the English language [8,9]. Clearly there is a need for more effective bedside tests of neurological function.

Saccades are rapid semi-voluntary ocular movements, which allow individuals to orient vision towards a target of interest. This is achieved by focussing visual targets of interest onto the fovea, a high acuity region in the retina [10]. The superior colliculus (SC) plays an important role in producing these movements, largely by determining the location of targets of interest [11]. The SC subsequently activates neurons in the brainstem, which project to extra-ocular muscles facilitating the motor arm of the saccade [12]. Saccades are the most commonly occurring movement made by humans, occurring up to three times each second [12]. Although they are fast in execution, lasting as little as some 20 ms, the time taken to react to a visual stimulus, also known as saccadic latency, is disproportionately longer [13,14]. This delay represents a procrastination process that appears to reflect the time taken for the brain to make a decision about what to look at next [15,16]. This process serves as a prioritisation algorithm, selecting the most salient visual stimulus at any one time. Whereas the SC facilitates the "where" processing of vision, the "what" processing is mediated by cortical structures that inhibit the SC from producing a saccade whilst the cortex "procrastinates", or decides which target to focus on next [12]. The frontal eye fields (FEF), located in the frontal lobe, play a major role in this decision making process. Described as a "saliency map", the FEF is responsible for prioritising amongst potential targets to determine the next saccadic response. Once the prioritisation process is complete, corresponding regions of the SC are activated to facilitate accurate orientation of the visual apparatus towards its chosen target [10]. This role has been validated in both human and primate studies. For example, reversible inactivation of the FEF in monkeys results in impaired production of saccades [17]. Several models exist with the aim of rigorously defining the relationship between saccadic latency and this higher cognitive process. The Linear Approach to Threshold with Ergodic Rate (LATER) model, for example, utilises saccadic latency to model higher cortical function in both humans and primates in a way that can be empirically tested [12].

Bedside saccadometry is a novel test that measures various saccadic parameters, including saccadic latency. Utilising the established models above, saccadic latency can uniquely allow quantitative measures of cerebral function at the hemispheric level to be estimated [12,16,18]. Saccadometry has been widely practised in the past, commonly in long-term follow-up experiments in patients with traumatic brain injury [19–22]. Previously, saccadometry was administered in a laboratory environment using set-ups that are uncomfortable for patients and impractical in an in-patient setting [19,23,24]. The miniaturisation of this apparatus has permitted transfer of the technique to the patient's bedside, allowing assessment of cognitive function rapidly and non-invasively in an in-patient clinical setting.

In this pilot study, we explored the feasibility of bedside saccadometry as a quick and easy method of providing objective and quantitative measures of hemisphere-specific neurological function in patients undergoing cranial surgery.

2. Methods

2.1. Subjects

With the approval of the National Research and Ethics Committee (London, UK) and the informed consent of the participants, 30 patients undergoing various neurosurgical procedures took part in the study. All patients were referred to the Imperial College Healthcare National Health Service Trust, London. Referred patients were screened against inclusion and exclusion criteria (Table 1), and suitable patients were offered participation in the trial.

2.2. Protocol

Following consent, the admitting neurosurgeon assessed and recorded subjects' baseline characteristics, including the presenting symptoms, past medical history, pupillary function, GCS score, and the presence of limb weakness and dysphasia.

Saccadometry was performed alongside other bedside observations for the duration of the study, specifically noting saccadic changes between the pre-operative period and approximately 2 days after surgery. In-patients with extended stays were followed-up with a second reading after surgery at approximately 5 days. This was collected to compare saccadic performance relative to baseline over two temporally distinct time periods.

2.3. Saccadic latency measurements

Saccadic latency was measured using a portable, head-mounted saccadometer (Ober Consulting, Poznan, Poland), sitting on the bridge of the nose and held in place by an elastic strap wrapped around the head (Fig. 1). The protocol was a simple step-task, which automatically administered 100 saccadic stimuli over the course of 4 minutes (Fig. 2). Scleral infrared oculometry was used to measure lateral scleral displacements and saccadic latency was determined accordingly. Artifactual readings, including blinks and anticipatory saccades (where reaction time is <60 ms) were omitted. The subjects performed the test sitting up or lying down, looking at a wall or the ceiling, respectively. The high contrast of the laser targets means that moderate variation in the background or level of brightness does not significantly affect the results. Because the stimuli lasers move with the head, no chin-rests or other forms of immobilization were required. Subjects were asked to follow the light with their eyes, whilst keeping their heads as still as possible. Prior to each trial, the saccadometer automatically performed a short calibration process.

2.4. Data analysis

As saccadic movements are lateralised, left sided saccades correspond to the right hemisphere and right saccades to the left hemisphere. Hemispheres were labelled "operated" and "unoperated" based on the side of surgical intervention, and their respective saccadic latency distributions analysed using the application SPIC (Roger Carpenter, Cambridge, UK). Latency distributions were plotted as reciprobit plots and median latency values determined (Supp. Fig. 1). The Kolmogorov–Smirnov (K–S) two-sample statistic was used to compare saccadic performance in each patient's hemisphere prior to and following surgery. Significant increases in latency values, which mean that the reaction time was longer, were assigned the term "deteriorations" and decreases accordingly referred to as "improvements". The Wilcoxon signed-rank (WSR) test was used to compare the median saccadic latency across the entire patient group before and after surgery in each hemisphere. It was also used to compare overall saccadic performance in all the patients across the two measurements above. The data were then further analysed using the LATER model, a model correlating the reciprobit plots to a higher cortical decision analysis framework [25]. The model has been verified in human experiments, as well as FEF studies in macaques [10,26–29].

The LATER model provided a platform for more detailed analysis. The net changes of these saccadic latency variables ($\Delta\mu$, $\Delta\sigma$,