

The Effect of Optimising Cerebral Tissue Oxygen Saturation on Markers of Neurological Injury during Coronary Artery Bypass Graft Surgery

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Background

Surgical revascularisation of the coronary arteries is a cornerstone of cardiothoracic surgery. Advanced age and the incidence of preoperative co-morbidity in patients presenting for coronary artery bypass graft surgery increases the potential for stroke and other perioperative outcomes. It is hypothesised that by using interventions during cardiac surgery to improve cerebral oxygenation, the risk of patients enduring adverse neurological outcomes would be reduced.

Methods

Forty patients (mean age 55.3, standard deviation 9.74 and range from 39 to 72 years) undergoing on-pump coronary artery bypass graft surgery were recruited at Inkosi Albert Luthuli Central Hospital, South Africa. Patients were randomised into a control group ($n = 20$) and interventional group ($n = 20$). Intraoperative regional cerebral oxygen saturation (rSO₂) monitoring with active display and Murkin treatment intervention protocol was administered for the interventional group. Arterial blood samples for the measurement of serum S100B were taken pre and postoperatively. An enzyme immunoassay (ELISA) was used for the quantitative and comparative measurement of human S100B concentrations for both groups. A prioritised intraoperative management protocol to maintain rSO₂ values above 75% of the baseline threshold during cardiopulmonary bypass was followed.

Results

There was a highly significant difference in the change in S100B concentrations post surgery between the interventional (37.3 picograms per millilitre) and control groups (139.3 pg/ml). The control group showed a significantly higher increase in S100B concentration over time than the intervention group ($p < 0.001$). There was a significant difference in cerebral desaturation time ($p < 0.001$) between the groups. The mean desaturation time for the control group was 63.85 min as compared to 24.7 min in the interventional group. Cerebral desaturation occurred predominantly during aortic cross clamping, distal anastomosis of coronary arteries and aortic cross clamp release. Predictors of cerebral oxygen desaturation included, partial pressure

Abbreviations: CABG, coronary artery bypass graft surgery; S100B, serum S100beta protein; MAP, mean arterial pressure; PcvCO₂, partial pressure of carbon dioxide; HR, heart rate; HCT, haematocrit; SpO₂, patient oxygen saturation; NIRS, near infrared spectroscopy; rSO₂, regional cerebral oxygen saturation; rSO₂R, right cerebral oxygen saturation; rSO₂L, left cerebral oxygen saturation; ScvO₂, central venous oxygen saturation

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of carbon dioxide ($p\text{CO}_2$), temperature, pump flow rate (LMP), mean arterial pressure (MAP), haematocrit, heart rate (HR) and patient oxygen saturation (SpO_2).

Conclusion

Monitoring brain oxygen saturation during on-pump CABG together with an effective treatment protocol to deal with cerebral desaturation must be advocated.

Keywords

Cerebral tissue oxygen saturation ($r\text{SO}_2$) • Serum S100beta protein (S100B) • Coronary artery bypass graft surgery (CABG) • Near infrared spectroscopy (NIRS) • Murkin protocol

Introduction

Inadequate oxygen supply is thought to play a vital role in the aetiology of brain injury detected in patients post coronary artery bypass graft surgery [1]. Monitoring of cerebral oxygenation can be used as a useful tool in the detection of hypoxic conditions associated with adverse neurological sequelae [2]. Serum S100B protein has been used as a biochemical marker in the detection of brain injury during cardiac surgery. Elevated levels serve as an indicator of brain cell damage and adverse neurological outcomes [3,4]. Near infrared spectroscopy (NIRS) can be employed as a non invasive monitor which measures real time cerebral oxygenation during cardiac surgery. The principal goal for the application of NIRS monitoring is to detect and hence optimise factors that affect cerebral oxygen supply [5]. The aim of the study was to maintain cerebral tissue oxygen saturation during cardiopulmonary bypass above 75% of the baseline level by implementation of the Murkin interventional protocol [1]. The analysis of S100B which is a marker of neurological injury and optimisation of regional cerebral oxygen saturation would allow for the formulation of specific intervention strategies which could be implemented by cardiovascular perfusionists during on-pump coronary artery bypass graft surgery as a preventive clinical measure further reducing the risk of neurological injury.

Materials and Methods

After ethical committee approval and informed consent, 40 patients undergoing elective on-pump coronary artery bypass graft surgery were enrolled in the study. Patients were randomised into a control group ($n = 20$) and interventional group ($n = 20$) using a sealed envelope system. In the interventional group, intraoperative regional cerebral oxygen saturation ($r\text{SO}_2$) monitoring was performed with active display and administration of the Murkin treatment interventional protocol [1]. In the control group, regional cerebral oxygen saturation monitoring was not visible to the cardiovascular perfusionist operating the heart lung machine during cardiopulmonary bypass (Blinded).

Inclusion Criteria

Age over 18 yrs, scheduled for elective on-pump coronary artery bypass graft surgery and a preoperative haematocrit greater than 36% (haemoglobin >12 g/dl).

Exclusion Criteria

Exclusion criteria were: pregnancy, history of stroke or persistent neurological residue, history of transient ischaemic attack (TIA), unilateral stenosis of carotid artery greater than 70%, bilateral stenosis of carotid artery greater than 50%, combined cardiac procedure, i.e. CABG plus heart valve replacement, left ventricular ejection fraction less than 40%, left main stem stenosis more than 70%, symptomatic chronic pulmonary disease requiring long term medication, renal insufficiency or anuric renal failure or creatinine above 1.5 mg/dl, HIV positive patients, patients in AF (atrial fibrillation), patients presenting with left ventricular thrombosis preoperatively, presence of aortic atheroma detected pre, intra or post operatively.

All patients received general anaesthesia using a standard technique, intravenous induction with propofol 2 mg/kg, and paralysis with pancuronium or rocuronium. Maintenance was with isoflurane and ventilation was adjusted to maintain normocarbida, as assessed by continuous end-tidal CO_2 monitoring and intermittent arterial blood gas analysis. Fentanyl was used for analgesia. A central venous line and arterial line was inserted for all patients as is routinely done for all cardiac patients.

Preoperative data collection included:

- Age
- Gender
- Body mass index
- Height
- Weight
- Calculated flow rate (cardiac index)
- Type II diabetes mellitus (Non insulin)
- Type I diabetes mellitus (Insulin)
- Baseline $r\text{SO}_2$ (Cerebral oxygen saturation)
- Baseline blood gas
- Activated clotting time (ACT)
- Heart rate
- Mean arterial pressure
- Temperature

Cerebral Monitoring

Cerebral monitoring constituted the use of Near-infrared spectroscopy (NIRS), a Somanetics INVOS model 5100c cerebral/somanetic oximeter (Covidien [Pty Ltd], Midrand South Africa) was employed to measure cerebral oxygen delivery and consumption [5].

Serum S100B Protein Sampling and Analysis

Arterial blood samples were taken from the arterial line preoperatively and postoperatively to determine levels of

serum S100B protein. Approximately 1–2.5 ml of blood was taken by the principle investigator and marked according to a number thus protecting patient identity (PR1 meaning pre bypass and patient number 1). Blood samples were centrifuged at 4000 rpm for 15 min in order to separate the serum from other blood components. The serum was pipetted into cryovials and stored in a biofreezer at -20°C . Samples were analysed using an ELISA kit (Human EIA 4555) to establish the levels of S100B protein. The Human S100B ELISA is a HRP labelled antibody based sandwich enzyme immunoassay for the quantitative measurement of human S100B protein in serum, cerebrospinal fluid, heparin plasma and tissue culture medium.

Assay Procedure

In the Human S100B ELISA Standards, Quality Controls and samples are incubated in microplate wells pre-coated with polyclonal anti-cow S100B antibody. After 120 min incubation and washing, biotin-labelled monoclonal anti-human S100B antibody was added to the wells and incubated for 60 min with captured S100B. After another washing step, streptavidin-HRP conjugate was added. After 30 min incubation and the last washing step, the remaining conjugate was allowed to react with the substrate solution. The reaction was stopped by addition of acidic solution and absorbance of the resulting yellow product was measured. The absorbance is proportional to the concentration of S100B. A standard curve was constructed by plotting absorbance values against concentrations of Standards, and concentrations of unknown samples were determined using this standard curve. The absorbance was established by reading the plate at 450 nm using a microplate reader (DAS Digital Analogic Systems). The total assay time was less than 5 h.

Data Collection during Cardiopulmonary Bypass

Eight time period measurements of mean arterial pressure (MAP), heart rate, temperature, activated clotting time (ACT), patient oxygen saturation (SpO_2), partial pressure of carbon dioxide (PCO_2), haematocrit, lactate, pH, haemoglobin (Hb), base excess/deficit (BE), potassium (K^+), sodium (Na^+), glucose, calcium (Ca^{2+}), central venous saturation (ScvO_2), cerebral oxygen saturation (rSO_2), fraction of inspired oxygen (FiO_2), sweep rate, pump flow rate (cardiac index) and percentage isoflurane administered were recorded on a data recording spread sheet for all patients. Blood samples were collected using heparinised blood gas syringes and were analysed using the Roche Omni S blood gas analyser. The blood gas results were recorded on the data recording sheet after each blood gas was analysed. Blood samples were discarded thereafter.

Additional data recorded included the number of grafts performed, cardiopulmonary bypass time, cross clamp time, red blood cells administered (pack cells), amount of adrenaline given per patient, urine output, time period of rSO_2 value $<75\%$ from baseline, time period of rSO_2 value $<70\%$ from

baseline, time period of rSO_2 value $<40\%$ from baseline and total cerebral oxygen desaturation time.

Eight time periods:

- 5 min into cardiopulmonary bypass
- Application of aortic cross clamp
- After arrest
- During distal anastomosis
- Removal of aortic cross clamp
- Proximal anastomosis
- During rewarming
- Termination of cardiopulmonary bypass

Murkin Interventional Protocol

A prioritised intraoperative management protocol was used for the interventional group to maintain rSO_2 values above 75% of the baseline threshold during cardiopulmonary bypass. Cerebral desaturation was defined as a decrease in oxygen saturation values below 70% of baseline for more than 1 min. Interventions commenced within 15 s of decrease below 75% of baseline value.

Interventions:

1. The position of the patient's head was checked to ensure that it was not inadvertently rotated and the face was observed to detect plethora.
2. If PCO_2 was <35 mmHg during positive pressure ventilation, ventilation was reduced to achieve $\text{PCO}_2 \geq 40$ mmHg.
3. Arterial blood gases were used without correction of temperature. This is known as the Alpha stat management of cardiopulmonary bypass.
4. Mean arterial pressure was increased above >60 mmHg by administration of adrenaline (vasoconstrictor).
5. Cardiac index (pump flow rate) was increased.
6. When partial pressure of carbon dioxide (PCO_2) was lower than 40 mmHg, the oxygenator fresh gas sweep rate on the pump was adjusted to achieve PCO_2 values of approximately 40 mmHg.
7. Red blood cells (pack cells) were administered to increase haematocrit (Hct) levels $>20\%$. This strategy was thought to increase oxygen carrying capacity.
8. Fraction of inspired oxygen (FiO_2) was increased for persistent rSO_2 values below the treatment threshold.
9. Pulsatile flow was used as opposed to laminar flow, to mimic the normal pulsatility of the body.

Statistical Methods

The standard curves were plotted and unknown values of S100B concentration were interpolated using Prism 5.03 (trial version 1992–2010 GraphPad Software Inc.) non linear standard curves module.

SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) was used for analysis of data. A p value <0.05 is considered as statistically significant. Clinical data were compared between the intervention and control groups using Mann–Whitney tests for non parametrically distributed dependant variables, t -tests for those which were normally distributed, and Pearson's chi square tests for categorical variables. Participants were randomised into intervention and control groups, and

the completeness of the randomisation process was checked statistically by comparison of baseline features between the two groups using t-tests in the case of quantitative variables and Pearson’s chi square tests or Fisher’s exact tests for categorical variables. S100B values were measured quantitatively at two time points and compared between the intervention and control groups using repeated measures ANOVA testing. Profile plots were used to assess the trend of the intervention effects. Within the intervention group the effect of the specific interventions were assessed using Generalised Estimating Equations within the family of Generalised Linear Models. Each intervention received was compared with no intervention within the same participant. This was done separately for each dependant variable specifying a normal distribution with an identity link function.

Demographics

The mean age was 55.3 years with a standard deviation of 9.7 years and range from 39 years to 72 years. The study consisted of 70% males, 28 of the 40 participants were male and

12 were female. The mean height was 169.5 ± 7.7 and weight 79.2 ± 12.9 .

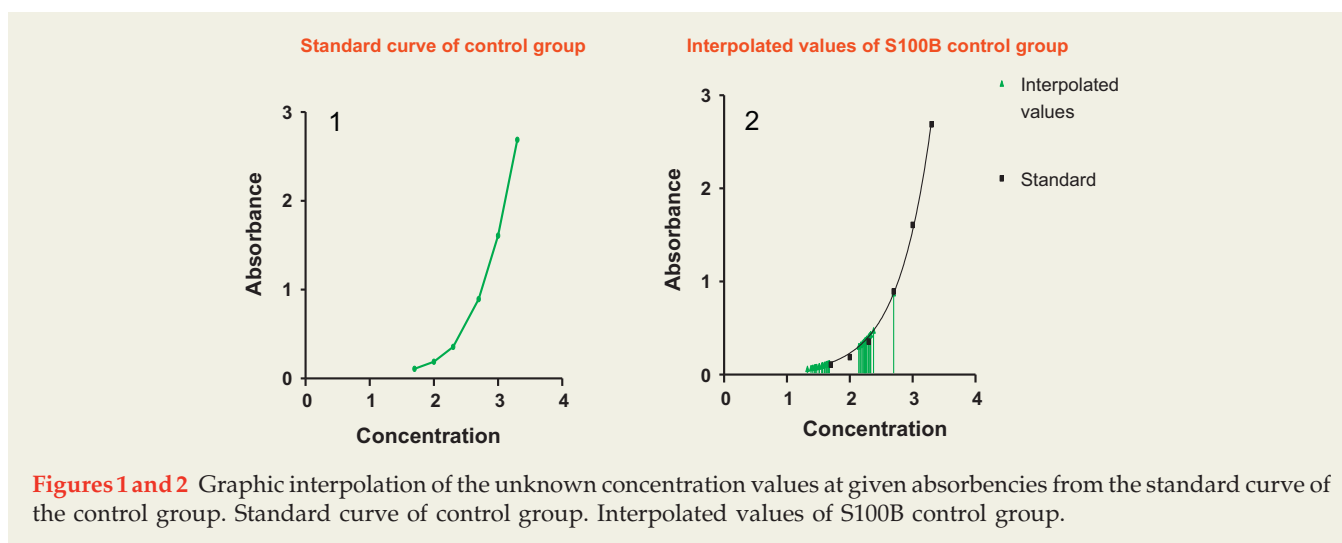
Results

Comparison of S100B values between control and intervention groups. Figs. 1 and 2 show graphically the interpolation of the unknown concentration values at given absorbencies from the standard curve of the control group.

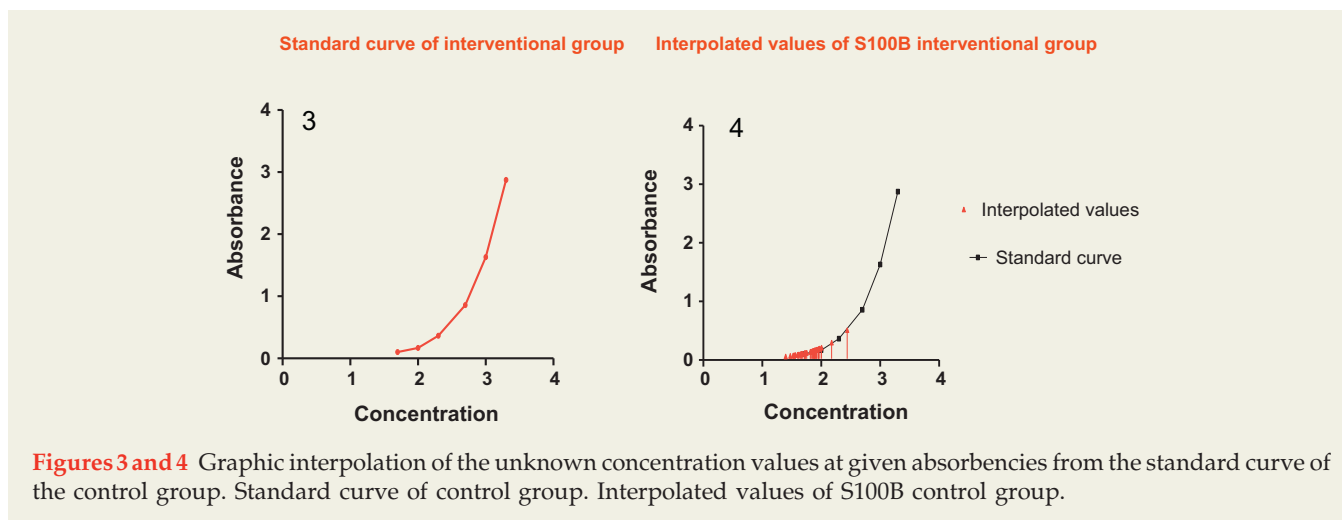
Graphic interpolation of the unknown concentration values at given absorbencies from the standard curve of the interventional group is shown in Figs. 3 and 4.

Standard curve of interventional group Interpolated values of S100B interventional group

There was a highly significant difference in the change in S100B concentration post surgery between the two groups. The control group showed a significantly higher increase in S100B concentration over time than the intervention group (Tables 1 and 2).



Figures 1 and 2 Graphic interpolation of the unknown concentration values at given absorbencies from the standard curve of the control group. Standard curve of control group. Interpolated values of S100B control group.



Figures 3 and 4 Graphic interpolation of the unknown concentration values at given absorbencies from the standard curve of the control group. Standard curve of control group. Interpolated values of S100B control group.

Table 1 Median Values of S100B Pre and Post Surgery in Both Groups.

Group	s100pre			s100post		
	Percentile 25	Median	Percentile 75	Percentile 25	Median	Percentile 75
Intervention	35.6	43.0	52.0	71.4	77.7	87.6
Control	29.1	36.7	42.6	160.8	176.8	199.5

Table 2 Change in S100B Values.

Group	Change in S100B		
	Percentile 25	Median	Percentile 75
Intervention	33.1	37.3	42.7
Control	123.8	139.3	159.0

Analysis of Interventions

In total four different interventions were applied 95 times at six different time points. Table 3 below shows that increasing pump flow rate (intervention 5) was implemented most frequently.

The Intervention Effect (Intervention vs. Control)

There was a highly significant difference between the intervention and control groups in terms of cerebral desaturation time ($p < 0.001$) (Table 4).

Comparison of Clinical Data between Intervention and Control Groups

There was no difference between the groups in terms of the clinical parameters except for adrenalin quantity where the control value was significantly higher than the intervention value ($p = 0.043$) (Table 5).

Discussion

Neurological injury during cardiac surgery is a serious healthcare problem. The implementation of neurological monitoring during cardiac surgery is thought to enhance the detection of hypoxic conditions associated with neurological insult. This technology may provide clinicians and perfusionists with key information to assist in reducing insult to the brain [6,7]. The Invos cerebral oximeter provides an estimation of regional oxygenation in the cerebral microvasculature. Studies conducted during cardiac surgery demonstrated a significant correlation between low cerebral oximetry readings and poorer neurological outcomes [8,9]. The common limitation in studies assessing the impact of

Table 3 Interventions.

	Time Period	Intervention				Total
		4	5	6	7	
5 min into CPB	1	0	3	0	0	3
Application of aortic cross clamp	2	4	17	11	1	33
After arrest	3	1	0	4	1	6
During distal anastomosis	4	3	9	11	5	28
Removal of aortic cross clamp	5	2	16	2	3	23
Proximal anastomosis	6	1	0	0	1	2
Total		11	45	28	11	95

Table 4 Cerebral Desaturation Time.

	Group	N	Mean	Std. Deviation	Std. Error Mean	p Value
Desaturation time	Intervention	20	24.70	11.819	2.643	<0.001
	Control	20	63.85	23.424	5.238	

Table 5 Statistics of Clinical Data.

	Group	N	Mean	Std. Deviation	Std. Error Mean	p Value
BSA	Intervention	20	1.947	.1785	.0399	0.323
	Control	20	1.893	.1623	.0363	
Fow rate (LPM)	Intervention	20	4.664	.4338	.0970	0.393
	Control	20	4.553	.3808	.0852	
CPB time (min)	Intervention	20	133.30	26.864	6.007	0.547
	Control	20	138.20	24.098	5.388	
Cross clamp time (min)	Intervention	20	80.80	17.781	3.976	0.146
	Control	20	91.85	27.972	6.255	
Adrenalin quant	Intervention	20	15.65	10.975	2.454	0.043
	Control	20	26.00	19.139	4.280	

BSA – body surface area; LMP – litres per minute; CPB – cardiopulmonary bypass time.

cerebral oxygen monitoring was the absence of a defined protocol to actively treat cerebral desaturation [10].

In this cohort of patients undergoing coronary artery bypass grafting with the use of cardiopulmonary bypass, the prospective investigation was to determine if cerebral tissue oxygen saturation could be optimised using the Murkin interventional protocol. The secondary aim was to compare the levels of serum S100B protein concentration which is a marker of neurological injury during cardiac surgery between a control group with no intervention and the interventional group with active treatment. The results of the study show that there was a highly significant difference in the change in S100B concentrations post surgery between the intervention and control groups. The intervention group showed a smaller increase in S100B concentration of 37.3 picograms per millilitre (pg/ml) while the control group showed a larger increase of 139.3 pg/ml. Therefore the control group showed a significantly higher increase in S100B concentration over time than the intervention group ($p < 0.001$). The median concentration of S100B for the interventional and control groups prior to surgery were 43 pg/ml and 36.7 pg/ml respectively which increased to 77.7 pg/ml in the interventional group and 176.8 pg/ml in the control group post coronary artery bypass graft surgery. These findings demonstrate the advantageous effect of optimising cerebral oxygen saturation using the Murkin interventional protocol on markers of neurological injury [11]. The clinical values of S100B have been demonstrated in stroke, cerebral complications associated with cardiac arrest and in patients with severe as well as minor head injury [12]. High concentrations of S100B have been demonstrated in brain injury, ischaemia and hypoxia [13].

Results show that four different interventions were applied 95 times at six different time points in the intervention group. Cerebral desaturation occurred predominantly during aortic cross clamping, distal anastomosis of coronary arteries and aortic cross clamp release. Increasing pump flow

rates was the most common intervention used (45 times) followed by maintaining partial pressure of carbon dioxide to approximately 40 mmHg (28 times), increasing mean arterial pressure by administration of adrenalin (11 times) and administration of red blood cells to increase haematocrit (11 times).

The findings of the study suggest that optimisation of these factors by cardiovascular perfusionists during on-pump CABG would result in increased cerebral oxygen saturation levels and a reduction in neurological injury. Denault and colleagues, proposed that an important requirement in the monitoring of cerebral oxygen saturation is the elaboration of a clinical algorithm to correct decreases in cerebral saturation values. The authors suggested that factors affecting cerebral oxygen supply and demand should be optimised [5].

The present study highlighted a significant difference between the intervention and control groups in terms of cerebral desaturation time ($p < 0.001$). The mean desaturation time for the control group was 63.85 min as compared to 24.7 min in the interventional group.

In order to establish which factors affected cerebral oxygen saturation, a backwards elimination technique was used to determine significant predictors of right and left cerebral oxygen saturation. Factors which significantly predicted cerebral oxygen saturation whilst controlling for time and central venous oxygen saturation, were partial pressure of carbon dioxide (PCO₂), temperature, pump flow rate (LMP), mean arterial pressure (MAP), haemoglobin (Hb), percentage isoflurane, heart rate (HR) and patient oxygen saturation (SpO₂).

The findings reveal that optimisation of cerebral oxygen saturation during on-pump coronary artery bypass graft surgery positively affect markers of neurological injury (S100B). The use of any monitoring modality in the clinical setting is directly influenced by an effective treatment protocol. The Murkin treatment protocol can be used as an effective tool to prevent cerebral desaturation during coronary artery bypass graft surgery. Monitoring cerebral oxygen

saturation for the early detection of hypoxic conditions in the brain is a fundamental requirement.

Limitations

The use of any monitoring modality can result in false positives. It is therefore, important to verify that the electrodes are well positioned and that there is no leakage of light as a consequence of peeling of the adhesive patch.

The use of S100B as marker of neurological injury in the clinical arena is limited by high financial costs and the time required for the performance of the enzyme-linked immunosorbent assay (ELISA). The level of S100B at which stroke or cerebral complication can be diagnosed is unknown and its pattern of release gives no information about the anatomical distribution of brain injury and functional impact [4].

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