A predictive parameter in patients with brain related complications after cardiac surgery?1

F. Isgro *, Ch. Schmidt, P. Pohl, W. Saggau
Herzzentrum Ludwigshafen, 'Clinic for Cardiac surgery', Klinikum Ludwigshafen, Klinik für Herzchirurgie, Bremerstr. 79,
67063 Ludwigshafen, Germany

Received 2 October 1995; received in revised form 21 December 1995; accepted 24 May 1996

Abstract

Objective: The prognostic estimation of cerebral complications after cardiac surgery is a major problem in the early postoperative period. Neuron specific enolase (NSE) is an enzyme involved in glycolysis, which is localized in neurons and axonal processes. It escapes into the blood and cerebrospinal fluid at the time of neural injury. Therefore we focused the study on the question of how far serum levels of neuron specific enolase can predict the neurological and neuropsychological outcome after cardiac surgery. Methods: We determined, with a prospective study design of NSE serum levels in 200 patients undergoing cardiac surgery preoperatively, right after the operation and 48 h later. The NSE was measured with a solid phase enzyme immuno assay which utilized a highly specific monoclonal antibody to NSE. We evaluated the neurological and neuropsychological status before and 72 h after surgical intervention. As a control group we recruited 50 patients undergoing general surgical treatment. Results: The preoperative serum levels of NSE are constantly low in all patients with a mean value of 11.1 ng/ml (8.3–13.6) and a mean ± S.D. of 3.12 in the main group and a mean value of 9.6 ng/ml (7.8–10.3) and a mean ± S.D. of 1.84 in the control group. The early postoperative measurements indicated a significant increase to a mean value of 19.7 ng/ml (8.7–70.9) with a mean ± S.D. of 2.89 in the main group. In contrast there is no increase of NSE serum levels after general surgery. The 48 h postoperative mean levels declined to 14.2 ng/ml (9.9–26.2), S.D. of 3.23. In 17 out of the 200 patients a neurological complication occurred. Elevated NSE levels were found in 16 of these 17 patients. The highest concentrations of NSE were measured in 7 patients with the most severe neurological complications being transient ischemic attack and stroke. Conclusions: The early serum levels of NSE after cardiopulmonary bypass, in those patients with severe neurological deficits, indicate that NSE is a suitable marker for the detection and quantification of cerebral injury after open heart surgery. Therefore, in addition NSE seems to be of predictive value for the clinical outcome and gives implications for the treatment and prognosis of patients with brain related complications in cardiac surgery. © 1997 Elsevier Science B.V.

Keywords: Cardiac surgery; Cerebral ischemia; Extracorporeal circulation; Neuron specific enolase

1. Introduction

Cerebral impairment during open heart surgery with the extracorporeal circulation, are not uncommon and has focused a new attention in the detection and quantification of cerebral ischemia. Although incidences of neurological and neuropsychological complications after cardiac operations have decreased during the last decades with improvements in surgical techniques and equipment [24]. The incidence of such complications varies considerably depending on the patient’s demographic characteristics such as, age, timing of the postoperative assessment, sensitivity of assessment procedures and whether prospective or retrospective study procedures were used [5,8,11,19,27]. Recent investiga-
Neuron specific enolase (NSE), an isoform of the glycolytic enzyme enolase, is a dimere peptide including a gamma subunit with a molecular weight of 78 kDa. NSE is mainly located in the cytoplasm of neuroendocrine tissues and axonal processes [15,29], and its structural and immunological behavior differs clearly from the other enolases [12,16,25]. The neuronal injury changes in membrane integrity can provide leakage of proteins, such as NSE from cytosol into the extracellular space. It has been observed in animal models of traumatic and ischemic brain damage, that there is an increase of NSE in the cerebrospinal fluid (CSF) [3,9,10,12,18,26]. In experimental focal ischemia, NSE levels in the CSF have been suggested to serve as a quantitative marker of the degree of focal cerebral infarction [3,9,10]. Very recently, increased NSE serum levels in human cerebral infarction, subarachnoid hemorrhage and head injury have been reported and also preliminary findings of NSE and Protein S-100 in the blood after open heart surgery [1,3,4,7,14,18,21,25]. But unlike its utility in CSF, the utility of serum NSE as a quantitative marker is not clear. Therefore, the purpose of the present paper, is to assess the value of NSE as a predictive and suitable parameter in patients with brain related complications after cardiac surgery.

2. Materials and methods

The experimental group consisted of 200 patients undergoing cardiac surgery with extracorporeal circulation during the last 18 months, who met the following criteria: sufficiently fluent in German to give informed consent and comprehend test instructions, stable heart function to allow the undertaking of neuropsychological testing, no cancer anamnesis, no recent neurological or psychiatric diseases, no malfunction of hemapoiesis or hemolytic anemia. Patients, 78% were treated with coronary artery bypass grafting, 12% with aortic valve replacement, 3% with mitral valve replacement and 3% with a combined aortic and mitral valve replacement. Average time of the operation was 157 min (ranging from 90 to 250 min). Extracorporeal circulation was performed with a 3M® heart-lung pump with a pulsatile flow and a membrane oxygenator was employed. Average cross clamping time was 46 min (ranging from 19 to 121 min). The lowest mean central body temperature was 32°C and an alphastud regime was used. The surgical control group consisted of 50 patients having operations in general and vascular surgery. Patients, 13, underwent a cholecystectomy operation, 14 patients had a Y-prosthesis operation, 8 patients a strumenectomy and 15 patients having other surgical interventions. The average time for operations was 190 min (ranging from 90 to 250 min). All patients in the control group were selected with the same criteria as the experimental group. Patients having previous cardiac surgery were excluded from the control group.

The experimental group (70%) and 50% of control group were men.

For psychometric measurements the mini mental status test (MMST) was used, which is an instrument, that can easily predict and explore cognitive dysfunction whilst disregarding the emotional aspects of the patient. The MMST derived a total of six neuropsychological indexes, these being: (i) orientation; (ii) memory; (iii) attention; (iv) concentration; (v) language; and (vi) conceptual reasoning, which are valued up to 30 points [2,6,19]. In order to evaluate norm values for the MMST, [6] investigated the correlation between points obtained in MMST and grade of neuropsychological alteration in four groups. These studies lead to the following mean values of patients with neuropsychological disorders: Dementia patients 9, 7 points in MMST; depressive patients with cognitive alterations 19 points; patients with affective alterations 25.1 points and normal volunteers 27.6 points [6]. The test has a very high interrater-reliability (Pearson-correlation coefficient $r = 0.887$) with a sensitivity of 87% and a specificity of 82%. The neuropsychological testing was typically completed within 1 day prior to the operation for each patient. Postoperative testing was carried out 48 and 72 h after operation.

NSE serum levels were examined with Cobas® Core NSE EIA Kit (Roche) [13,16,17]. This enzyme immunoassay (EIA) is a solid phase EIA based on the sandwich technique. The assay utilizes a highly specific monoclonal antibody to NSE immobilized on a polystyrene bead in conjunction with a polyclonal (rabbit) antibody. Patients serum samples were incubated in one step with beads coated with monoclonal mouse anti-NSE and with rabbit anti NSE. During this incubation period, the NSE reacts simultaneously with the monoclonal antibody bound to the beads and with the rabbit antibody to form the sandwich. Following this initial incubation period, the beads were washed to remove any unbound rabbit antibody and subsequently incubated in a highly purified goat antibody to rabbit immunoglobulin conjugated to horseradish peroxidase. In this phase, the goat antibody-horseradish peroxidase conjugate binds to the rabbit antibody already bound to the bead through NSE. Following this period, the
beads are again washed to remove any unbound antibody-enzyme conjugate and are then incubated with an enzyme-substrate/chromogen solution. Colour intensity is directly proportional to the amount of NSE present in samples and standards. Patient samples can be directly obtained by photometry. The measuring range of this EIA kit is 1–200 ng/ml. The intraassay and interassay coefficients of variation have been <8% over the entire measuring range. Normal serum levels ranges in 95% below 13.2 ng/ml, with a mean value of 8.5 ng/ml.

In order to avoid increased NSE serum levels caused by hemolysis [15] we measured the following parameters in every patient: Total bilirubin, free hemoglobin, haptoglobin and HBDH. All patients with positive hemolysis parameter meaning total bilirubin >1 mg/dl, free hemoglobin >55 mg/dl, haptoglobin <3 g/l and hydroxybutyrate dehydrogenase $<140$ U/l were excluded from the experimental group. Blood samples were taken from a periphery vein 24 h before the operation (T1), 24 h (T2) and 48 h (T3) after the operation.

3. Results

Fig. 1 shows the mean values of NSE serum levels for each group at pre-, postoperative and 48 h postoperative measurements. Overall differences between the experimental and the control group were significant ($P = 0.002$). In the experimental group (group I) the NSE mean level increases significantly ($P < 0.005$) in 154 patients from 11.8 pre- to 20.2 ng/ml postoperatively and declines to approximately the normalized mean value of 14.4 ng/ml 48 h postoperatively. Patients, 46 (23%) of group I showed no significant changes of NSE serum levels. In the control group (group II) no significant change of NSE serum levels was detected.

Fig. 2 shows the mean values of MMST points for each group studied preoperatively, 48 and 72 h postoperatively. Postoperative mean scores of group 1 differed from preoperative examination about 2.18 points less. Points lost were examined in 123 patients of group I. Pre- and postoperative mean scores of group II had nearly similar point levels.

To gain better results in psychometric analysis we use a specified form of MMST combined with an extended form of neuropsychological screening in case of postoperative MMST point loss in present studies.

Fig. 3 demonstrates the changes of preoperatively right through to postoperatively NSE values and points loss of 13 patients in experimental group. In these patients we measured the highest postoperative NSE serum levels. In eight of these patients we found signs of an exogene psychosis such as minor confusion up to subacute delirious states. Three patients suffered a transient ischemic attack (TIA) and out of these 3 patients, two suffered a motorial disorder and 1 patient a sensory disorder. Two patients suffered from incomplete hemiparesis which was fully reversible in the following 14 days. There is a high correlation of $r = 0.92$ between the postoperative loss of points in MMST and the increase of the postoperative NSE serum levels. The postoperative increases of NSE in the 8 patients with the postoperative psychosyndrome ranging between 10

![Fig. 1](https://academic.oup.com/ejcts/article-abstract/11/4/640/350151/1460450151)

![Fig. 2](https://academic.oup.com/ejcts/article-abstract/11/4/640/350151/1460450151)

![Fig. 3](https://academic.oup.com/ejcts/article-abstract/11/4/640/350151/1460450151)
and 18 ng/ml, the loss of points in MMST between 2 and 4 points. The 3 patients who suffered postoperative TIA had an average postoperative increase of 20 ng/ml and similar loss of 4 points in MMST. Maximum NSE releases we found in 2 patients with a prolonged reversible ischemic neurological deficit (PRIND) 1 patient with a NSE serum level of 69 ng/ml and 29 points loss in MMST the other patient with a NSE serum level of 45 ng/ml and 8 points loss in MMST.

Three more patients with a postoperative NSE increase between 6 and 9 ng/ml and point loss in MMST between 2 and 4 points showed cerebral disturbances with disorientation and confusion.

4. Discussion

Similar to previous reports, the patients in this study showed evidence of neurological and neuropsychological impairment relative to general surgery control patients. The incidence of such complications in this patient sample was 8%. This figure is similar to the findings of other investigators who discuss an incidence of brain related complications after cardiac surgery about 5–15%. Although it was found, that postoperatively the patient sample was used, performed poorer on neuropsychological testing [8]. However, their performance is significantly different from other patients with atherosclerotic disease undergoing non-cardiac operations and caused by nonspecific aspects of surgery we have to investigate with more specific and sensitive neuropsychological testing. We measured postoperative NSE increases in over 80% of the patients, that could be explained as transient cerebral impairment during the operations. Thirteen patients with evident postoperative neurological or neuropsychological occurrences showed significant increases of postoperative NSE serum levels. Regarding these results, there seems to be an increase of NSE serum levels in case of neurological and neuropsychological disorder. The good correlation ($r = 0.96$) between point loss in MMST and increases of NSE indicates, that the extent of cerebral injury correlates to the NSE release into the blood. Elevated NSE levels in CSF have been reported earlier in experimental studies, which demonstrated by animal testing, the correlation between the extent of cerebral ischemia and the release of NSE [3,9,10]. However, the mechanism of how NSE is transferred through the hematoencephalic barrier is still not clear, but there seems to be a relationship between the elevated NSE levels in CSF and in blood serum. Our observations are indicating a possible quantification of cerebral ischemia by the NSE releases in the early postoperative period. NSE values exceeding 35 ng/ml point to an unfavorable postoperative neurological outcome. In contrast NSE concentrations under 35 ng/ml mostly indicate a good recovery in the first few following the operation [21].

In order to prove this hypothesis we are still working on analysis with perioperative measurements of protein S-100, which could be a new and promising marker enzyme to evaluate cerebral risk during cardiac surgery.

References