Copeptin as a diagnostic marker in the management of neurosurgical patients with disturbance of water homeostasis (NCT01465672)

Lead investigators:

Christian Zweifel[1,2], Mirjam Christ-Crain[3]

Co-investigators:

Basel: Bettina Winzeler[3], Nicole Nigro[3], Christopher Kelly[2], Luigi Mariani[2]

Aarau: Birsen Arici[4], Philipp Schuetz[4], Beat Müller[4], Sven Berkmann[5], Hans Landolt[5]

Toronto: Gelareh Zadeh[2], Fred Gentili[2]

[1]Department of Neurosurgery, University Hospital of Basel, Switzerland

[2]Neurosurgery Division, Toronto Western Hospital, 399 Bathurst St., Toronto, Canada

[3]Department of Endocrinology and Clinical Nutrition, University Hospital of Basel, Switzerland

[4]Department of Endocrinology, Medical University Clinic Kantonsspital Aarau, Switzerland

[5]Department of Neurosurgery, Kantonsspital Aarau, Switzerland

Correspondence:

Dr. Christian Zweifel

Skullbase/Neurovascular Fellow

Neurosurgery Division

Toronto Western Hospital

399 Bathurst St.

Toronto, ON CA M5T 2S8

Email: zweifelch@gmx.ch

Protocol

1. SYNOPSIS

Background: Water imbalance and consecutive electrolyte disturbances are common in the postoperative course of neurosurgical patients after pituitary surgery. Diabetes insipidus (DI) may complicate the postoperative course in as many as 30% of patients. Early and accurate diagnosis of water and electrolyte disturbances postoperatively is important for an adequate fluid and drug administration. However, identifying the causes is challenging/ ambiguous in clinical practice. Levels of antidiuretic hormone (ADH) might contribute to a straightforward diagnosis, though, its measurement is cumbersome. ADH is derived from a larger precursor peptide along with copeptin, which is a more stable peptide directly mirroring the production of ADH. Copeptin can be assayed readily in plasma.

Aim: To investigate whether copeptin can accurately diagnose postoperative disturbances of water homeostasis (i.e. Diabetes insipidus and SIADH) in a cohort of patients undergoing intracranial tumor surgery.

Design: Prospective, observational study.

Location Setting: Department of Neurosurgery and Endocrinology, University Hospital of Basel, Aarau and Toronto.

Patients: Patients undergoing transphenoidal pituitary adenoma resection and patients with transcranial surgery of tumors close to the pituitary gland and hypothalamus.

Intervention: All routinely determined baseline data will be assessed including medical history, clinical items (i.e. vital signs, neurological status, volume status including weight) and laboratory parameters (e.g. urine / serum osmolality, electrolytes). Blood will be drawn during routine blood measurements. All patients will undergo daily clinical and laboratory follow-up until the day of discharge.

Study hypothesis: We hypothesize that copeptin shows significantly lower values in patients with complete DI, compared to patients with transient DI and compared to patients with a normal postoperative course. Second, we expect that copeptin shows higher values in patients with SIADH compared to patients with a normal postoperative course.

Analysis: Based on preliminary results from a previous study with patients after transphenoidal surgery, patients with permanent DI had copeptin levels of 2.5pmol/l (±0.5) and uneventful patients had copeptin levels of 3.5pmol/l (±1.5). Based on the literature and own experience, we expect 25 (20%) patients out of 125 patients to develop DI. With 125

patients, we will thus have a power of 84% to detect a difference in copeptin levels of 1pmol/l with a standard deviation of 1.5pmol/l.

Significance: A more timely and accurate diagnostic approach to determine the etiology of water and electrolyte disturbances in postoperative neurosurgical care would improve patient management. Copeptin could become an innovative tool to guide early treatment decisions, fluid management, and management of patients.

2. RESEARCH PLAN

2.1 Introduction

Disorders of water balance caused by disturbances in vasopressin (ADH) secretion and posterior pituitary function remain a common cause of morbidity among patients undergoing transsphenoidal surgery. Abnormalities of ADH secretion resulting in postoperative central Diabetes insipidus (DI) and the syndrome of inappropriate secretion of ADH (SIADH) are the most common early postoperative endocrine complications. (Singer and Sevilla 2003) The overall incidence of any postoperative (transient or permanent) DI in transsphenoidal pituitary surgery series has been reported to range from 1.6 to 31% (Black et al. 1987; Hensen et al. 1999; Singer and Sevilla 2003). Risk factors which have been identified as being associated with increased risk for DI after microsurgery included having a microadenoma, craniopharyngioma, Rathke's cleft cyst, or intraoperative cerebrospinal fluid (CSF) leak (Nemergut et al. 2005). Although the disease is transient and benign in the overwhelming majority of cases, prolonged or permanent DI may also occur. (Black et al. 1987; Seckl and Dunger 1989; Seckl et al. 1987) A timely and accurate diagnosis followed by a correct treatment is crucial (Anderson 1986; Berl 1990).

Besides measurement of plasma osmolality and sodium concentration in urine, determination of the extracellular fluid volume remains the most important discriminatory element. Its prediction based on clinical signs and routine laboratory evaluation, however, has a limited sensitivity and specificity of <50% (Chung et al. 1987; Musch et al. 1995).

Levels of ADH might contribute to a straightforward diagnosis. Unfortunately, the measurement of circulating ADH levels is challenging, since the mature hormone is very unstable, largely attached to platelets and rapidly cleared from plasma with a half-life of 5 to 15 minutes. ADH is derived from a larger precursor peptide (pre-provasopressin) along with two other peptides, neurophysin II and copeptin. Released in an equimolar ratio, the amount of copeptin mirrors the production of ADH. Plasma copeptin concentration have recently been shown to be an easy to determine, steady parameter (Morgenthaler et al. 2005; Struck et al. 2005).

A rapid and accurate diagnosis leading to adequate treatment and fluid management is important, as DI may occur within a short time period postoperatively. Herein, we aim to evaluate copeptin as a diagnostic marker for water balance disturbances in an adequately powered cohort of patients undergoing pituitary surgery.

2.2 Preliminary results

Katan et al. showed that copeptin levels with a cutoff of 2.5pm/l (±0.5) is diagnostic for permanent DI in patients one year after transsphenoidal surgery. (Katan et al. 2007) Preliminary data comparing copeptin values in patients with central DI and healthy volunteers are shown below (**Figure 1**).

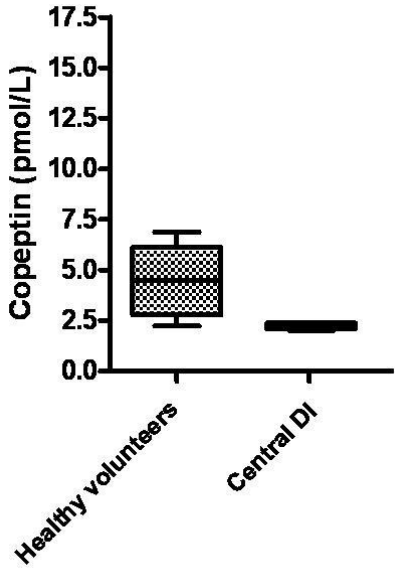

Figure 1: Copeptin levels from healthy volunteers compared to patients with central DI. Patients with DI have markedly lower values than healthy volunteers ($p<0.01$) (preliminary results).

In a pilot study (EKBB 157/06), we assessed copeptin as a diagnostic marker for electrolyte and water balance disturbances in 13 patients after pituitary surgery. Three of these patients developed DI. Thereby, copeptin levels determined at the time of diagnosis of DI were significantly lower compared to patients without the diagnosis of DI at the same time points **(Figure 2)**.

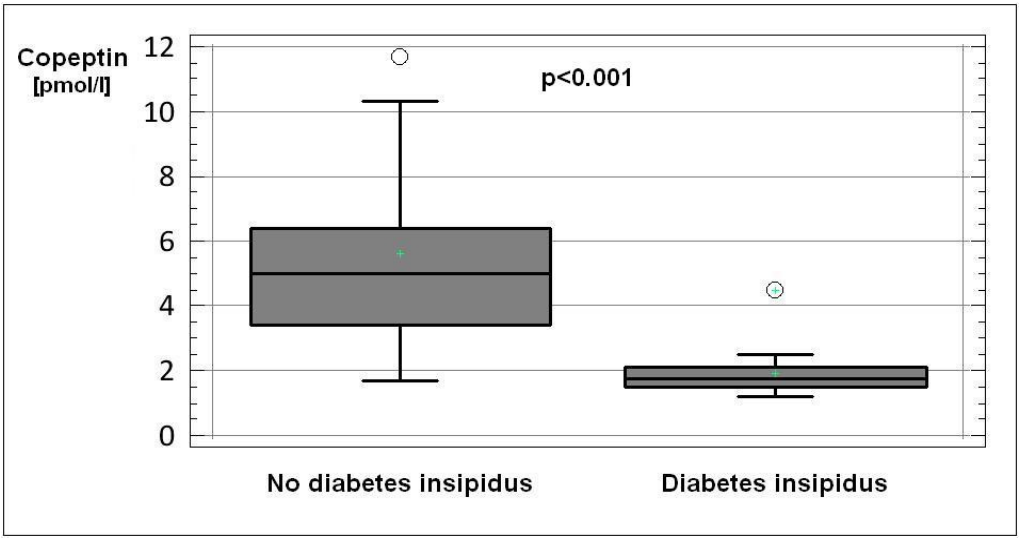

Figure 2: Serum copeptin levels in patients with symptoms of DI (n=3) and without (n=10). Solid lines denote median values, boxes represent 25 to 75 percentiles and whiskers indicate the range from 12.5 to 87.5 percentiles. The median copeptin value in patients without symptoms of a DI was 5 pmol/l [3.47; 6.32 pmol/l] and was significantly higher compared to 1.76pmol/l [1.54; 2.08 pmol/l] ($p<0.001$) when DI was present.

2.3 DETAILED RESEARCH PLAN

A. Objectives

The **primary objective** of this trial is to evaluate the diagnostic value of copeptin levels in the diagnosis of postoperative DI in patients undergoing surgery of intra- and suprasellar lesions, which occurs in about 20% of patients.

Our **second objective** is to evaluate copeptin as a diagnostic tool in patients with postoperative water disturbances as a result of SIADH which occurs in about 5% of patients undergoing pituitary surgery (Hensen et al. 1999). For the final diagnosis of DI and SIADH, we will use a standardized clinical algorithm based on medical history, drug history, clinical assessment of the extracellular fluid volume and laboratory parameters during hospitalization.

B. Definition of Diabetes Inspidus and SIADH

Diabetes insipidus

The leading symptom of DI is polyuria. DI is diagnosed when polyuria is present (>50ml/kg/day), serum osmolality is over 295mosmol/l, serum sodium above 145mmol/l and urine osmolality lower than 400mosmol/l in the presence of normoglycemia (Kumar and Berl 1998). For the diagnosis of partial DI, polyuria is required (>50ml/kg/day), serum osmolality above 295mosmol/l and urine osmolality between 400-800 mosmol/l.

SIADH

The leading symptom of SIADH is hyponatremia and will be diagnosed as follows (Kumar and Berl 1998): A positive water balance must be present with serum osmolality below 275 mmosmol/l and urine sodium below 130mosmol/l. Urine osmolality is above 275mosmol/l, or above 100mosmol/l, respectively, in case when serum osmolality is very low.

C. Hypothesis

We hypothesize that copeptin shows significantly lower values in patients with complete DI (Copeptin < 2.5pmol/l), compared to patients with partial DI (Copeptin > 3.5pmol/l) and compared to patients with a normal postoperative course. Second, we expect that copeptin shows higher values (Copeptin > 10pmol/l) in patients with SIADH compared to patients with a normal postoperative course. This copeptin threshold of 10pmol/l is based on a previous published study demonstrating that copeptin values in patients with SIADH are significantly higher than in healthy volunteers (Fenske et al. 2009).

D. Statistical Analyses

This is a prospective observational study to evaluate copeptin as a diagnostic marker in neurosurgical patients. All relevant clinical and laboratory parameters obtained by interview, clinical tests and review of the medical records will be entered into an Excel® database. Statistical Analysis System (SAS® Institute, Cary, NC, USA) will be used for data analysis.

Copeptin levels will be assessed in batch analysis upon completion of the plasma asservation. Discrete variables will be expressed as counts (percentage) and continuous variables as means ± standard deviation (SD) or median (interquartile range), unless stated otherwise.

First, the overall prevalence of elektrolyte and water balance disturbances will be assessed. Two-group comparison of normally distributed data will be performed by Students t-test. For multigroup comparisons, one-way analysis of variance with least square difference for posthoc comparison will be applied. For data not normally distributed, the Mann-Whitney-U test is used if only two groups are compared. The Kruskal-Wallis one-way analysis of variance will be used if more than two groups were being compared.

We will do a correlation analysis of copeptin levels with sodium levels, serum osmolality and other diagnostic laboratory parameters. Correlation analyses will be performed by using Spearman rank correlation. Levels that are non-detectable will be assigned a value equal to the lower limit of detection for the assay. All testing will be two-tailed and P values less than 0.05 will be considered to indicate statistical significance. Scatterplot data will be shown with

GraphPad Prism®, Version 4.00 for Windows (GraphPad Software, San Diego California, USA).

We will calculate receiver operating characteristic (ROC) curves and compare areas under the curve for copeptin and other parameters, i.e. urine and serum osmolality and sodium levels. The sensitivity and specificity to predict the correct diagnosis of elektrolyte and water balance disturbances will be determined, based on the above standardized algorithm (Reynolds et al. 2006). This ascertainment will be done on the basis of the review of the complete patient charts by two blinded doctors. Discordant cases will be mutually discussed and resolved. Patients will be managed as usual according to the state of the art treatment.

Sample Size considerations

Our sample size calculation is based on the assumption that patients with DI have a copeptin value of ≤2.5pmol/l (SD ±0.5) and uneventful patients without DI have copeptin values of ≥3.5pmol/l (SD ±1.5) and an incidence of DI of around 20% within our population. A total of 125 included patients with 25 patients developing a DI will give this study a power of 84% to detect a difference in copeptin levels of 1pmol/l. Moreover, this will allow us to calculate multivariate logistic regression analysis and adjust for 2-3 parameters without overfitting the regression model

E. Study Design

Study setting

Department of Neurosurgery and Endocrinology, University Hospital of Basel, Aarau and Toronto.

Inclusion criteria

All consecutive patients who undergo surgery for an intra- or suprasellar lesion, either by craniotomy or by transphenoidal resection.

Exclusion criteria

None

F. Procedures

Baseline data collection in patients will be collected by the investigators and contain

a) age

b) gender

c) Tumor specific items: location, size, histology.

d) General medical history items: actual history that preceded the hospitalization; family history; relevant co-morbidities; co-morbidities increasing the risk for dysnatremia (e.g.:

smoking history (pack-years) and status (pack per day); current medication; alcohol consumption (glass and grams per day); time from onset of symptoms to admission).

e) Clinical items: physical examination including neurological status on admission, body temperature.

f) Imaging: Computer tomography or MRI of the neurocranium (T1, T2, diffusion-weighted image sequence, with or without contrast).

g) Clinical symptoms and *water balance* will be assessed daily.

h) Routine/Standard laboratory tests: The first blood sampling will be done preoperative and endocrinological markers will be determined according to the endocrinologist' recommendation. In patients after pituitary surgery, the follow up blood sampling will be done with the everyday routine blood sampling from day 1 postoperative until discharge (usually day 3). Routine postoperative blood samplings include serum sodium, serum potassium, serum and urine osmolality and is a standard procedure to detect any postoperative electrolyte imbalances. All blood sampling will be done before any food intake, or smoking, if feasible. Importantly, all these investigations are currently performed in the routine setting.

Measurement of copeptin concentrations

For every routine blood sampling, residual blood is left over and stored for about 5 to 8 days. We will use this residual blood for copeptin measurement. Therefore, no additional blood sampling will be done as a residual blood amount of 0.1ml is sufficient to determine copeptin. Copeptin levels will be measured as a batch analysis with a new improved chemiluminescens sandwich immunoassay with a lower detection limit of the assay of 0.4 pmol/l (Fenske et al. 2009).

G. Potential risks

We consider the risks of this study to be minor and limited to the risk of routine blood sampling which is 5ml per sampling. No additional blood will be taken.

H. LIMITATIONS

Confidentiality

All informations will be kept strictly confidential. All data forms will be handled as confidential information.

I. REGULATORY AND LIABILITY CONSIDERATIONS

Regulatory Considerations

This study will be conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable International Conference on

Harmonization (ICH) guidelines on good clinical practice, whichever represents the greater protection of the individual.
As it is an observation of the current triage process, there are no additional risks involved for the patients. There will be no interview during the hospitalization and after discharge. Patients willing to participate are required to provide written informed consent for their agreement for the use of their data for scientific purposes. The consent can be obtained preoperatively or in the postoperative hospital course (Appendix1). Data collected will be kept confidential and accessible only to researcher involved.

Liability
This is an investigator driven study. Liability for the technical reliability of the copeptin measurement is with the producer of the test (Brahms, Hennigsdorf, Germany). There are no additional costs for the patient or the health insurance to bear.

2.4 TIMETABLE

Start patient enrolment	July 1st 2011
End of patient recruitment	June 30st 2013

2.5 SIGNIFICANCE OF THE PROPOSED STUDY

An abnormality of ADH secretion resulting in postoperative central DI is the most common early postoperative endocrine complication. Copeptin may be an important new diagnostic marker in the management of patients with disturbance of the neuroendocrine homeostasis due to pituitary surgery. A better diagnostic approach to determine the etiology of water homeostasis disturbances would improve patient management, especially fluid management and monitoring of desmopressin treatment. Dependent on the results, we will perform an intervention study to evaluate whether copeptin levels provide a useful tool to guide fluid and drug management in these patients.

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