PRACA ORYGINALNA

Cystatin C as potential marker of Acute Kidney Injury in patients after Abdominal Aortic Aneurysms Surgery – preliminary study

Cystatyna C jako marker ostrego uszkodzenia nerek u pacjentów po operacji tętniaków aorty brzusznej – badanie wstępne

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ABSTRACT

INTRODUCTION

The management of asymptomatic abdominal aortic aneurysms (AAA) includes elective surgery. Among perioperative complications, postoperative acute kidney injury (AKI) appears to be one of the most severe. A rise in serum creatinine (sCr) may not be noticed in the early stage of AKI. According to some reports, a higher level of AKI novel biomarker- cystatin C (CysC) can be detected in serum 24–48 hours earlier than an increase in the sCr level.
The purpose of this study was to compare CysC and sCr as indicators of the early phase of AKI in patients after AAA surgery.

METHOD

The study protocol included patients classified for elective AAA surgery. The ultimate number of patients who fulfilled the inclusion criteria and did not meet the criteria for exclusion from the study was 14. CysC and sCr were measured one day before surgery (day-1) and 12, 24, 48 and 72 hours after surgery. The operative time and aortic clamping time were also recorded.

RESULTS

There was a tendency for both sCr and CysC to rise, though not significantly. No statistically significant connection was shown between the aortic clamping time release and sCr and CysC. The correlation between sCr and serum CysC revealed a statistical significance ($p < 0.05$). No correlation was shown between sCr and CRP nor CysC and CRP.

CONCLUSIONS

The CysC serum level is not superior to the sCr level in the diagnosis of AKI after AAA surgery.

KEY WORDS

Acute Kidney Injury, Cystatin C, Abdominal Aortic Aneurysm Surgery

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STRESZCZENIE

WSTĘP

Planowe operacje chirurgiczne są jedną z metod postępowania w leczeniu bezobjawowych tętniaków aorty brzusznej. Jednym z najpoważniejszych powikłań okołooperacyjnych jest ostre uszkodzenie nerek. Zwiększenie stężenia kreatyniny nie zawsze koreluje z czasem powstania ostrego uszkodzenia nerek. Według niektórych doniesień, zwiększenie stężenia cystatyny C w surowicy może wyprzedzać o 24–48 godzin zwiększenie stężenia kreatyniny.

Celem pracy było porównanie stężeń Cystatyny C i kreatyniny w surowicy jako wskaźników wczesnego uszkodzenia nerek u pacjentów po operacjach tętniaków aorty.

METODA

Protokół badania obejmował pacjentów zakwalifikowanych do operacji tętniaka aorty brzusznej. Wyselekcjonowano 14 pacjentów spełniających kryteria włączenia do badania i niespełniających kryteriów wyłączenia z badania. Cystatynę C oznaczano w surowicy w dniu przed planowaną operacją tętniaka oraz w 12, 24, 48 i 72 godzinie po operacji. Stężenie kreatyniny w surowicy oznaczano w pierwszym oraz w kolejnych pięciu dniach po zabiegu. Zanotowano również czas zabiegu operacyjnego oraz czas zacisku aorty.

WYNIKI

Obserwowano tendencję do wzrostu stężenia Cystatyny C i kreatyniny w surowicy nieistotną statystycznie. Nie odnotowano istotności statystycznej między czasem zwolnienia zacisku aorty a stężeniem kreatyniny oraz Cystatyny C. Korelacja między stężeniem Cystatyny C a stężeniem kreatyniny w surowicy była istotna statystycznie ($p < 0,05$). Nie uwidoczniono korelacji między stężeniami kreatyniny i Cystatyny C a stężeniem CRP.

WNIOSKI

Nie stwierdzono wyższości oznaczenia stężenia Cystatyny C nad oznaczeniem stężenia kreatyniny w rozpoznaniu ostergo uszkodzenia nerek (AKI) u chorych operowanych z powodu tętniaków aorty.

SŁOWA KLUCZOWE

ostre uszkodzenie nerek, Cystatyna C, operacja tętniaków aorty brzusznej

INTRODUCTION

The prevalence of abdominal aortic aneurysm (AAA) increases with age, and is higher in men than in women [29].

The pathogenesis of aortic aneurysms is likely associated with the abnormal production and regulation of matrix metaloproteinases (MMPs) resulting in the inflammatory infiltration of cytokines leading to vessel wall destruction [30]. A vast majority of abdominal aortic aneurysms are asymptomatic and detected incidentally. Abdominal ultrasound and contrast enhanced computed tomography imaging are widely used for the detection of AAA. The management of asymptomatic AAA is the prevention of rupture, including prophylaxis and non-invasive medical treatment as well as elective surgery [31]. The risk of perioperative complications includes cardiac and respiratory events as well as postoperative renal failure.

Following some recent publications, acute kidney injury (AKI) defined using RIFLE criteria occurred in approximately one fourth (24%) of patients after AAA surgery [32], whereas Tallgren M [33] reported acute kidney dysfunction in 22% of patients undergoing infrarenal aortic repair.

However, based on serum creatinine (sCr), a commonly used marker of AKI, it is highly possible to overlook the proper onset of AKI due to a delayed increase in sCr.

In recent years, many articles have been published regarding more sensitive AKI biomarkers. One of the most investigated appears to be Cystatin C (CysC) [34,35,36,37,38]. This novel biomarker can be detected in serum 24–48 hours earlier than sCr. Cystatin C does not undergo tubular secretion and therefore its serum concentration is determined by glomerular

filtration. In fact, many investigators focused on the role of CysC in contrast-induced acute kidney injury [18,33] coronary and cardiac surgery [39,41], acute heart failure [40]. However, up until now, little is known regarding the influence of AAA surgery and the early stage of AKI measured by serum cystatin C concentration.

Table I. Patients' characteristics
Tabela I. Dane pacjentów

Parameters	Results
Demographic parameters	
Number of patients	14
Males/females	12/4
Age	66.39 ± 6.31
Body mass index, kg/m^2	26.41 ± 3.86
Comorbidities (number of patients)	
Current smokers	7
Diabetes	3
Coronary artery disease	5
Hypertension	8
Peripheral vascular disease	6
Aneurysm characteristics	
Neck diameter, mm	24.4 ± 6.5
Neck length, mm	25.6 ± 8.0
Aneurysm diameter, mm	59.2 ± 10.9
Kidney long axis	
Right kidney, mm	93.5 ± 9.3
Left kidney, mm	96.7 ± 8.5
Kidney Doppler examination	
Right kidney Pulsation Index	0.9 ± 0.17
Left kidney Pulsation Index	0.8 ± 0.2
Right kidney Resistance Index	0.6 ± 0.08
Left kidney Resistance Index	0.6 ± 0.1
Serum levels	
Total cholesterol, mg/dL	218.4 ± 64.2
High density cholesterol, mg/dL	38.4 ± 7.7
Low density cholesterol, mg/dL	145.8 ± 58.7
Triglycerides, mg/dL	178.3 ± 88.2
Fasting glucose, mg/dL	94.07 ± 15.6
Sodium, mmol/L	140 ± 2.18
Potassium, mmol/L	4.26 ± 0.4
Glycosylated hemoglobin, %	6. 14 ± 0.71
Blood count parameters	
Erythrocyte count before surgery, × 10^{12}/L	4.8 ± 0.4
Erythrocyte count 4 h after surgery, × 10^{12}/L	3.9 ± 0.48
Hemoglobin concentration before surgery, mmol/L	14.6 ± 1.3
Hemoglobin concentration 4 h after surgery, mmol/L	11.7 ± 1.4
Hematocrite before surgery , %	43.6 ± 3.5
Hematocrite 4 h after surgery , %	35.48 ± 4.15
Platelets count before surgery, × 10^9/L	228 ± 57.15
Platelets count after surgery, × 10^9/L	185.4 ± 50.55*
C-reactive protein	
Before surgery, mg/L	10.38 ± 14.6
72 h after surgery, mg/L	214.9 ± 63.6
Estimated GFRs according to MDRD Study and CKD-EPI Study equations	
Before surgery mL/min/1.73 m^2	74.39 ± 25.6
After surgery mL/min/1.73 m^2	88.8 ± 23.4

Number or mean ± SD
* - $p < 0.05$ vs. prior to surgery

The purpose of this study was to estimate the value of cystatin C as a marker of an early stage of AKI following abdominal aortic aneurysm surgery.

As a part of ongoing research regarding the occurrence of AKI in post abdominal aortic aneurysm operation patients, we prospectively studied elective patients admitted to the Department of Vascular Surgery for surgical treatment.

Cystatin C as well as creatinine concentration were used to evaluate the incidence of postoperative AKI.

The research was approved by the Bioethics Committee of the Medical University of Silesia. All the criteria of Good Medical Practice and informed consent procedure were executed prior to the study. Each patient was given a research protocol and signed an informed consent.

PATIENTS CHARACTERISTICS

The patients were initially diagnosed by abdominal ultrasound and renal artery Doppler, then classified for elective AAA surgery (aneurysm diameter > 5.5 cm). A tentative number of 14 patients, who fulfilled the inclusion and did not meet the exclusion criteria, were involved in the study. The protocol of exclusion criteria included negative medical history of:

- recent acute/chronic renal failure, hemodialysis or other forms of renal replacement therapy during the last six months
- an ongoing acute inflammatory process
- urinary tract obstruction
- use of antibiotics (in particular aminoglicosides within one month prior to surgery), immunosuppressants or cytostatics
- neoplastic diseases
- recent stroke (during two months prior to surgery)
- recent myocardial infarction (up to three months)
- previous operations (up to one month)
- major neurological or internal organ disorders. The details regarding the patients' demographics, comorbidities, aneurysm characteristics, kidney features and laboratory results are shown in Table I.

SURGICAL PROCEDURE

Based on the preoperative contrast-enhanced computed tomographic angiography (performed at least 3 days before the procedure), all the participants were diagnosed to have an infrarenal aortic aneurysm. Surgery was performed through a midline incision. The posterior parietal peritoneum was exposed. The retroperitoneal arteries were identified. The aorta was cross-clamped below the kidney arteries and reconstructed with a PTFE graft. The surgical procedure was performed under general anesthesia. During the

procedure, on average 3000 ml intravenous fluid, 1000 ml erythrocyte mass and blood plasma were transfused to the patients. The details are shown in Table II.

Table II. Surgery details
Tabela II. Dane operacji chirurgicznej

Operative time, min	121.7 ± 36.3
Aorta cross-clamping time, min	35.7 ± 11.9
Blood loss during surgery, mL (14)	928.5 ± 849.8
Intravenous fluid supplementation during surgery, mL (14)	3496.4 ± 1018.7
Erythrocyte mass transfused during surgery, mL (2)	1120; 560
Blood plasma transfused during surgery, mL (1)	1020

METHODS AND STUDY PROTOCOL

14 patients were enrolled in the study (two patients with an initial boundary serum creatinine level). Each participant underwent initial enquiry regarding previous medical history. Prior to AAA surgery, all the subjects had abdominal ultrasound and a renal artery Doppler done to exclude renal or vascular disorders. Within the whole procedure, no significant blood pressure drops or threatening tachycardia/bradycardia were recorded, nor was there need for catecholamine usage. After the AAA surgery, 24-hour urine collection was measured to determine proper urine output. Although full blood counts after the AAA surgery dropped slightly, the patients' vital signs remained stable.

All the patients classified for our research underwent the study protocol.

On admission and in the following days, a basic physical examination was performed on each patient. Medications such as metformin, NSAIDs, diuretics and other potentially nephrotoxic drugs were withdrawn 24 hours before the procedure. The day before the surgical procedure (day '-1'), blood samples for full blood counts (FBC), creatinine and electrolytes (sCr&E), Cystatin C, total cholesterol (TC), high density cholesterol (HDL), triglicerydes (TG), glucose, glycosylated hemoglobin (HbA1c) and C-reactive protein (CRP) were taken from a peripheral vein. A urine sample was taken for general analysis. 24-hour urine collection was administered.

On the procedure day (day '0'), urine output was monitored via a Foley catheter. The operative time, aortic clamping time, total intravenous fluids volume, blood loss volume, supplemental erythrocyte mass and blood plasma volume as well as heart rate, blood pressure, anesthetic and analgetic drugs (including catecholamines) and potential diuretics within the procedure were recorded.

FBC was collected 4 hours after the surgery.

Serum cystatin C was obtained 12 hours, 24 hours, 48 hours, 72 hours after clamp release.

On the following days: (day 1 to day 5) 24-hour urine collection and serum creatinine concentration were administered. CRP was obtained 72 hours after the surgery.

Cystatin C was measured by using the sandwich enzyme immunoassay RD191009100 Human Cystatin C ELISA manufactured by BioVendor Laboratorini medicina a.s., Czech Republic. Serum and urine creatinine were assessed by the Jaffe colorimetric method. Commercially available tests were used to determine other laboratory parameters.

Statistical analysis

Because of the number of participants selected for our research and the collected data, we relied on non-parametric tests (Kruskall-Wallace, Man-Whitney U) for not normally distributed variables. The Spearman test was used for the correlation rate and Spearman's rank correlation coefficient was calculated. The outcomes were presented as mean = standard deviation (SD) or median with ranges. $P < 0.05$ was considered as statistically significant. Statistica 8.0 software was used for statistical analysis. The results of the statistical analysis are shown in Table III–VI.

Table III. Changes in serum creatinine levels (mg/dl)
Tabela III. Zmiany stężenia kreatyniny (mg/dl)

Parameters/day	Day-1	Day 1	Day 2	Day 3	Day 4	Day 5
Mean	1.098	1.330	1.339	1.310	1.284	1.333
SD	0.290	0.466	0.660	0.866	0.651	1.092

Table IV. Changes in serum Cystatin C levels (ng/ml)
Tabela IV. Zmiany stężenia Cystatyny C (ng/ml)

Parameters/day	Day-1	12 h	24 h	48 h	72 h
Mean	1523.8	1658.9	1509.1	1652.8	1329.3
SD	935.9	1246.3	917.2	1072.4	637.9

Table V. Creatinine vs aortic clamping release time – Spearman's rank correlation
Tabela V. Stężenie kreatyniny vs czas zwolnienia zacisku aorty – korelacja rang Spearman

Variable	Day-1	Day 1	Day 2	Day 3	Day 4	Day 5
sCr	0.192	0.048	0.086	0.246	0.225	0.112
Clamping time	1.000	1.000	1.000	1.000	1.000	1.000
P	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

Table VI. Cystatin C vs aortic clamping release time – Spearman's rank correlation
Tabela IV. Stężenie Cystatyny C vs czas zwolnienia zacisku aorty – korelacja rang Spearman

Variable	Day-1	12 h	Day1	Day2	Day3
CC	0.265	0.328	0.223	0.090	0.090
Clamping time	1.000	1.000	1.000	1.000	1.000
P	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

RESULTS

Based on the statistical findings, we found that all the participants with preoperative normal kidney function (mean creatinine concentration 1.098 mg/dl) developed a postoperative rise in creatinine levels (mean creatinine concentration in the following days varied about 1.3 mg/dl). As proposed by the Acute Kidney Injury Network, AKI is characterized by a 0.3 mg/dl increase in baseline serum creatinine or a reduction in urine output of < 0.5 ml/kg/h within 6 hours. Our investigated serum creatinine reached its peak between 24–48 hours. The observed changes in the serum creatinine and serum cystatin C concentration were not significant. No correlation was proved between serum creatinine, serum cystatin C and C-reactive protein, measured before the procedure and 3 days after the surgery. The correlation between the serum creatinine and serum cystatin C revealed a statistical significance ($p < 0.05$). There was no significant correlation between aortic clamping time release and sCr or CysC.

DISCUSSION

The objective of our study was to determine whether a novel kidney biomarker cystatin C has prognostic ability and may be a potent indicator to diagnose an early stage of AKI in patients after AAA surgery.
We focused more on the serum creatinine concentration change before and after the procedure rather than its initial result. As an end point, we assumed the occurrence of AKI (based on the AKIN definition) comparing the serum creatinine versus serum cystatin C concentration changes. Our findings suggest that a rise in serum creatinine concentration of 0.3 mg/dl from the baseline (mean 1.098 mg/dl) to day 1 (mean 1,330 mg/dl), may evidence acute kidney injury. However, from the statistical point of view, the rise in serum creatinine was not significant. Similarly, the cystatin C serum concentration changes were not meaningful. We hypothesized whether the rise in serum creatinine concentration in the absence of urine output reduction may be an indicator of AKI, however, the serum creatinine rise had no significant importance.
Until recently, there have been numerous publications regarding the importance of cystatin C in indentifying an early stage of AKI [12,13,15,17]. One of the first pioneers who worked on this "gamma-trace" protein were Grubb and Lofberg. In 1979, they published an article proving that this trace protein was present in body fluids and increased in patients with advanced renal failure [8]. Nowadays Cystatin C is described to be an endogenous protein consisting of 120 amino acids, encoded by a gene located on chromosome 20 [2]. The protein occurs in all body fluids and is produced by all nucleated body cells [2]. In humans, cystatin C plays an important role by inactivating lysosomal cysteine proteinases and is filtered by glomerulus and entirely reabsorbed by the tubular cells. The assessment of serum cystatin C concentration is a sensitive indicator of glomerular filtration due to its independence of body mass and hydration level [6]. This unique feature determines cystatin C to be a significant marker of early acute kidney injury as well as its increased level correlates with renal failure, amyloid deposit-related and autoimmune diseases [1,2,5]. Cystatin C is detected in the early stage of renal dysfunction, approximately 24–48 hours earlier than serum creatinine. sCr measurements reveal poor sensitivity depending on the number of damaged nephrons [6,7]. There have been many articles published proving the importance of cystatin C in detecting early contrast-induced AKI [7,18], post cardiac surgery kidney injury [19,21,22] and being a good predictor of GFR damage caused by cisplatin [20].
Apart from its estimable value in kidney injury, cystatin C contributes to the protection against aortic aneurysm development [24,25]. Abisji et al. confirmed that reduced a cystatin C level in the aneurismal wall caused insufficient cysteine proteinases blockage and a potentially magnified aneurysm [16].
In our research we considered this a possibility, however, we focused on the absence of a significant increase between baseline CysC concentration (presented as mean concentration) and its concentration in the

following days (Table III). Thus, we failed to evidence an alteration in pre- versus postoperative serum cysC. Different studies have revealed inconsistent findings demonstrating the superiority of CysC and other renal indicators [26,27,28].

On the other hand, one should bear in mind the possible defects in cystatin C metabolism in patients with aortic aneurysms and its latter issues (lack of cystatin C rise in serum).

Serum creatinine was evaluated at the same time points on consecutive days following surgery and its outcomes disclosed a growth in concentration in relation to the baseline (day-1). Based on the established AKI definition (according to the Acute Kidney Injury Network), we postulate that we were dealing with transient kidney injury. Apparently, by surveying an available article [23], we took into consideration the fact of infrarenal aortic clamping time as a potential cause of transient lower limb ischemia and a possible reason for a rise in the creatinine level. The etiology of AKI is multifactorial in nature and can be induced by different agents such as primary kidney diseases, multiorgan disorders, sepsis, rhabdomiolysis, as well as hypertension, diabetes, vascular diseases and operative treatment. The morbidity of AKI definitely increases in the eldery with coexisting diseases. Many publications have shown an incidence of AKI after different types of surgery [32,33,41,42]. Thus, our participants were at risk of developing AKI due to their average age, comorbidities (Table II) and type of procedure. However, it is impossible to eliminate these factors in estimating the origin of AKI after AAA surgery. Infrarenal aortic clamping should not compromise proper blood supply to the renal arteries, however, transient lower limb ischemia might cause local rhabdomyolysis and latter renal implications.

It is still an open question whether a transient postoperative rise in serum creatinine concentration might have a different reason than AKI alone.

The limited number of patients classified for our research might be the reason we failed to prove a significant increase in the cystatin C level in the early stage of AKI after AAA surgery. However, the number of participants can only reflect the possible trend in favoring cystatin C over traditional kidney injury markers following such a procedure.

Undoubtedly, the role of cystatin C in aneurismal wall pathogenesis and evaluating post AAA surgery kidney injury requires further research.

CONCLUSIONS

Our pilot study revealed that the serum cystatin C level is not superior to the serum creatinine level in the diagnosis of acute kidney injury after abdominal aortic aneurysm surgery.

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