Hellenic Journal of Surgery (2018) **90**:5, 232-238

Pilot Trial Evaluating Mid-Regional Pro-Atrial Natriuretic Peptide as a Marker of Sepsis after Abdominal Surgery

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Abstract

Introduction: Mid-regional pro-atrial natriuretic peptide (MR pro-ANP) has been shown to be a diagnostic marker for sepsis. The objective of this pilot study was to evaluate the potential of MR pro-ANP in the diagnosis of postoperative sepsis.

Methods: We enrolled 18 patients with postoperative sepsis, 19 patients who underwent major abdominal surgery without sepsis and 9 healthy individuals as control subjects. MR pro-ANP, interleukin-6 (IL-6) and procalcitonin (PCT) were measured on the day of inclusion in the study, and at days 3, 7 and 10.

Results: The mean levels of MR pro-ANP were significantly higher in patients with postoperative sepsis than in patients without sepsis (two-way ANOVA $p < 0.0001$). The best cut-off level for MR pro-ANP was determined to be 162.5 pmol/l, with a sensitivity of 100% and specificity of 68%. On the day of inclusion in the study, MR pro-ANP detected postoperative sepsis equally as well as PCT (Youden test $P = 0.17$). MR pro-ANP levels in patients with postoperative sepsis remained significantly elevated for 10 days, regardless of the clinical state, whereas falling levels of IL-6 and PCT indicated improvement of sepsis. The overall correlation of MR pro-ANP with IL-6 and PCT was therefore low (Pearson´s r 0.15 and 0.36, respectively).

Conclusions: MR pro-ANP may contribute to the diagnosis of postoperative sepsis, as its level can differentiate between elevation of other inflammatory markers due to abdominal surgery alone or postoperative sepsis.

Key words: *Sepsis markers; mid-regional pro-atrial natriuretic peptide (MR pro-ANP); abdominal surgery; postoperative sepsis*

Introduction

Despite extensive clinical experience and research, sepsis and septic shock are still leading causes of death in the modern intensive care unit (ICU) [1,2]. Postoperative sepsis accounts for about 30% of cases of sepsis, overall, with an incidence of 1.2% in all patients undergoing surgery [1,3]. The diagnosis of sepsis can be difficult in surgical patients, as established biomarkers of sepsis, such as leukocyte count or blood C-reactive protein (CRP) level, may be markedly altered by the surgical intervention itself [4].

Pro-atrial natriuretic peptide (pro-ANP) belongs to a family of natriuretic peptides that function as antagonists of the renin-angiotensin-aldosterone system and facilitate natriuresis and vasodilatation [5]. It is secreted mainly by the atria [6] in response to atrial volume and pressure overload [7]. Pro-ANP up-regulation, therefore, occurs in heart failure, and it has been established as a diagnostic and prognostic marker in this disease [8].

Although intrinsic myocardial dysfunction may occur in septic shock, the cardiac index usually increases after adequate volume resuscitation [9,10]. Characteristically, the stroke volume is normal, the ventricular ejection fractions are reduced and end-diastolic and end-systolic volumes are increased [11]. Furthermore, left ventricular dysfunction has been linked to poor survival in patients with sepsis [10].

Because of these cardiovascular changes during sepsis, atrial natriuretic peptide (ANP) and pro-ANP attracted interest as novel markers for its evaluation [12,13]. ANP is reported to be degraded from the N- and C-terminus of the protein, which influences its stability in the serum or plasma [14]. A novel assay system was therefore designed to target mid-regional pro-ANP (MR pro-ANP), which can be measured reliably in the serum and plasma [15,16].

With the aim of evaluating the value of MR pro-ANP as a marker of postoperative sepsis, the plasma level of MR pro-ANP was measured in patients with postoperative

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Received Nov 9, 2018; Accepted Nov 16, 2018

sepsis, in patients after major abdominal surgery without complications and in healthy individuals. The prognostic value of MR pro-ANP was compared with that of other well validated biomarkers, including interleukine 6 (IL-6), procalcitonin (PCT), leukocyte count, and clinical scoring systems, specifically the acute physiology and chronic health evaluation (APACHE II) score, and sequential organ failure assessment (SOFA) score.

Material and Method

Patients

This prospective pilot trial was conducted with 46 individuals, classified in 3 groups. Group 1 (postoperative sepsis) consisted of 18 patients with sepsis or septic shock after major abdominal surgery. Sepsis and septic shock were defined according to the American College of Chest Physicians and the Society of Critical Care Medicine Consensus Conference [17-19]. Further criteria were an identifiable site of infection and evidence of a systemic inflammatory response, manifested by at least two of the following criteria: 1) temperature > 38° Celsius (°C) or < 36°C; 2) heart rate > 90 beats per minute; 3) respiratory rate > 20 breaths per minute or PaC02 < 32 mmHg; 4) leukocyte count > 12,000/mm^3 or < 4,000/mm^3; 5) organ failure. All the subjects in group 1 were included in the study within 24 hours of onset of septic symptoms. Group 2 (postoperative patients) consisted of patients who had undergone major abdominal surgery and showed no signs of sepsis. They were enrolled on the first postoperative day. Patients with pancreatitis and those who had undergone hepatic resection were excluded. Group 3 (healthy individuals) consisted of healthy individuals who had not undergone operation. The study was approved by the hospital Ethics Committee. Data recording and evaluation was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. In order to exclude potential bias, the laboratory personnel analyzing MR pro-ANP received no clinical information on the study subjects.

Study protocol

After inclusion in the study, venous blood samples from the patients in groups 1 and 2 were taken at 4 time points over a period of 10 days. The first sample was drawn as soon as the patient presented symptoms of postoperative sepsis (group 1) or on the first postoperative day (group 2), and subsequent samples on days 3, 7 and 10. A single blood sample was drawn from each healthy control subject (group 3) at one arbitrary point in time. At each sampling time point, measurement was made of MR pro-ANP, IL-6 and PCT, and the leukocyte count was recorded.

Assays for MR pro-ANP, PCT and IL-6

At each time point, 1 EDTA, 1 citrate and 1 heparin tube were taken. The citrate and heparin tubes were centrifuged at 3,000 g at 4 °C for 10 minutes. The serum was then stored at -24 °C for later analysis.

Cytokines were measured using commercial Enzyme-linked Immuno-absorbent Assay Kits (ELISA). Il- 6 was measured with Immulite-System 2000 (Random Access Immunoassay Analyzer, DPC Biermann, Germany). The plasma level of PCT was measured with the Liason® Analyzer (BRAHMS, Germany). MR pro-ANP (epitopes covering amino acids 53-90 of the prohormone) was detected in serum from all patients by a sandwich immunoassay (BRAHMS AG, Hennigsdorf/Berlin, Germany), as described in detail elsewhere [15,16]. The lower detection limit of the assay is 4.3 pmol/l and the functional sensitivity of the assay (i.e., an interassay coefficient of variation <20%) is 11 pmol/l. The 97.5th percentile in 325 healthy individuals was 163.9 pmol/l (median 45pmol/l), with no difference between sexes.

Statistical analysis

Statistical analysis was conducted using Prism 5 for Mac OS X (GraphPad Software, Inc.). The Mann-Whitney-U test was used for group comparison, curves were analyzed with two-way ANOVA, with Bonferroni post-test, where applicable. Receiver operating characteristic (ROC) plot analysis was used to detect suitable cut-off levels for the analyzed biomarkers. The method of DeLong, DeLong and Clarke-Pearson was used to compare areas under the ROC curves [20]. P value < 0.05 was considered significant.

Results

Descriptive data

The study population consisted of 46 subjects, 27 males and 19 females, with a mean age of 56.8 years: 18 patients with postoperative sepsis (group 1), 19 postoperative patients without sepsis (group 2), all of whom had undergone major abdominal surgery, and 9 healthy control subjects who had not undergone surgery. The detailed characteristics of the patients are shown in Table 1. The focus of postoperative sepsis in group 1 was primarily abdominal (66%) or pulmonary (33%).

Biomarkers and diagnostic power

In the blood samples taken on the initial diagnosis of sepsis (group 1), the levels of MR pro-ANP, IL-6 and PCT were significantly higher than in postoperative patients without sepsis (group 2) (Mann Whitney P < 0.0001 for all). The leukocyte count was similar in both groups (Mann Whitney P=0.475). In patients with abdominal surgery with-

Table 1. *Characteristics of the population in the study of postoperative sepsis (n=46).*

	Postoperative period with sepsis	Postoperative period without sepsis	Healthy control subjects	P
Patients (n)	18	19	9	
male / female	11/7	10/9	6/3	
Mean age (years)	61.3	56.8	48.0	
APACHE II score	19.39 ±	3.42 ± 0.90		
	4.35			<0.0001[T]
Type of surgery				
Upper GI	2	5		
Pancreatic	3	7		
Colorectal	5	7		
Small intestinal	5	0		
Other	3	0		

Values are expressed as absolute numbers or mean ± standard deviation
[T]Mann Whitney
GI: Gastrointestinal, APACHE: Acute Physiology and Chronic Health Evaluation

out postoperative sepsis (group 2) significantly higher levels of MR pro-ANP and IL-6 were recorded than in healthy control subjects (group 3) (Mann Whitney P < 0.0001 for both). As determined by the ROC analysis, with post-hoc Youden test, we calculated ideal cut-off values for all biomarkers, as shown in Table 2.

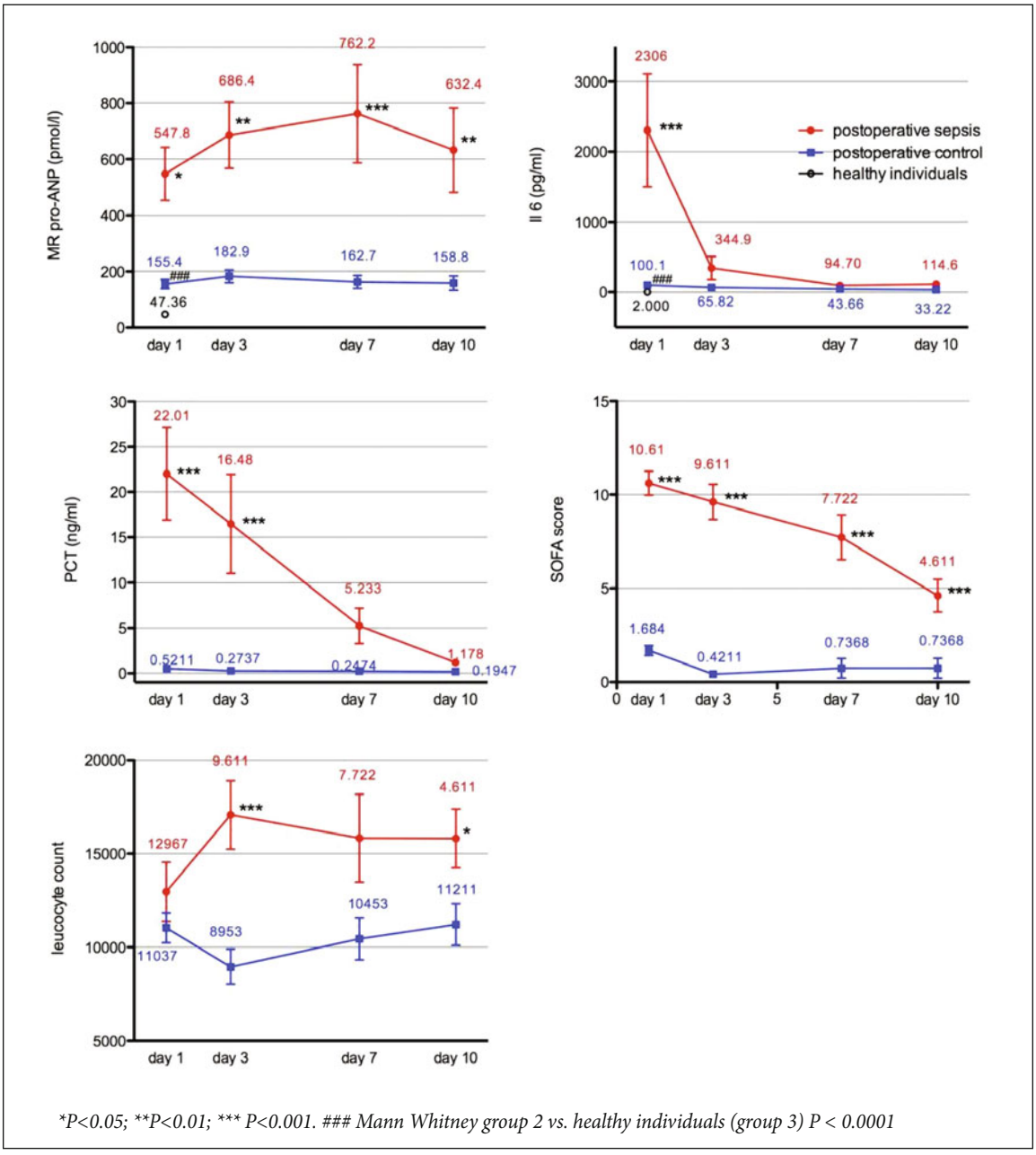
Compared with the other biomarkers, MR pro-ANP detected sepsis equally as well as PCT or IL-6 and significantly better than the leukocyte count. ROC curve comparison revealed only the APACHE II score to be superior to MR pro-ANP (Table 2).

Figure 1 shows the course of the biomarkers and the SOFA score over the 10 days of the study. The time dependent analysis of the serum markers revealed consistent significant elevation of MR pro-ANP levels in patients with postoperative sepsis throughout the whole time period studied (i.e., 10 days), and the MR pro-ANP levels in postoperative patients without sepsis also remained above the levels of the healthy control subjects. Conversely the levels of, PCT and IL-6 decreased rapidly after the initial diagnosis of sepsis, in parallel to clinical improvement as indicated by the SOFA score. Hence, in patients with postoperative sepsis, correlation of MR pro-ANP with PCT, IL-6 and SOFA score is strong on day 1 (Pearson's r MR pro-ANP vs. PCT 0.58, vs. IL-6 0.47, vs. SOFA 0.53), but decreases on the following days with only a moderate correlation of MR pro-ANP with the other biomarkers (day 10: Pearson's r MR pro-ANP vs. PCT 0.46, vs. IL-6

Table 2. *Diagnostic power and cut-off values for biomarkers of sepsis and APACHE, determined by receiver operating characteristic (ROC) plot analysis.*

Parameter	Cut off	Sensitivity (95% CI)	Specificity	AUC	P (versus MR pro ANP)
MR pro-ANP	162.5 pmol/l	100 (81-100)	68 (43-87)	0.91	
PCT	2.35 ng/ml	94 (73-100)	95 (74-100)	0.98	0.1678
Leucocyte count	13,000/μl	68 (43-87)	56 (31-78)	0.57	0.0017
IL-6	81.4 pg/ml	94 (73-100)	68 (43-87)	0.87	0.6383
APACHE II	9	100 (82-100)	100 (81-100)	1.0	0.0474

Values are expressed as absolute numbers
[T]Youden test
MR pro-ANP: Mid-regional Pro-atrial Natriuretic Peptide, PCT: Procalcitonin, IL-6: Interleukin-6, APACHE II: Acute Physiology and Chronic Health Evaluation, AUC: Area Under the Curve



**P<0.05; **P<0.01; *** P<0.001. ### Mann Whitney group 2 vs. healthy individuals (group 3) P < 0.0001*

Figure 1. Mean levels of mid-regional pro-atrial natriuretic peptide (MR pro-ANP), procalcitonin (PCT) and interleukin-6 (IL-6), leukocyte count and sequential organ failure assessment (SOFA) score from day 1 to day 10 in patients with postoperative sepsis (group 1) and post-operative patients without sepsis (postoperative control) (group 2). Significant difference was demonstrated between group 1 and group 2 for all determined parameters (two-way ANOVA group 1 vs. group 2 P < 0.0001 for all). Significance as indicated by the Bonfferoni post test between (group 1) and (group 2).

0.23, vs. SOFA 0.42). Overall, correlation of MR pro-ANP was moderate with PCT (Pearson's r 0.36) but weak with IL-6 (Pearson's r 0.15).

Three of the patients with sepsis died. MR pro-ANP levels were no different in the survivors and the non-survivors. In this small cohort, there was also no significant difference in PCT or IL-6 between survivors and non-survivors.

Discussion

An early and accurate diagnosis of sepsis is crucial for the critically ill postoperative patient, in order for a full diagnostic workup to be carried out and timely treatment to be initiated. A widely accepted score for risk stratification and survival is the APACHE II score, but the evaluation is

comprised of numerous single items, partly depending on clinical experience [21]. The APACHE II score is a good general prognostic tool for use on admission, but it is not validated for follow-up measurement, or specifically for the diagnosis of sepsis. For this reason, serum biomarkers play an important role in the diagnosis of postoperative sepsis, particularly as the operation alone usually alters common signs of infection, such as fever and leukocyte count [22], and especially the widely used inflammatory marker CRP [4], because of which diagnosis of sepsis in the postoperative patient may be impaired.

Depending on the extent of surgical trauma, IL-6 is raised for 48 to 72 hours after elective surgery, with the highest levels documented on postoperative day 1 [23]. This marker is thus highly surgery-dependent. Accordingly, in the current series levels of IL-6 were elevated on day 1 in postoperative patients both with and without sepsis, and remained significantly above those of healthy control subjects for at least 10 days. Furthermore, IL-6 levels were significantly higher in patients with postoperative sepsis than in postoperative control subjects without sepsis, but falling with improvement of the sepsis. This stands in contrast to earlier reports where, in a similar setting, no significant difference in IL-6 was detected between postoperative patients with and without sepsis [4]. Our data confirm those of Mokart and colleagues, who found elevated IL-6 levels on the first postoperative day to be predictive of development of postoperative sepsis [24]. Tschaikowsky further linked non-declining IL-6 levels to non-survival in postoperative patients [25].

PCT may be able to help close the diagnostic gap between the uncomplicated postoperative patient and the patient with postoperative sepsis. Major abdominal surgery alone leads to a significant rise in PCT on the first postoperative day [24]. The rise in PCT has been shown to be considerably greater in patients developing postoperative sepsis, facilitating diagnosis of sepsis as early as postoperative day 1 [24] or day 2 [26]. In the current series, patients with sepsis had significantly higher levels of PCT than postoperative patients without sepsis, and the diagnostic value was comparable with the APACHE II score [27].

Diagnosis of postoperative sepsis with PCT may not be simple in the individual patient. In non-surgical patients, a PCT value of > 0.25 ng/ml strongly correlates with the presence of systemic infection. In surgical patients, however, Mokart and colleagues determined a cut-off value of 1.1 ng/ml, with a sensitivity of 81%, while others set a considerably higher cut-off value, of 3.18 μg/l, with a similar sensitivity [24,26]. In contrast to other studies that reported PCT elevation through surgery alone, in our series, PCT remained low in postoperative patients throughout the study period despite major abdominal operations in all cases. In our series, any rise in postoperative PCT all could be considered suspicious of sepsis. The course of PCT levels over time in postoperative sepsis has not been shown to correlate with the clinical outcome [28], demonstrating that the interpretation of well-established biomarkers can be ambiguous.

As a possible new marker for the diagnosis of sepsis, Morgenthaler and colleagues evaluated MR pro-ANP in 101 patients consecutively admitted to an ICU. The source of infection in this study was mainly pulmonary. MR pro-ANP level was shown to be dependent on the clinical severity of the infection, and also strongly correlated with the level of PCT and IL-6. The predictive value of MR pro-ANP for survival was significantly better than that of PCT or CRP, and still higher than that of the APACHE II score [15].

In postoperative patients, the primary issue was to determine the impact of surgery alone on the level of MR pro-ANP. As with IL-6, surgical trauma significantly raised the MR pro-ANP level. This rise is not the result of direct cell stimulation at the surgical site, as described for IL-6, but is due to the releasing mechanism of MR pro-ANP which is dependent on cardiocirculatory impairment [7, 23].

Regarding patients with postoperative sepsis, MR pro-ANP levels in this series were significantly higher than in postoperative patients without sepsis on day 1. The cardiocirculatory changes observed in sepsis that provoke ANP secretion are characteristic of the disease and are linked to the levels of tumor necrosis factor alpha (TNF-α) and IL-1β, and therefore cannot be expected to be of the same extent after surgery alone [29]. It is of interesting that the MR pro-ANP levels remained higher in the patients with sepsis throughout the study period (10 days). This may be due to an ongoing cardiocirculatory impairment in patients with sepsis, although the sepsis overall improved rapidly in these patients, as indicated by a decrease in PCT level. Cardiac dysfunction during sepsis is triggered by direct and indirect effects of endotoxin on myocardial cells [30, 31]. In this context, the release of pro-and anti-inflammatory cytokines plays an important role, and IL-6 appears to be of special interest [30,32]. The release of ANP may be potentiated by IL-6; several studies showed a significant correlation between IL- 6 and MR pro-ANP levels [7,33]. Our study data, however, give reason to hypothesize that MR pro-ANP release may be independent of IL-6. While the IL-6 level of patients with sepsis decreased rapidly to that of postoperative control subjects without sepsis, the MR pro-ANP level remained almost stable throughout the study period, so the overall correlation of IL-6 with MR pro-ANP was weak.

With respect to the diagnostic capacity of MR pro-ANP in postoperative sepsis, the optimal cut-off level for MR pro-ANP on the first day was 162.5 pmol/l, which corresponds to the 97.5th percentile of healthy individuals,

as described elsewhere [16]. With a sensitivity of 100%, MR pro-ANP correlated with postoperative sepsis significantly better than the leukocyte count and equally as well as IL-6. IL-6, however, typically presents with a sharp rise, followed by a rapid fall within hours; in our study, the IL-6 levels had returned to normal in all patients by the second measurement on day 3, indicating that in postoperative sepsis, the peak IL-6 levels are likely to be missed. The slow dynamics of MR pro-ANP may be a diagnostic advantage in these patients. The better comparison for MR pro-ANP as a marker in postoperative sepsis is with PCT, which is currently considered the best available biomarker [27]. MR pro-ANP has already been shown to correlate with PCT regarding the severity of sepsis, and, more importantly, to predict outcome on the day of admission to ICU significantly better than PCT [15]. Is MR pro-ANP possibly also a better biomarker for sepsis than PCT in postoperative patients? In our series, there was strong correlation between PCT and MR pro-ANP levels on day 1, and sepsis was detected equally well by both markers, but MR pro-ANP did not predict prognosis in patients with postoperative sepsis. Correlation of MR pro-ANP with PCT and with the SOFA score, as a well-established clinical severity index, was strong on day 1 but decreased over time, when lowering in both PCT and SOFA score indicated improvement of the sepsis. One limitation of our study was the small size of the study groups, and the low event rate, which made it difficult to compare outcomes between groups. We therefore found no difference between survivors and non-survivors, and none of the parameters tested predicted mortality. The aim of this study, however, was not prognosis evaluation, but preliminary assessment of MR pro-ANP as a marker of sepsis in postoperative patients.

Conclusions

Significant elevation in the levels of PCT, IL-6, leukocyte count and MR pro-ANP occurs due to surgery alone. The level of MR pro-ANP can differentiate between abdominal surgery alone and postoperative sepsis, and may function as an additional diagnostic tool for the detection of sepsis in postoperative patients. MR pro-ANP remains elevated in patients with sepsis for at least 10 days, thus facilitating the diagnosis of sepsis at any point in time during the postoperative course. Prospective trials, especially regarding the prognostic value of this marker, are needed before MR pro-ANP can be introduced into clinical routine.

Acknowledgments: *The authors wish to thank BRAHMS AG, Henningsdorf/Berlin, Germany for providing the measurement of MR pro-ANP, and Silke Hempel and Bettina Waldvogel for excellent technical support.*

Conflict of Interest: *The authors declare that they have no conflict of interest.*

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