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CONCISE ARTICLE

Extension of antimicrobial treatment in patients with left-sided native valve endocarditis based on elevated C-reactive protein values

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Abstract The aim of this non-randomized study was to investigate whether there is any benefit in the extension of antimicrobial treatment in patients with left-sided native valve endocarditis in whom C-reactive protein levels are still elevated after a standard course of therapy. There was no statistically significant difference in outcome between the group of patients in which treatment was extended in comparison to the group in which treatment was ended at the recommended time. It is unlikely that there is much to gain from extending treatment based on elevated C-reactive protein levels alone.

Introduction

Guidelines about the treatment of infective endocarditis (IE) standardize the duration of antimicrobial therapy [1, 2]. Elevated C-reactive protein (CRP) values at the end of therapy are regarded by some as a sign of active disease. Therefore, antimicrobial therapy is sometimes prolonged beyond the treatment period recommended in current guidelines. The aim of this observational study was to investigate whether patients with left-sided native valve endocarditis in whom antimicrobial treatment is extended because of elevated CRP levels have a better clinical outcome than patients in whom antimicrobial treatment is ended at the recommended time.

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Methods

The study was designed as a multicenter cohort study in 23 hospitals in the Netherlands, of which eight are cardiothoracic surgery centres. The selection of hospitals was based on an earlier nationwide epidemiologic study in the Netherlands in which 70% of the cases of IE were admitted to those centres [3]. The study was approved by the medical ethical committees of all participating hospitals. From November 2000 to October 2003, all adult patients suspected of having left-sided native valve IE were reported to the study centre. Patients with right-sided native valve endocarditis, patients with prosthetic intracardiac material, and patients who were already started on antimicrobial therapy in the absence of CRP measurements were excluded. Only cases which fulfilled the Duke criteria for definite endocarditis were included in the analysis [4]. Written informed consent was obtained from all patients. CRP measurements were performed at the start of antimicrobial treatment and each Monday, Wednesday, and Friday thereafter until antibiotics were stopped. Standard duration of antimicrobial treatment (SDoT) was defined according to the American Heart Association guidelines [1]. Patients with elevated CRP levels (>5 mg/L) at the end of a standard course of therapy broke up into two groups based on the local hospital policy which either advocated ending

antimicrobial treatment in spite of CRP levels (Standard Duration of Treatment group, SDoT group) or extending antimicrobial treatment (Extended Duration of Treatment group, EDoT group). Duration of treatment was calculated from the first day that antimicrobial therapy was considered to be adequate for the treatment of endocarditis until the day that antibiotics were stopped. Duration of hospitalization was calculated from the first day of effective antimicrobial treatment until discharge. Osteomyelitis, arthritis, visceral and cardiac abscesses, mycotic aneurysms, and intracranial haemorrhages or infarcts were considered as serious infectious complications. The following concomitant diseases were recorded: diabetes mellitus with secondary organ complications, end stage renal disease requiring haemodialysis, cancer, auto-immune diseases requiring immunosuppressive medication, and chronic obstructive pulmonary disease with chronic bronchitis. Follow-up data were collected by contacting the patient or his/her general practitioner 12 weeks after the last day of antimicrobial therapy. When the patient had been readmitted in this period, data were collected from the hospital. Relapse of infection was defined as infection with the same micro-organism within 3 months.

Statistical analysis

We compared the clinical characteristics, infecting micro-organisms, duration of antimicrobial treatment and hospitalization, serious infectious complications, and relapse and mortality rates between the SDoT and the EDoT groups. Chi-square test statistics were used for categorical variables and Wilcoxon-Mann-Whitney test statistics for continuous data. When the expected frequencies in a cell were less than five, Fisher's exact test was used.

Results

Two hundred fifty-one patients were reported to the study centre. Reasons for exclusion were: prosthetic intracardiac material (n=42), diagnosis rejected (n=28), treatment before C-reactive protein measurements (n=27), right-sided endocarditis (n=4), death before inclusion (n=3), and age <18 years (n=2). Twenty-two patients refused to participate. Of the 123 (49%) remaining patients, 35 underwent cardiac surgery, ten died, two were transferred to non-participating hospitals, and in 15 patients CRP levels normalized before the end of the standard therapy course. Thus, 61 patients remained with an elevated CRP level at the end of the standard duration of therapy. Twenty-one (34%) of these patients were admitted into hospitals where the duration of antimicrobial treatment did not depend on CRP levels, and in these patients treatment was ended (SDoT group). The 40 (66%) other patients were admitted into hospitals where antimicrobial therapy was continued beyond the standard duration if CRP values had not normalized (EDoT group). Clinical characteristics, infecting micro-organisms, and CRP levels of the patients in both groups are summarized in Table 1. The distribution of

Table 1 Clinical characteristics, infecting micro-organisms and CRP values in 61 patients with elevated CRP levels at the end of the standard course of antimicrobial therapy[1]

	SDoT group[2] n=21	EDoT group[3] n=40	p value
Age, median (range)	65 (18–82) years	69 (25–82) years	0.32
Male : female	16:5	25:15	0.28
Micro-organism, distribution			0.04
Number (%)			
Viridans streptococci	8 (38%)	20 (50%)	
S. aureus	6 (29%)	2 (5%)	
Str. bovis	2 (9.5%)	9 (23%)	
Enterococci	2 (9.5%)	4 (10%)	
HACEK[4]	0 (0%)	4 (10%)	
CNS[5]	2 (9.5%)	1 (2.5%)	
Other	1 (4.8%)	0 (0%)	
Total	21 (100%)	40 (100%)	
CRP[6], median (range)	18 (6–171) mg/l	21 (6–94) mg/l	0.90

[1] Standard duration of treatment (SDoT) as defined by the American Heart Association [1]
[2] SDoT group: patients in whom treatment was ended after standard duration
[3] SEoT group: patients in whom treatment was extended after standard duration
[4] HACEK: *Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* spp. and *Kingella kingae*
[5] CNS: coagulase negative staphylococci
[6] C-reactive protein at the end of standard treatment duration in mg/l

micro-organisms was significantly different between the two groups ($p=0.04$). There was no significant difference in mean CRP values at the end of the standard course of therapy between the SDoT and the EDoT groups, which were 38.1 mg/l and 29.6 mg/l, respectively.

At the end of the standard course of therapy, 11 patients had had serious complications (Table 2). Cerebrovascular accident was the most frequently observed complication. The mean duration of antimicrobial treatment was 31 days (range 14–42) in the SDoT group and 44 days (range 31–104) days in the EDoT group ($p<0.01$). As would be expected, the mean duration of hospitalization was also significantly shorter in the SDoT group versus the EDoT group: 43 days (range 15–129) versus 53 days (range 31–122), respectively ($p<0.05$). There were no relapses of infection in either group. The number of patients undergoing cardiac surgery after the standard course of antimicrobial therapy was 6 (29%) in the SDoT group and 17 (42%) in the EDoT group ($p=0.29$). There were no deaths in the SDoT group versus two deaths in the EDoT group ($p=0.41$). One patient died from cardiac failure caused by heart valve regurgitation. There were no signs of infection at the time of death. The other patient died from complications of cardiac surgery while she was still on antimicrobial therapy. Of the 61 patients, 24 (39%) had at least one of the following concomitant diseases: autoimmune diseases requiring immunosuppressive medication ($n=9$), diabetes with secondary complications ($n=8$), cancer ($n=6$), chronic obstructive pulmonary disease with chronic bronchitis ($n=3$), and end stage renal disease requiring haemodialysis ($n=3$). Some patients had more than one concomitant disease. There was no significant difference in the number of patients with concomitant disease between the SDoT group and the EDoT group ($p=0.60$).

Discussion

The aim of this study was to assess the effect of continuing antimicrobial therapy in patients with left-sided native valve endocarditis if CRP is still elevated at the end of standard therapeutic courses. The results suggest that there is no benefit in prolonging antimicrobial therapy in those patients. There were no differences in outcome—as measured by cardiac surgery, relapse rate, or mortality—between patients in which treatment was ended (SDoT group) and patients in which treatment was extended (EDoT group). Several studies have been performed to establish the diagnostic value of CRP measurement in patients with IE [5–10]. In these studies, CRP is shown to be elevated in almost every patient. Also, serial CRP measurements during treatment have been studied as a predictor of clinical outcome of endocarditis [11–14]. The present study is the first to explore the role of CRP in determining the duration of antimicrobial treatment. None of the patients in the group in which treatment was ended, in spite of elevated CRP levels (SDoT group), suffered a relapse of infection or died. This was not a randomized trial, so we cannot be completely sure that the differences between the SDoT group and the EDoT group were governed by chance only. However, the fact that the policy of stopping or extending antimicrobial treatment beyond the standard duration in the case of elevated CRP levels was based on local hospital policy, and not on individual patient characteristics, makes large differences unlikely. The hospitals that followed the policy of prolonging antimicrobial treatment included both cardiothoracic surgery centres and centres that did not perform surgery. Although the difference in the number of serious infectious complications between the SDoT group (2 of 21 patients)

Table 2 Serious complications in patients with elevated CRP concentration at the end of the standard treatment

	Infecting micro-organism	Complication	Days of antimicrobial treatment
SdoT group, $n=21$			
Patient 1	*S. aureus*	Psoas abscess	28
Patient 2	*S. aureus*	CVA*	28
EdoT group, $n=40$			
Patient 1	Viridans streptococci	CVA	38
Patient 2	*S. aureus*	CVA	45
Patient 3	Enterococ	Osteomyelitis	42
Patient 4	Viridans streptococci	Liver abscess	49
Patient 5	Viridans streptococci	CVA, cardial abscess	104
Patient 6	Viridans streptococci	CVA, cardial abscess	58
Patient 7	*Kingella* spp.	CVA	31
Patient 8	*S. aureus*	Arthritis	50
Patient 9	Viridans streptococci	Osteomyelitis	32

**CVA* cerebrovascular accident

and the EDoT group (9 of 40 patients) was statistically not significant, it was remarkable that there were more serious infectious complications in the group in whom antimicrobial treatment was extended. The question remains why CRP levels remain elevated in some patients. One explanation may be the presence of concomitant disease which is still present after the endocarditis has been cured. In our population, 24 of the 61 patients (39%) had concomitant disease. Another explanation for failure of CRP levels to normalize after adequate antimicrobial treatment is the existence of immunologic phenomena caused by endocarditis as already mentioned in the first description of the disease by William Osler [15]. These immunologic sequelae can persist for some time after the micro-organisms that caused the disease have been eradicated. A large and randomized trial is required to provide a definite answer to the question of whether there is any added benefit in extending antimicrobial treatment in patients with elevated CRP levels at the end of standard therapeutic courses. The chance that such a trial will ever be performed is very small. Because the incidence of endocarditis is low, it would require a lengthy trial in a large number of hospitals. However, the positive outcome in patients with elevated CRP levels in which treatment was ended after a standard course makes it unlikely that there is much to gain from extending treatment based on elevated C-reactive protein alone.

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