Early Antibiotic Prophylaxis Prior to Bypass Surgery Improves Tissue Penetration

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Abstract

Background We previously identified preparation of the internal mammary artery as a risk factor significantly impairing antibiotic tissue penetration into the presternal subcutaneous tissue. We, therefore, adapted our dosing schema regarding preoperative timing to overcome this risk factor.

Methods Eight patients who underwent coronary artery bypass grafting with a left internal mammary artery and vein grafts were included in this clinical trial. Cefazolin (4 g) was administered twice (3 hours and 1 hour) prior to skin incision and once during skin closure (2 g). Antibiotic concentrations were measured with subcutaneous microdialysis probes on both sternal sides. Results were directly compared with the previously published patient cohort receiving the standard schema (4 g cefazolin prior to skin incision and 2 g during closure).

Results All patients (7 male, 1 female, 69 ± 7 years, $26.3 \pm 3.9\,kg/m^2$) survived the perioperative period. Mean area under the curve on the right and left sternal side was 117.0 ± 92.5 µg/mL and 114.5 ± 83.2 µg/mL, respectively ($p = 0.95$). This was well above the previously measured mean peak tissue concentrations without early preoperative antibiotic administration on the side of mammary artery harvesting (52.4 ± 48.5 µg/mL vs. 13.1 ± 5.8 µg/mL; $p = 0.039$). The %fT > minimal inhibitory concentration (MIC) for *Staphylococcus epidermidis* and *Staphylococcus aureus* during the first 10 hours in presternal tissue was $\geq 70\%$ but did not differ compared with standard schema.

Conclusions Early, additional preoperative administration of cefazolin was able to significantly increase peak tissue concentrations during surgery compared with the standard protocol. No difference, however, could be achieved in the percentage of time during which the concentration exceeded the MIC.

Keywords
- coronary artery bypass grafts surgery
- experimental
- pharmacology
- sternum
- wound infection

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Introduction

Patients undergoing cardiac surgery are at an increased risk of surgical site infections.[1] Deep sternal wound infection involving the sternal bone represents a severe complication after cardiac surgery and is related to an increased mortality.[2] Perioperative antibiotic prophylaxis with cefazolin is the standard approach for the prevention of deep sternal wound infections.[3–5] However, optimal dosage is still under discussion and recent data indicate insufficient coverage with the standard protocol.[6,7] The majority of available trials applied perioperative prophylaxis an hour prior to skin incision.[8] The rationale behind this dosing interval is to gain appropriate blood concentrations at the time of skin incision. However, target tissue antibiotic concentration may vary significantly from blood concentrations and may therefore require adapted dosing schemas for specific surgical procedures.[9,10]

We routinely administer a higher perioperative dose (4 g cefazolin 1 hour prior to skin incision and additional 2 g of cefazolin during skin closure) and were able to show improved plasma coverage and sufficient protection in areas not affected by surgery.[4,7] We further analyzed penetration of cefazolin into presternal tissue on the side of mammary artery harvesting compared with the right sternal side and compared with a reference probe on the thigh.[11] Although a higher antibiotic dose was applied, relevant pathogens were not covered at the side of mammary artery harvesting. Therefore, we designed the current trial to evaluate an optimized perioperative prophylaxis with earlier antibiotic administration 3 hours prior to skin incision in addition to our standard prophylaxis.

Methods

Ethics

The local ethics committee approved this study (1495/2013) and written informed consent was obtained from all patients and they are maintained at the study center.

Study Design

An interventional, single group, open, pharmacologic trial (phase IIB) was performed to investigate the effect of early, additional administration of 4 g cefazolin. The results were directly compared with the measurements obtained in a comparable, previously published study in a similar setting with our standard antibiotic prophylaxis (4 g cefazolin administered over 30 minutes starting 1 hour prior to skin incision and 2 g administered during skin closure).[11]

Patients

Eight patients undergoing isolated coronary artery bypass grafting (CABG) applying only the left internal mammary artery (LIMA) and veins were included. Patients who were unable to give informed consent had a known allergy to cephalosporins or penicillin, re-do surgery, preoperative renal failure, chronic severe renal insufficiency including hemodialysis, body mass index above 35 kg/m^2, preoperative clinical signs of infection or antibiotic therapy, left ventricular ejection fraction $< 20\%$, long-standing diabetes (>7 years), and positive pregnancy test in patients with childbearing potential were excluded.

Experimental Setting

On-pump CABG was performed via a full sternotomy. Two doses of cefazolin (4 g each) were administered over 30 minutes starting 3 hours and 1 hour prior to skin incision. A third dose of cefazolin (2 g) was administered during skin closure.

Microdialysis probes (CMA63 microdialysis probe, CMA/Microdialysis AB, Solna, Sweden) were inserted 3 cm left and right to the sternal midline. Sampling, in vivo measurement, probe calibration, and determination of cefazolin concentration were performed as previously described.[11,12]

Statistical Analysis

Pharmacokinetic analysis was performed with Kinetica (Kinetica 2.0.2, Innaphase, Philadelphia, United States). Data are presented as the mean and standard deviation. A paired Student's *t*-test was applied to compare pharmacokinetic parameters between the sternal sides and an unpaired *t*-test was applied to compare demographic and pharmacokinetic parameters between study groups (Statistica, StatSoft, Inc., Tulsa, Oklahoma, United States and SPSS 23.0, IBM, Armonk, New York, United States). A p-value <0.05 was considered significant.

Results

Eight patients were included in this trial assessing the preoperative study-dosing schema with an early, additional dose of cefazolin and directly compared with eight previously reported patients with our standard perioperative prophylaxis schema. All patients underwent on-pump isolated CABG with LIMA harvesting in skeletonized technique applying electric cautery. Patients' characteristics are depicted in ►**Table 1**. No wound infection was observed. One patient suffered from a seizure during the early postoperative course but recovered completely.

The intraoperative plasma peak was significantly earlier and higher compared with our standard protocol (►**Table 2**, ►**Fig. 1**). Furthermore, the area under curve$_{0–10}$ was significantly increased in the advanced dosing protocol (►**Table 2**, $p = 0.02$). Tissue concentrations of cefazolin were above the required minimal inhibitory concentrations for relevant pathogens at the time of skin incision (12.8 ± 4.1 µg/mL right side, 11.2 ± 2.6 µg/mL left side; $p = 0.67$). They were significantly higher compared with the standard protocol during the first 40 minutes of surgery (sampling period 0–20 minutes—right: 12.8 ± 9.9 µg/mL vs. 0 ± 0 µg/mL, $p < 0.001$; left: 11.2 ± 6.0 µg/mL vs. 0 ± 0 µg/mL, $p < 0.001$; sampling period 20–40 minutes—right: 17.0 ± 9.7 µg/mL vs. 2.5 ± 0.8 µg/mL, $p = 0.003$; left: 20.8 ± 23.0 µg/mL vs. 1.9 ± 1.0 µg/mL, $p = 0.035$, ►**Fig. 1**). Mean peak tissue concentrations on the right and left sternal side were 48.3 ± 43.0 µg/mL and 52.4 ± 48.5 µg/mL, respectively (►**Fig. 2**; $p = 0.78$). This was well above the previously measured mean peak tissue concentrations without

Table 1 Demographic, laboratory, hemodynamic, and intraoperative data

Parameter	Standard protocol ($n = 8$)	Early prophylaxis ($n = 8$)	*p*-Value
Sex, m/w	6/2	7/1	0.522
Age, years	69 (11)	69 (7)	0.893
Size, cm	170 (8)	174 (12)	0.450
Weight, kg	79 (13)	81 (20)	0.826
BMI, kg/m^2	27.1 (3.2)	26.3 (3.9)	0.647
Creatinine, mg/dL	1.1 (0.3)	1.0 (0.3)	0.570
Number of grafts	2.8 (0.7)	2.9 (0.6)	0.717
Ejection fraction, %	48 (8)	50 (12)	0.683
ECC, min	135 (42)	139 (41)	0.854
ACC, min	85 (36)	88 (27)	0.853
Lactate max, mmol/L	3.3 (1.3)	3.3 (0.9)	0.948
Norepinephrine, µg/kg/min	0.07 (0.03)	0.06 (0.04)	0.694

Abbreviations: ACC, time of aortic cross-clamping; BMI, body mass index; ECC, time of extracorporeal circulation.
Note: Data are presented as the mean (standard deviation) or as total number (gender).

early preoperative antibiotic administration on the side of mammary artery harvesting (52.4 ± 48.5 µg/mL vs. 13.1 ± 5.8 µg/mL; $p = 0.039$). Peak concentrations did not differ significantly on the right sternal side (48.3 ± 43.0 µg/mL vs. 24.1 ± 4.7 µg/mL; $p = 0.14$).

Mean percentages of the free target concentration above the minimal inhibitory concentrations (MIC_{90}) for *Staphylococcus epidermidis* (MIC_{90} 4.0 mg/L) and for *Staphylococcus aureus* (MIC_{90} 2.0 mg/L) during the measurement period were high for both protocols and did not differ between study protocols (►**Table 2**).

Comments

We report the effect of early, additional preoperative antibiotic administration to improve perioperative antibiotic coverage. This project was stimulated by our previous studies, which highlighted a severely disturbed tissue penetration of antibiotic prophylaxis during cardiac surgery in the surgically affected area.[11] The sternal spreader and the preparation of the internal mammary artery probably induced this effect. We developed this protocol to overcome impaired tissue penetration by achieving sufficient tissue concentrations prior to surgical manipulation.

Antibiotic prophylaxis with a first-generation cephalosporin is currently regarded as a class I recommendation.[8] The recommended dose is 2 g at incision and 1 g prior to closure, which is half the dose of our institutional standard. We believe that the guideline-recommended dose is too low

Table 2 Pharmacokinetic parameters of cefazolin in plasma and tissue

Plasma parameter	Standard protocol ($n = 8$)		Early prophylaxis ($n = 8$)	*p*-Value
t_{max} I plasma (min)	45 (9)		25 (9)	<0.001
t_{max} II plasma (min)	413 (60)		390 (85)	0.549
C_{max} I plasma (µg/mL)	264 (57)		462 (137)	0.002
C_{max} II plasma (µg/mL)	139 (45)		131 (46)	0.711
AUC_{0-10} plasma (µg/h/mL)	1078 (257)		1415 (256)	0.020
%fT > MIC (4 mg/L for *Staphylococcus epidermidis*)	0.995 (0.012)		1 (0)	0.240
%fT > MIC (2 mg/L for *Staphylococcus aureus*)	0.995 (0.012)		1 (0)	0.290
Tissue parameter	**Standard protocol ($n = 8$)**		**Early prophylaxis ($n = 8$)**	
	Left sternum	**Right sternum**	**Left sternum**	**Right sternum**
C_{max} I tissue (µg/mL)	13.1 (5.8)[a]	24.1 (4.7)	52.4 (48.5)[b]	48.3 (43.0)
C_{max} II tissue (µg/mL)	14.9 (7.8)	17.4 (5.8)	10.3 (10.5)	12.0 (8.2)
AUC_{0-10} tissue (µg/h/mL)	74.2 (31.0)[a]	110.4 (25.0)	114.5 (83.2)	117.0 (92.5)
%fT > MIC (4 mg/L for *Staphylococcus epidermidis*)	0.790 (0.219)	0.936 (0.042)	0.811 (0.334)	0.696 (0.278)
%fT > MIC (2 mg/L for *Staphylococcus aureus*)	0.894 (0.209)	0.972 (0.008)	0.904 (0.225)	0.913 (0.103)

Abbreviations: AUC, area under curve; MIC, minimum inhibitory concentration.
Note: Plasma parameters (total concentrations) are presented as the mean (standard deviation); t_{max} I, t_{max} II = time until maximum drug concentration after the first (I) and the second (II) dosage; Tissue parameters are presented as the mean (standard deviation).
[a] $p < 0.05$ versus right sternum.
[b] $p < 0.05$ versus standard protocol; For both C_{max} I, C_{max} II = maximum drug concentration after the first (I) and the second (II) dosage; AUC_{0-10} = area under the concentration curve (from 0 to 10 hours); %fT > MIC: mean percentage of the free target concentration above the MIC_{90} for specified organisms.

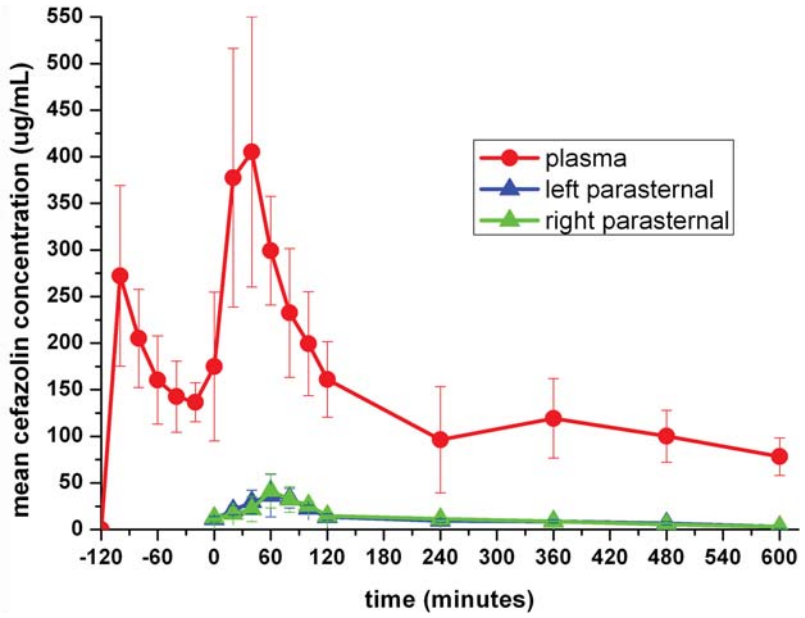

Fig. 1 Comparison of cefazolin concentrations after standard and early dosing. Data are presented as the mean and standard deviation for each time-point with a logarithmic scale. Plasma concentrations (circles) are total concentrations, and tissue concentrations (triangles) are free concentrations.

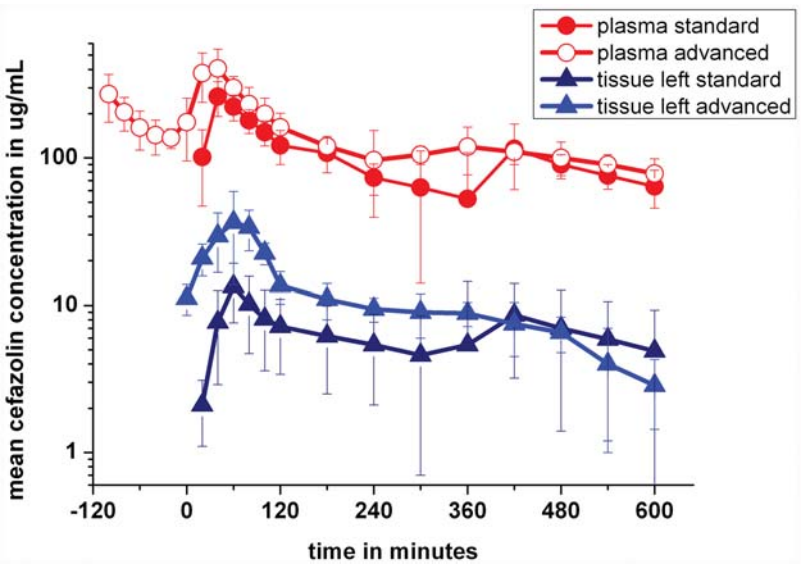

Fig. 2 Cefazolin concentrations in plasma and tissue after early, additional preoperative administration. Data are presented as the mean and standard deviation for each time-point with a linear scale. Plasma concentrations (circles) are total concentrations, and tissue concentrations (triangles) are free concentrations.

to provide sufficient protection for all patients.[7] Tissue concentration is known to have a high patient-specific variability, which may be due to body weight, diabetes, vascular disease, catecholamine therapy, protein binding, cardiopulmonary bypass, or other unknown factors.[4,9,10]

Data regarding the early preoperative antibiotic administration for prophylaxis are scarce. Classen et al showed in his retrospective analysis an optimal protective effect of the first antibiotic dose if administered up to 2 hours prior to skin incision, which led to the current recommendations.[13] An earlier administration without redosing was worse compared with the administration directly prior to skin incision. The results are difficult to extrapolate to cardiac surgery as the analysis was retrospective and included several surgical procedures not limited to cardiac surgery. Cardiac surgery patients may have altered requirements for antibiotic prophylaxis due to an increased cardiovascular risk profile, the specific risk of deep sternal wound infection after median sternotomy, and the pharmacokinetic effects of extracorporeal circulation. Hollenbeak et al described a negative impact of early antibiotic administration $>$ 1 hour prior to surgery.[14] Only a single antibiotic dose (1 g cefazolin) was administered in this retrospective case–control analysis. It seems likely that antibiotic coverage is impaired if no repeated dose is

applied and antibiotics are administered too early prior to surgery. This dosing schema cannot be compared with multiple dosing during surgery, which was investigated in the current trial.

Our dosing schema with an early, additional dose led to protective antibiotic tissue concentrations at the time of skin incision. Cephalosporins are most effective if a sufficient tissue concentration is present for a significant period between the dosing intervals.[15] Therefore, we believe that a high tissue concentration from the time of skin incision onwards is a relevant beneficial factor, providing inhibition of pathogen growth from the first time of potential infection. Furthermore, the second peak concentration was significantly higher on the left sternal side and provided sufficient tissue concentrations compared with the previous protocol in all patients. Therefore, it seems reasonable that early antibiotic administration improves antibiotic coverage of subcutaneous presternal tissue. Despite a higher and earlier mean peak concentration, the mean percentage of time during the observational period above the relevant MIC_{90} did not differ between study protocols. Although this parameter is designed for therapy of manifest infections and not validated for the assessment of prophylaxis, a time above the MIC_{90} of at least 70% suggests sufficient coverage with both study protocols. Again, we want to emphasize that our standard protocol is the double or quadruple dose of recommended dosing during surgery. But even with this approach, some patients fail to gain sufficient tissue concentrations with both prophylactic protocols.

A high-dose antibiotic prophylaxis may lead to an increased rate of adverse events. We observed a postoperative seizure in one patient, a causative relation to the antibiotic dosage cannot be ruled out with this analysis.[16]

Limitations

The control group of this trial was studied earlier and was initially not designed as a control group. However, surgical settings and standards were similar between both groups.

Conclusions

Early preoperative administration of cefazolin was able to significantly increase peak tissue concentrations during surgery compared with the standard protocol. No difference, however, could be achieved in the percentage of time during which the concentration exceeded the MIC.

Authors' Contribution

M.A., D.H., M.Z., G.L., W.J., and J.H. drafted the protocol and developed the study design. M.A., W.W., and A.K. performed surgical procedures and probe placement. M.E., R. T., and D.H. performed the anesthesia, probe placement, and sample collection. S.S. performed sample collection, sample transfer, and data preparation. A.M. and W.J. performed the sample analyses and calculated the tissue concentrations. M.A., M.Z., and D.H. wrote the manuscript and calculated the results.

All authors reviewed the manuscript critically and approved the final version.

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Conflict of Interest

None declared.

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