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Reduction of Sternal Wound Infections with a Refined Surgical Technique and Single Shot Systemic and Sternal Spongiosa Topical Antibiotic Prophylaxis Compared to 24 Hours Systemic Antibiotics

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Abstract

Background: Sternal wound infections continue to be a major source of morbidity and mortality after cardiac surgery. We undertook a multinational study to determine whether a detailed infection prevention protocol using a specific pre-, intra- and postoperative strategy including topical application of antibiotics would reduce the incidence of sternal infections.

Design: Quasi-Experimental Observation.

Setting: Four heart centres in three different countries.

Patients: 8,168 consecutive patients undergoing cardiac surgery from February 2006 to June 2015.

Method: In both groups, a second-generation cephalosporin was given prior to surgery and repeated if surgery exceeded six hours. Group A, but not Group B patients, received additional three doses of antibiotics after surgery while group B received intraoperative topical antibiotics and a special sternal closure protocol. Welch's t-tests and χ^2 analyses were used to test statistical significance. Additionally, logistic regression analyses were applied separated into Group A and B in order to examine the potential impact of established risk factors for sternal wound infections.

Results: There was a significant difference of major outcome parameters in favour of Group B *vs.* Group A: incidence of superficial wound infection: 0.4% *vs.* 2.9% (p<0.001); deep sternal wound infection: 0.6% *vs.* 2.2% (p<0.001); number of infection related reoperations: 81 *vs.* 241 (p<0.001) and number of muscle flap reconstruction in patients with sternal destruction: 0.2% *vs.* 1.1% (p<0.001).

Conclusion: The presented infection prevention protocol reduces postoperative sternal wound infections and limits the use of systemic postoperative antibiotics.

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Objectives

Postoperative sternal wound infections occur in up to 9% of patients [1]. Several procedures have been used to reduce the incidence of postoperative sternal wound infection such as Vacuum-assisted suction systems [2], omental grafts, breast flaps, allogenic bone grafts or reconstruction of the chest wall with various muscle flaps [3]. However post-sternotomy mediastinitis remains a risk factor for early and late mortality [4,5] and despite improved results with muscle flap reconstruction [6] sustained disability occurs in up to 30% of patients after deep sternal wound infection [7].

The aim of this multinational study was to determine whether a sophisticated surgical/medical

Table 1: Management protocols for the two study groups.

Management	Item	Group A	Group B
Preop	Reduction of the bacterial load in the nasal mucosa through application of mupirocin nasal ointment starting the day before surgery and continuing for four days after the operation.	-	+
	At the day of surgery, patients take a total body shower with chlorhexidine gluconate 4% or octenidin-dihydrochlorid 0.1% prior to transfer to the operating room.	-	+
	Surgical site disinfection at least twice with Isopropyl alcohol 70% - chlorhexidine gluconate 2%; the skin must be allowed to completely dry spontaneously before the patient is covered.	-	+
	Systemic intravenous antibiotic prophylaxis with a second-generation cephalosporin is given at least 30 minutes before starting surgery	+	+
	Second intravenous antibiotic dose is given if surgery takes more than six hours.	+	+
Intraop	No or very limited pinpoint use of electrocautery in subcutaneous tissue	-	+
	Preservation of the caudal bifurcation of the left and right mammary artery at the level of the epigastrium in coronary revascularization	-	+
	3gram vancomycin with 4ml NaCl resulting in a bone wax like material is applied into the sternal spongiosa	-	+
	Use of 6 to 8 “figure-of-8” sternal wires particularly reinforcing the lower sternum	-	+
	Irrigation of the sternum and the wires after refixation of the bone with 80mg of gentamycin	-	+
	No suture of the subcutaneous fat layer, even in obese patients	-	+
	Intracutaneous skin suture or interrupted single sutures	+	+
	No episternal drainage tubes or drains	+	+
	Routine change of gloves after sternotomy and insertion of the sternal retractor, after two hours and before sternal wire fixation.	-	+
	Three dosages of the second-generation antibiotic after surgery	+	-
Postop	Dressings of the median sternotomy wound are changed after 48 hours only, or if the wound is wet	+	+
	External thoracic stabilization with chest jackets	-	-

+ part of routine protocol; - not part of routine protocol

infection prevention protocol reduces the incidence of sternal infections compared to standard treatment.

Methods

Study design

With approval of the ethics committee of the Medical University of Vienna (EK Nr 1416/2016) an observational cohort analysis with two sequential patient groups after introduction of a new infection control protocol as part of the institutions quality assurance programmes, was performed at four different sites (Hirslanden Klinik, Zurich, Switzerland, Military Medical Academy St. Petersburg, State Cardiovascular Surgery Center Penza, both in Russia, Medical University of Vienna, Austria).

Study population

8,168 patients undergoing cardiac surgery *via* full sternotomy were included and either received the standard (Group A) or the revised infection prevention protocol (Group B) depending on the time period of operation. Table 1 summarized the management protocols. In Zurich Group A patients were operated on between May 2006 and September 2009 (n=564) and Group B patients between October 2009 and October 2014 (n=812), respectively. In St. Petersburg, Group A patients were operated between February 2006 and September 2009 (n=263) and Group B patients operated between October 2009 and June 2013 (n=220). In Penza Group A patients were operated between January 2011 and May 2012 (n=1,807) and Group B patients between June 2012 and April 2014 (n=2,651). Finally, in Vienna Group A patients were operated between March 2013 and February 2014 (n=919) and Group B patients between July 2014 and June 2015 (n=932) [8].

Data management

Patients’ characteristics and risk factors were retrieved using the electronic data capture systems of the individual hospitals in compliance with applicable data protection regulations. Risk scores (additive and logistic EuroSCORE I as well as the EuroSCORE II) were calculated and stored. For practical purposes wound infection was defined as superficial (without sternal reopening), or deep (with sternal reopening). Central venous line associated blood stream infection data were investigated in Switzerland only.

Statistical analysis

Descriptive statistics were used in order to describe the sample regarding preoperative patient characteristics. Continuous variables are presented as mean and Standard Deviation (SD) and categorical variables as total numbers and percentages. Preoperative patient characteristics were compared between the two cohorts by conducting Welch’s t-tests (continuous variables) 0 or χ^2 tests (categorical variables). Regarding the number of infections related reoperations a χ^2 Goodness-of-Fit test was applied assuming a uniform distribution. If necessary, Fisher’s exact test was used to compute the p-value related to the χ^2 tests. Effect sizes were estimated according to Cohen’s δ and Cramer’s ω rule of thumb with a $|\delta| \approx 0.2$ indicating small, $|\delta| \approx 0.5$ indicating medium; and $|\delta| \approx 0.8$ indicating a large difference and $\omega \approx 0.1$ indicating small, $\omega \approx 0.3$ indicating medium and $\omega \approx 0.5$ indicating large difference. Finally, two binary regressions were applied in order to assess an independent effect of the infection prevention protocol including established risk factors as control variables. If no sternal wound infection occurred after the surgery these patients were coded as 0 and if any (superficial or deep) sternal wound infection occurred a 1 was assigned.

All descriptive as well as inferential statistics were conducted using patients from all four sites as well as at the national level (Russia, Austria and Switzerland) in order to enable national comparisons. All analyses were conducted by STATWORX using RStudio (Version 1.1.338) A p-value less than 0.05 was considered as significant.

Table 2: Preoperative patient characteristics (continuous variables) according to country.

Level of analysis		Age (SD) years	Height (SD) cm[1]	Weight (SD) kg[1]	Body mass index (SD) kg/m²
All sites	Group A	61.46 (11.32)	171.88 (8.78)	79.69 (14.95)	27.64 (4.33)
	Group B	61.31 (10.94)	172.07 (9.07)	80.03 (15.08)	28.02 (4.54)
	p-value	0.565	0.544	0.525	<0.001
	Effect size	0.01	-0.01	-0.01	-0.09
Russia	Group A	57.72 (8.94)	-	-	28.15 (4.14)
	Group B	58.3 (9.28)	-	-	28.68 (4.51)
	p-value	0.026	-	-	<0.001
	Effect size	-0.06	-	-	-0.12
Austria	Group A	66.02 (12.98)	172.33 (9.11)	81.00 (15.39%)	27.25 (4.7)
	Group B	65.22 (12.87)	172.59 (9.95)	81.84 (16.54)	27.39 (4.63)
	p-value	0.182	0.547	0.259	0.534
	Effect size	0.06	-0.03	-0.05	-0.03
Switzerland	Group A	67.73 (10.75)	171.15 (8.16)	77.55 (13.94)	26.42 (4.11)
	Group B	67.48 (9.95)	171.47 (7.9)	77.94 (12.91)	26.45 (4.05)
	p-value	0.655	0.471	0.595	0.897
	Effect size	0.02	-0.04	-0.03	-0.01

Note: [1]Data only available for Switzerland and Austria (Group A: n=1,483, Group B: n=1,744 for all sites). Effect size:Cohen's δ.

Table 3: Preoperative and perioperative patient characteristics (categorical variables).

Level of analysis		Gender (m/f)	Diabetes (yes/no)	Type of surgery Bypass surgery/ Valve surgery/Bypass and Valve/other surgeries)
All sites	Group A	2665 (75%)/888 (25%)	585 (16.5%)/2968 (83.5%)	1863 (53.8%)/870 (25.1%)/523 (15.1%)/204 (5.9%)
	Group B	3462 (75%)/1153 (25%)	790 (17.1%)/3825 (82.9%)	2227 (49.3%)/935 (20.7%)/853 (18.9%)/499 (11.1%)
	p-value	0.992	0.434	<0.001
	Effect size	0.0001	0.01	0.11
Russia	Group A	1617 (78.1%)/453 (21.9%)	219 (10.6%)/1851 (89.4%)	1309 (63.2%)/441 (21.3%)/286 (13.8%)/34 (1.6%)
	Group B	2200 (76.6%)/671 (23.4%)	426 (14.8%)/2445 (85.2%)	1625 (56.6%)/455 (15.9%)/590 (20.1%)/201 (7%)
	p-value	0.218	<0.001	<0.001
	Effect size	0.02	0.06	0.16
Austria	Group A	631 (68.7%)/288 (31.3%)	289 (31.5%)/630 (68.5%)	325 (39.4%)/239 (28.9%)/142 (17.2%)/120 (14.5%)
	Group B	673 (72.2%)/259 (27.8%)	283 (30.4%)/649 (69.6%)	312 (37.6%)/199 (24 %)/160 (19.3%)/160 (19.3%)
	p-value	0.093	0.614	0.014
	Effect size	0.04	0.01	0.08
Switzerland	Group A	417 (73.9%)/147 (26.1%)	77 (13.7%)/487 (86.3%)	229 (41.6%)/190 (33.7%)/95 (16.8%)/50 (8.9%)
	Group B	589 (72.5%)/223 (27.5%)	81 (10%)/731 (90%)	290 (35.7%)/281 (34.6%)/103 (12.7%)/138 (17%)
	p-value	0.565	0.035	<0.001
	Effect size	0.02	0.06	0.13

Note: Effect size: Cramer's ω

Results

Of the 8,168 patients operated in one of the four sites, 3,553 (43.5%) received the standard and 4,615 (56.5%) received the infection prevention protocol, respectively. The allocation of patients in Russia was: Group A 2,070 (41.9%), Group B 2,871 (58.1%) patients; in Austria Group A 919 (49.6%) and Group B 932 (50.4%) patients and, in Switzerland Group A 564 (41%), Group B 812 (59%) patients.

In total Group A and B were comparable in terms of preoperative and perioperative patient characteristics (Tables 2 and 3). Although there was a significant difference regarding body mass index and type of surgery, the difference did not have an impact on the outcome parameters. Patients operated in Russia differed significantly in all preoperative and perioperative patient characteristics except gender (p=0.218), but the differences between the cohorts were also very small to small [1]. Patients from Austria differed solely in type of surgery and patients from Switzerland differed in diabetes and type of surgery but it was only a very small difference.

Table 4 shows the wound infection related indicators and Table 5 the binary regression analyses including the novel closure protocol and established risk factors for sternal wound infections. In the total sample as well as at the national level, the incidence of wound infections and infection related reoperations were significantly reduced in the infection prevention protocol group (p<0.001, respectively). Further analysis of the kind of wound healing with differentiation between no infection, superficial wound infection and deep sternal wound

Table 4: Wound infection related indicators.

Level of analysis		Number of infection related reoperations	Wound infection (yes/no)	Muscle flap plasty surgery (yes/no)	Duration of hospita-lisation (days)	Duration of stay on ICU (days)
All sites	Group A	241	182 (5.1%) /3365 (95.9%)	40 (1.1%)/3516 (98.9%)	13.11(13.21)	3.86(8.59)
	Group B	81	48 (1%)/4565 (99%)	10 (0.2%)/4602 (99.8%)	12.85(13.5)	4.04(9.74)
	p-value	<0.001	<0.001	<0.001	0.415	0.369
	Effect size	0.5	0.12	0.06	0.02	-0.02
Russia	Group A	64	75 (3.6%)/1995 (96.4%)	16 (0.8%)/2054 (99.2%)	10.62(7.59)	2.35(3.77)
	Group B	30	20 (0.7%)/2851 (99.3%)	4 (0.1%)/2867 (99.9%)	10.46(6.74)	2.63(4.36)
	p-value	<0.001	<0.001	<0.001	0.485	0.017
	Effect size	0.36	0.11	0.05	0.02	-0.07
Austria	Group A	309	47 (5.2%)/866 (95.8%)	15 (1.6%)/904 (98.4%)	17(19.32)	7.12(14.63)
	Group B	123	17 (1.8%)/913 (98.2%)	5 (0.5%)/927 (99.5%)	17.82(22.11)	7.95(18.41)
	p-value	<0.001	<0.001	0.023	0.391	0.277
	Effect size	0.43	0.09	0.05	-0.04	-0.05
Switzerland	Group A	54	60 (10.6%)/60 (10.6%)	9 (1.6%)/558 (98.4%)	13.84(11.68)	4.1(5.99)
	Group B	22	11 (1.4%)/801 (98.6%)	1 (0.1%)/808 (99.9%)	14.22(13.62)	4.59(7.54)
	p-value	<0.001	<0.001	0.002	0.594	0.193
	Effect size	0.42	0.21	0.08	-0.03	-0.07

Note: Effect sizes: Cramer's ω for number of infection related reoperations, wound infection and muscle flap plasty surgery. Cohen's δ for duration of hospitalisation and stay on ICU

Table 5: Binary regression analyses including the novel closure protocol and established risk factors for sternal wound infection.

Level of analysis		Factor	Beta	Odds ratio	95% CI	P-value
All sites	Group A (n=2611)	Length of stay in hospital	0.052	1.054	1.043-1.065	<0.001
		Mammary artery harvesting One IMA	0.482	1.62	1.037-2.593	0.039
		BIMA	0.464	1.591	0.951-2.690	0.079
		Diabetes	0.673	1.959	1.322-2.867	**<0.001**
		Body mass index	0.067	1.069	1.029-1.111	**<0.001**
		Nagelkerke's R^2	0.15			
	Group B (n=3659)	Length of stay in hospital	0.056	1.058	1.046-1.070	< 0.001
		Mammary artery harvesting One IMA	0.359	1.432	0.639-3.386	0.394
		BIMA	0.135	1.145	0.435-3.058	0.783
		Diabetes	0.786	2.195	1.058-4.402	**0.03**
		Body mass index	0.029	1.029		0.414
		Nagelkerke's R^2	0.21			

Note: IMA: Internal Mammary Artery; BIMA: Bilateral IMA

infection revealed a significant, protective effect of the infection prevention protocol, too (both in the total sample and at the national levels, p<0.001 respectively). The effect was largest in Switzerland (Cramer's ω=0.21) and somewhat smaller in all sites (Cramer's ω=0.12), and Russia (Cramer's ω=0.11) and Austria (Cramer's ω=0.09). Accordingly, adjusted standardized residuals showed, there were significantly less patients with no infections (3,365 [94.9%]) and more patients with superficial (104 [2.9%]) as well as deep sternal wound infections (78 [2.2%]) in Group A patients. Complementary, there was an increased number of patients with no infections (4,565 [99%]) and less patients with superficial (19 [0.4%]) and deep wound infections (29 [0.6%]) in Group B.

Furthermore, in Group B patients, the number of muscle flap plasty was significantly reduced in every country (p<0.024, respectively). The duration of hospitalisation did not differ between groups at any level (p>0.39). The duration of stay on ICU was significantly increased in Russia for patients in Group B (p<0.018). However, this increase was merely small (Cramer's ω= -0.07) indicating that this did not have an impact on outcome parameters.

In binary regression analysis (one for each group), uni- or bilateral mammary artery harvesting and body mass index as independent risk factors for postoperative sternal wound infection were eliminated by the infection prevention protocol. Accordingly, use of the infection prevention protocol was associated with a significant reduction in the incidence of sternal wound infections (odds ratio =7.004; 95% CI [4.830; 10.429]). In order to enable comparisons with future research, Nagelkerke's R^2 is additionally reported. It is comparable to R^2 in ordinary least squares regressions; hence it has an effect size for binary regression analyses.

The incidence of central venous line associated blood stream infections decreased from 4.3/1000 in Group A to 1/1,000 day in Group B (p>0.1).

Limitations

This is not a randomized controlled study. The control group undergoing standard sternal closure was analyzed retrospectively and was compared with prospectively included patients in whom the new infection prevention protocol was used. Thus, there may be other biasing variables over time and there was no control for other local practice changes regarding general hygiene.

Discussion

Surgical wound infection represents the most frequent complication after cardiac surgical procedures with standard access via median sternotomy. Sternal wound infection is associated with increased early and late morbidity and mortality rates [9]. Even in the current era, hospital mortality for deep sternal wound infection with or without mediastinitis is reported between 14% and 49% [10,11].

The overall risk of deep sternal wound infection prior to the introduction of the novel protocol was 5.1%, which is in the range of previous reports [1,12-15]. Up to 58% of postoperative wound infections are diagnosed after hospital discharge [16]. This explains, why the highest overall surgical site infection rate in the standard group was observed in Switzerland (10.6%), where post discharge surveillance is conducted [17].

The novel infection prevention protocol focuses on an adaptation of simple surgical rules in conjunction with topical use of antibiotics directly administered into the sternal wound while reducing systemic antibiotics to a single shot regimen. However, given the design of the study we cannot assess the individual value of each part of the bundle.

Bacteria from the deep roots of the hairy follicles can be found in the subcutaneous layer after skin incision because they cannot be reached even by adequate skin disinfection. Furthermore, reduced antibiotic tissue penetration into the subcutaneous tissue, related to skeletonized harvesting of the mammary artery has been described [18,19]. Hence, the subcutaneous layer, traumatized and ischemic by electrocautery and running suture may represent the starting point for a low-grade infection evolving into full sternal wound infection with or without deep mediastinitis. Topical application of antibiotics achieves higher local antibiotic concentrations [20]. Therefore, we hypothesized that a combined protocol including the abolishment of electrocautery in the subcutaneous layer, an increased number of sternal wires [21] and topical antibiotics would have an additional effect with the other pre- and postoperative measures such as the use of nasal mupirocin and antiseptic showering, known to reduce surgical site infection [22-24] while reducing systemic antibiotics to a single shot regimen.

The topical application of vancomycin or gentamycin for the prevention of sternal wound infection or as infection prevention in open fractures was previously described [25-28], but results are not consistent [29-30] and antibiotic wound irrigation is not recommended by the WHO [31]. Therefore, we speculate that spongiosa injection of vancomycin rather than irrigation with gentamicin is the key component of the topical antibiotic regimen.

Topical application of antibiotics was not associated with negative effects. While measurable serum concentrations have been shown up to six days after surgery Vancomycin blood concentrations during the first three days after surgery were below any clinically relevant levels in our study population [32].

Neither the presence of COPD, the smoking status, cortisone therapy, open-chest treatment after complex surgery and obesity, nor the combination of these risk factors had an impact on the incidence of sternal wound infection in the group treated with the novel infection prevention protocol. Only insulin-dependent diabetes was found to be a stable risk factor for sternal wound infection in both groups, however it was a strong risk factor in group A but only marginally significant in group B. Incidentally, a decrease of the central venous line associated blood stream infections was found in group B, but not group A pointing to the association between the surgical site and central venous catheter-related infections in cardiac surgery, known as "cross-talk" because the prevention bundle for central line placement and maintenance was not changed during the study period [33].

Our infection prevention protocol significantly reduces postoperative superficial and deep sternal wound infections and limits the systemic use of postoperative antibiotics. The bundle proved to be effective in a large, diverse international population of patients under real-life conditions. However future randomized studies are needed to assess the specific value of each bundle component.

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