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Confirmation of Safety of Titanium Wire in Sternotomy Closure, A Randomized Prospective Study

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Abstract

Background There are many factors that are known to increase the risk of sternal wound infection (SWI); some studies have reported that nickel is a risk factor for SWI. Titanium wires have only been used as an alternative to steel wires in patients with known allergy to nickel. However, there is a paucity of literature regarding the safety of using titanium wires compared to that on the safety of steel wires for sternum closure after cardiac surgery. Therefore, this study aimed to demonstrate the noninferiority of titanium wires, even in patients without a known allergy.

Methods A total of 322 patients who underwent elective full median sternotomy were randomly assigned to sternal closure either by titanium wires ($n = 161$) or by stainless steel wires.

Results Fourteen patients had sternal instability, six (3.7%) patients in the titanium group and eight (5%) patients in the stainless steel group ($p = 0.585$). There was no statistically significant difference between both groups in terms of postoperative wound infection ($p = 0.147$). Patients in the titanium group experienced statistically significant lower postoperative pain than those in the stainless steel group ($p = 0.024$). The wire type was not an independent risk factor for SI, as shown by univariate and logistic regression analyses.

Conclusion Titanium wires are a good alternative and have been proven to be safe and effective for sternal closure. The surgeon should be aware of the possibility of developing an allergic reaction to the wires, especially in patients with previous multiple allergic histories.

Keywords
- titanium wires
- nickel allergy
- sternal instability
- sternotomy closure

Introduction

Despite several technical variations and improvements in sternal closure over the years, a small percentage of patients experience sternal wound complications, among which deep infections involving the sternal bone and mediastinum are the most relevant.[1]

Although many factors are known to increase the risk of sternal wound infection (SWI), some studies have reported that nickel is a risk factor for SWI. Sternum closure using steel wires containing nickel is a potential risk factor due to the known allergic reactions to this material and the number of patients with an "undiscovered" allergy is underreported.[2,3]

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Allergic reactions to metals are well described in traumatology and odontology practice; however, few cases have been reported in cardiac surgery.[4] The reported cases of nickel allergy correlated with the use of stainless steel wires, presenting with pruritus, sternal pain, chronic tissue overgranulation, wound nonhealing, erythema, and osteomyelitis (see ►**Fig. 1**). Removal of sternal wires in these patients resulted in improvement or complete resolution of symptoms. More severe complications of nickel allergy, such as pericarditis and pericardial tamponade, have been reported in patients after atrial septal defect closure using devices containing nickel, such as the Amplatzer (St. Jude Medical, Inc, Saint Paul, MN, United States) septal occluder device. The other nonspecific symptoms, such as migraines, chest pain, palpitations, and dermatitis, have also been documented in these patients and required surgical removal of the device.[5]

Stainless steel wires have been extensively used for decades and are well established as surgical suture materials. Titanium wires have only been used as an alternative to steel wires in patients with known allergy to nickel. However, there is a paucity of literature regarding the safety of using titanium wires compared to that on the safety of steel wires for sternum closure after cardiac surgery in terms of early sternal dehiscence, sternal infection, and wound pain. Therefore, this study aimed to demonstrate the noninferiority of titanium wires, even in patients without a known allergy.

Patients and Methods

Study Design

This randomized controlled prospective single-blinded study (parallel design) included 322 patients who underwent elective cardiac surgery between October 2019 and October 2020 at Heart Center Dresden, Technical University of Dresden. The Ethics Committee of University of Technology, Dresden, Germany, approved this study in June 2019. Informed written consent was obtained from all patients.

The participants were randomly divided into two groups of 161 participants each according to the sternum wire closure method—the study group (titanium wires) and the comparison group (stainless steel wires).

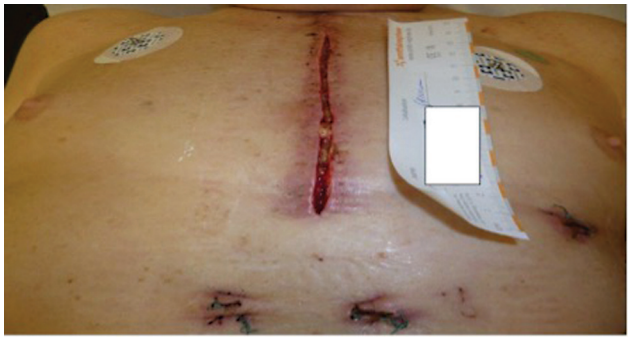

Fig.1 A postcoronary artery bypass grafting patient showing hypersensitivity reaction/intolerance to skin nickel staplers. Source: Wound clinic, Heart Center Dresden.

Inclusion Criteria

All patients undergoing elective median sternotomy and provided written informed consent were included.

Exclusion Criteria

- Exclusion criteria were:
- Redo median sternotomy.
- Presence of infection as infective endocarditis.
- Early postoperative reexploration due to postoperative bleeding.
- Participation in another interventional trial.
- Emergency operation.
- Corticosteroids or immunosuppressive therapy such as methotrexate therapy.
- History of pathological sternal fracture.
- Pregnancy and lactating.

All patients were admitted 1 day before surgery and received the following treatment according to our protocol: prophylactic IV cefuroxime 1.5 g or 3 g based on body weight (>80 or <80 kg) at the time of induction of anesthesia and repeated after the termination of cardiopulmonary bypass.

Intervention

Titanium wires (FSSB Chirurgische Nadeln GmbH) were used.

Control

Stainless steel wires (FSSB Chirurgische Nadeln GmbH) were used as the standard wires in Heart Center Dresden.

Outcome

- Outcomes were:
- Primary endpoint: incidence of postoperative sternal instability.
- Secondary endpoints: severity of wound infection (according to the CDC classification), ASEPSIS score for assessing the severity of the wound (score: 0–40),[6] and pain rating score for assessing the individual pain impression.

Sample Size Calculation

Considering an alpha of 0.05 (alpha = level of significance/type I error) and a power of 0.8 (1-β = power and β = type II error), the estimated effect size based on our clinical experience to identify the noninferiority margin using a minimal clinical significance difference (MCSD) between the treatment groups was 10 to 12%, which was calculated using a two-sided test with the chi-square test for comparing two independent proportions and categorical outcome (SI). The drop-out rate was <5% as all patients in the early postoperative period according to the standard of postoperative care in Germany are adherent to the wound clinic of the operating cardiac center. In addition, sensitivity analysis was performed to manipulate the MCSD range. In total, 131 to 177 patients should be included in each group.

Due to the lack of a previous pilot study and the lack of appropriate analogies to our study in the literature, a clinical judgement was used to set the noninferiority margin.

Postoperative pain assessment: on the 3rd postoperative day and 7th or 1 day before the discharge, to exclude any confounding pain that might have been caused due to the presence of the chest tubes, the patients were assessed for surgical site pain at least three times daily (before administering analgesics). Further, they were assessed when they complained of pain. The pain score was calculated using the 0 to 10 numeric pain rating scale.

Sternal Closure Technique

The sternum was closed using either no. 6 or no. 7 steel wire or no. 7 titanium sutures on a taper cut needle. In both groups, closure was performed using an interlocking multitwisted technique using eight sutures.

The pain was graded as mild, moderate, or severe. For analysis, the highest daily pain score for each patient was considered. After pain assessment, all patients received the same standard painkillers—tramadol 100 mg twice daily and metamizole 30 to 40 drops maximum five times daily as needed. The wounds were assessed daily by the nursing staff. Consultation with our wound clinic team was sought if there was any suspicion or early signs of wound infection.

The wound was inspected for erythema, serous or purulent discharge, separation of deep tissue, and SI. Cultures were performed using samples from discharged wounds, and bacterial growth was identified. The main investigator calculated ASEPSIS scores.

The following well-known potential risk factors for postoperative surgical site infection were considered.

Preoperative factors: age, sex, body mass index (BMI), logistic Euroscore II, smoking, chronic obstructive pulmonary disease (COPD), peripheral vascular disease, renal insufficiency, and diabetes mellitus.

Intraoperative factors: single or bilateral left internal mammary harvesting, aortic cross-clamp time, cardiopulmonary bypass time, and operation time.

Postoperative factors: duration of mechanical ventilation, reintubation, delirium, and renal insufficiency.[7]

Blinding and Randomization Technique

Double blinding is not possible because the surgeon recognizes the type of wire when the sternum is closed. Patients and ward nurses, who assessed the degree of postoperative pain according to the pain rating scale, were blinded. Neither the data collector/main investigator nor the statistician was blinded. Regarding randomization, patients who underwent surgery on even days received stainless steel wire, while those who underwent surgery on odd days received titanium wire. Both the chief operating nurse and main investigator took responsibility for the randomization technique (allocation concealment).

Data Collection and Documentation

Data collection was performed during the entire in-hospital stay of patients and rehabilitation. The postoperative observation period was 3 months. To ensure the validity of the clinical results, data were collected from several sources—patient files, internal and external medical reports, anesthesia protocols and protocols from the normal surgical ward, intermediate care, intensive care unit, and our wound clinic.

For documentation purposes, considering data confidentiality, a questionnaire was created in Microsoft Excel, in which the relevant patient parameters were systematically recorded.

Statistics

Statistical analyses were performed using SPSS for Windows (version 26.0, SPSS Inc., United States). Continuous variables are presented as mean values, whereas the measures of dispersion are presented as standard deviations.

Continuous variables were measured using the Shapiro–Wilk test to check for normal distribution.

For normally distributed samples, the two independent samples *t*-test was used. For samples that were not normally distributed, the Mann–Whitney U test was used as a nonparametric method. Categorical data were compared using the chi-square test. Univariate analysis was used for the nominal variables.

Binary logistic regression with forward inclusion was used for multivariate analysis using the likelihood ratio criterion (inclusion $p \leq 0.05$; exclusion $p > 0.1$). A two-sided significance check was performed for all tests, where a *p*-value of ≤ 0.05 was considered statistically significant for all statistical tests.

Results

There were neither preoperative nor intraoperative significant differences in the risk profiles of both groups (see ►**Table 1**).

Fourteen cases of sternal instability occurred postoperatively, which is 4.3% of the entire group ($n = 322$). In group 1 (titanium wire), 6 out of 161 (3.7%) patients developed postoperative SI. In group 2 (nickel wire), 8 out of 161 (5.0%) patients had postoperative sternal instabilities. There was no statistically significant difference in the occurrence of SI between the groups.

Postoperatively, the number of patients with pain on the third and seventh days in group 1 (titanium wire) was significantly lower than that in group 2 (nickel wire; $p = 0.032$ and $p = 0.024$, respectively). For simpler statistical analysis, we divided the patients into two groups according to the ASEPSIS cutoff score of 40:[6] ASEPSIS score <40, mild-to-moderate wound infection or no wound infection, and ASEPSIS score >40, severe wound infection. Both suture materials led to satisfactory wound healing, as shown by a mean ASEPSIS score of <10 (2.4 ± 9.5) in both groups. The incidences of moderate and severe wound infections were comparable between the groups. The percentage of severe wound infection with an ASEPSIS score of >40 in the study and comparison groups was 3.1 and 1.9%, respectively; it was slightly higher in the study group but was statistically not significant ($p = 0.474$; see ►**Table 2**).

Logistic regression analysis showed BMI (odds ratio [OR]: 1.15; $p = 0{,}006$) to be an independent risk factor for the

Table 1 Patients' characteristics

Parameter	Group 1 (titanium) $n = 161$	Group 2 nickel (stainless steel) $n = 161$	*p*-Value
Sex Men Women	 131 (81.4%) 30 (18.6%)	 130 (80.7%) 31 (19.3%)	0.887
Age (years)	69.2 ± 8.8	68.2 ± 9.7	0.387
BMI (kg/m^2)	27.8 ± 4.3	28.7 ± 4.9	0.127
Euroscore	2.7 ± 2.6	2.6 ± 2.6	0.887
Smoking No Yes	 121 (75.2%) 40 (24.8%)	 127 (78.9%) 34 (21.1%)	0.427
COPD No Yes	 143 (88.8%) 18 (11.2%)	 142 (88.2%) 19 (11.8%)	0.861
Peripheral vascular disease No Yes	 142 (88.2%) 19 (11.8%)	 136 (84.5%) 25 (15.5%)	0.330
Diabetes mellitus No Diet Tablet Insulin	 92 (57.1%) 15 (9.3%) 30 (18.6%) 24 (14.9%)	 104 (64.6%) 5 (3.1%) 29 (18.0%) 23 (14.3%)	0.123
Renal failure (GFR, mL/min)	73.1 ± 19.2	74.1 ± 17.3	0.958
Mammary artery No LIMA RIMA	 10 (6.2%) 146 (90.7%) 5 (3.1%)	 20 (12.4%) 135 (83.9%) 6 (3.7%)	0.146
Operation time (minutes)	167.9 ± 33.7	168.0 ± 33.7	0.983
Aortic clamp time (minutes)	48.0 ± 19.5	49.8 ± 21.3	0.486
Cardiopulmonary bypass (minutes)	66.4 ± 22.7	68.2 ± 25.3	0.507

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; LIMA, left internal mammary artery; RIMA, right internal mammary artery.
Note: Data are presented as mean ± standard deviation. If not labeled, absolute numbers are given.

development of sternal instability. There was no association between the type of wire and the incidence of sternal instability ($p = 0.815$; see ►**Table 3**).

Discussion

The stainless steel wire is the standard wire in most cardiac centers worldwide, and it is well established; the standard wire is also used in our center. The titanium wire is less frequently used, and its application is limited to only patients allergic to nickel; however, titanium is a well-established material for use in the medical field, including dental surgery and orthopaedics.[8] To the best of our knowledge, no prospective randomized or retrospective study has compared the two common sternal wires in cardiac surgery in terms of postoperative SI, wound infection, and postoperative pain.

We found that the titanium wire is comparable to the stainless steel wire in terms of postoperative SI, which was our primary outcome. The incidence of SI for all patients was 4.3%; the study group had 3.7 % while the comparison group had 5% (p = 0.585).

Several factors increase the risk of postoperative SI. Univariate analysis showed that BMI is the only independent risk factor for SI, with mean BMI of 31.7 ± 4.4 kg/m^2 among patients with SI and 28.1 ± 4.6 kg/m^2 for those without SI (p = 0.002). This positive finding was confirmed by further logistic regression analysis, which revealed a positive association between event/obesity and outcome/SI ($p = 0.006$, OR = 1.151, 95% confidence interval [CI] = 1.042–1.271).

This risk factor was also reported by Abboud et al; obesity was an independent risk factor for surgical site infection in 9,136 patients (OR = 6.49; 95% CI = 2.24–18.78).[9]

Milano et al studied 6,459 patients and concluded that obesity was the most important independent risk factor for the development of postoperative sternal complications (OR = 1.3, $p = 0.0002$).[10]

Different studies have implicated that suture materials increase the risk of developing SWI. Therefore, Malhotra

Table 2 Primary and secondary outcomes of the study

Parameter	Group 1 (titanium) $n = 161$	Group 2 (nickel [stainless steel]) $n = 161$	*p*-Value
Sternal instability No Yes	 155 (96.3%) 6 (3.7%)	 153 (95.0%) 8 (5.0%)	0.585
Pain third day classification 0–3 >3	 159 (98.8%) 2 (1.2%)	 152 (94.4%) 9 (5.6%)	0.032
Pain seventh day classification 0–3 >3	 161 (100.0%) 0 (0.0%)	 156 (96.9%) 5 (3.1%)	0.024
Wound No Yes	 148 (91.9%) 13 (8.1%)	 140 (87.0%) 21 (13.0%)	0.147
Wound revision No Yes	 153 (95.0%) 8 (5.0%)	 154 (95.7%) 7 (4.3%)	0.791
ASEPSIS score	2.1 ± 9.4	2.8 ± 9.6	0.113
ASEPSIS score classification 0–40 >40	 156 (96.9%) 5 (3.1%)	 158 (98.1%) 3 (1.9%)	0.474

Table 3 Logistic regression analysis for sternal instability

a. The only significant variable						
		Wald	Significance	Odds ratio	95% confidence interval for odds ratio	
					Lower	Upper
	BMI	7.674	0.006	1.151	1.042	1.271
b. Nonsignificant variables						
				Score	Degree of freedom	Significance
Sex				0.001	1	0.979
Smoking				0.024	1	0.876
COPD				1.097	1	0.295
Peripheral vascular disease				1.618	1	0.203
DM				2.361	3	0.501
Renal failure (GFR)				0.025	1	0.876
Wire				0.055	1	0.815
BIMA				0.446	1	0.504
Delirium				1.953	1	0.162

Abbreviations: BIMA, bilateral internal mammary artery; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; GFR, glomerular filtration rate.

et al compared two conventional techniques of sternal closure (steel wire vs. polyester suture) and concluded that the use of polyester sutures for sternal closure in adult patients results in increased wound infection, wound pain, and late wound complications, but lower mediastinal drain output.[11]

Additionally, Clauss et al have reported that infection is a serious complication of operative therapy and can be related to implant materials. Biofilm formation can be reduced by the materials used. Titanium implants have less biofilm formation than stainless steel implants, and infections may be acute and easy to detect, but can also present as low-grade infections that are difficult to diagnose and likely to be missed.[12]

In this study, there was lower postoperative pain on the third and seventh days in the study group than in the comparison group. The percentage of patients who experienced

postoperative pain >3 on the numeric pain rating scale on the third day was 1.2 and 5.6% in the study and comparison groups, respectively ($p = 0.032$). This finding was confirmed on the seventh day, with an incidence of 0.00 and 3.1% in the study and comparison groups, respectively ($p = 0.024$). No postoperative pain of >7 on the numeric pain rating scale was recorded in either group.

The etiology of increased postoperative pain with stainless steel wires compared to that with titanium wires is unclear. We presume that a mild allergic response (subclinical) to stainless steel wires may lead to edema, inflammation, swelling, and subsequently pain.[2,5,13–15] We have noticed that there is an increasing number of patients in whom the sternum was closed with stainless steel wires presented to our wound clinic with pain affecting their quality of life in the absence of cachexia, infection, and wire fistula, which could support our assumptions of a subtle or subclinical allergic response to nickel-wire intolerance. Persistent sternal pain after median sternotomy for open heart surgery is a relatively common complaint. Many poststernotomy pain syndromes have been considered to have a specific cause–effect relationship directly related to an underlying pathological process (e.g., infection, nonunion, protruding wire, and ischemia). Most cases appear to be poorly defined; however, they have been attributed to nonspecific anxiety-related or muscular pain disorders. Fine and Karwande reported a case of disabling chest pain after open heart surgery through a median sternotomy incision in which stainless steel sutures were used for sternal closure. Removal of sternal wires led to complete pain relief.[14]

Lopez et al presented a case of a patient who developed chronic tissue overgranulation over a sternotomy wound 8 weeks postoperatively (see ►**Fig. 2**). The wires were made of standard surgical stainless steel, which is an alloy of nickel and chromium. The sternal wires were removed as they were the most likely cause of the local tissue reaction.[2]

Persistent postoperative incisional pain after aortocoronary bypass surgery was reported by a patient in whom allergies to metals contained in the stainless steel suture used for sternal closure were confirmed by patch testing. The symptoms resolved promptly after the sutures were removed.[13] Another possible explanation for the greater postoperative pain in the stainless steel group may be attributed to the increased stiffness of the stainless steel wire compared to that of the titanium wire; in other words, the stainless steel wire is harder than the titanium wire.

Although some surgeons have expressed skepticism that allergy to the sternal wire is a real condition, there is ample evidence in the published literature on such hypersensitivity reactions, especially in orthopaedic surgery.[16] A German consensus paper has suggested that titanium implants should be used in all patients with a history of metal allergies.[3]

Conclusion

The wire type was not an independent risk factor for SI, as shown by univariate and logistic regression analyses. This means that the titanium wire is not inferior to the stainless steel wire in this context, and we can reject the null hypothesis. In our study, the titanium wire was associated with lower postoperative pain than the stainless steel wire, an exploratory finding. Further randomized controlled, multicentric studies are needed to prove or refute our findings.

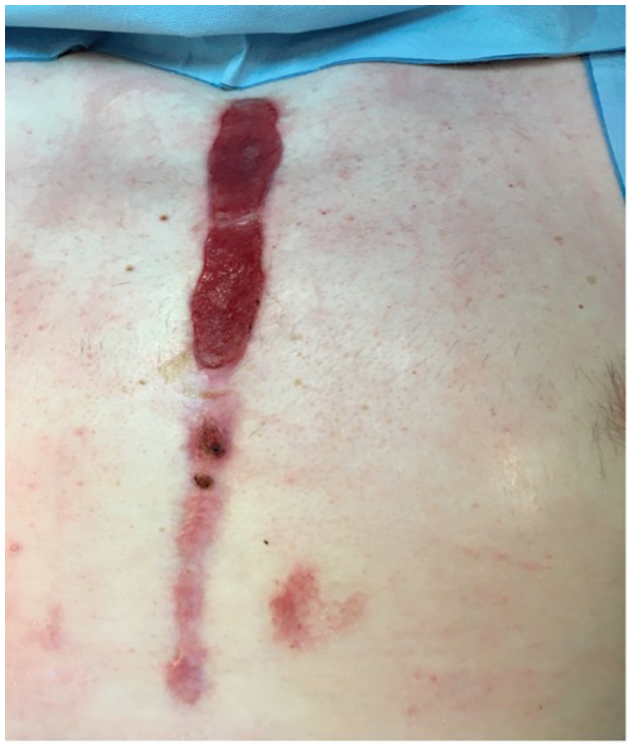

Fig. 2 Eruptions along the sternotomy wound due to overgranulation. Source: Wound clinic, Heart Centre Dresden.

Limitations of the Study

Given the paucity of the literature on this topic, we have intentionally decreased the eligibility criteria of this study (see exclusion criteria) to increase the internal validity and used the "decrease the noise to amplify the signal approach." Therefore, further randomized studies should be conducted to compare the use of titanium wires with that of steel wires in patients at a high risk for mediastinitis to confirm their safety and increase the external validity (generalizability) of our results.

Blinding in surgical research is not an easy task because it is very difficult to blind the surgeon, who can be a source of bias.

Regarding postoperative pain, one may argue that pain, being a clinical scale, is subject to bias (observer bias or reporting bias) due to subjectivity in symptoms assessed, but the patients and outcome assessors/ward nurses were unaware of the type of wire used. Considering that postoperative pain was the secondary endpoint in our study. Therefore, we consider these findings as exploratory findings, and another study should be recommended and designed to answer this specific question.

Although the skin patch test is the gold standard method in diagnosing contact allergy, its efficacy is debatable in

cardiac surgery and is not well established in preoperative workup. Therefore, our patients were asked for a history of hypersensitivity to metals, without patch skin testing.

Considering that nickel hypersensitivity is more common in women than in men, with a ratio of 5:1, our study was not balanced in terms of sex (18.9% women vs. 81.1% men) as most of our patients underwent coronary artery bypass graft (90.7%), and men were more affected than women. It would be interesting to know the prevalence of poststernal wiring pain in women compared to that in men.

The take-home message for surgeons is to be aware of the possibility of developing an allergic reaction to wires, especially in patients with a history of multiple allergies. This could be due to persistent unexplained postoperative chest pain or chronic nonhealing yet stable overgranulating sternotomy wound in the absence of cachexia, infection, and wire fistula. In patients with documented hypersensitivity to nickel, other alternative closure methods should preferably be considered, such as the titanium wire, which has been proven to be safe and noninferior to the stainless steel wire in our study.

Conflict of Interest
None declared.

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