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Healing Characteristics of a New Silver-Coated, Gelatine Impregnated Vascular Prosthesis in the Porcine Model

Das Einheilungsverhalten einer neuen Silber-beschichteten, Gelatine-imprägnierten Gefäßprothese am Schweinemodell

Abstract

Objectives: To investigate the intraluminal and extraluminal healing behaviour of a new metallic silver coated, gelatine impregnated vascular graft. **Design:** Comparative animal experimental investigation with randomisation of the animals to control and experimental groups. **Material and Methods:** 24 pigs were assigned to two control and two experimental groups. The prostheses were interposed in the pigs' infrarenal aorta. For the evaluation, macroscopic, histological and immunohistochemical criteria were applied. **Results:** The macroscopic evaluation after explantation of the prosthesis revealed similar healing characteristics in the control and experimental groups. The microscopic determination of neo-intimal thickness showed no significant differences between the groups; nor did the immunohistochemical investigations show any significant difference between the control group and the silver-coated prosthesis group. **Conclusions:** No disadvantage of the silver coating in terms of healing and graft patency was found. A possible advantage in terms of the antibacterial effect of the silver coating must be investigated in the clinical setting.

Key words
Metallic silver-coated vascular prostheses · polyester vascular prostheses · healing characteristics

Zusammenfassung

Hintergrund: Untersuchung der intra- und extraluminalen Einheilung einer neuen metallisch Silber-beschichteten, Gelatine-imprägnierten Gefäßprothese. **Design:** Vergleichende tierexperimentelle Untersuchung mit Randomisierung in Kontroll- und Versuchsgruppen. **Material und Methode:** 24 Schweine wurden in 2 Kontroll- und 2 Versuchsgruppen randomisiert. Die Gefäßprothesen wurden in die infrarenale Aorta interponiert. Zur Auswertung wurden makroskopische, histologische und immunhistochemische Kriterien verwendet. **Ergebnisse:** Die makroskopische Beurteilung stellte nach Prothesenexplantation ein vergleichbares Einheilungsverhalten von Kontroll- und Versuchsgruppen dar. Die mikroskopische Neointimadickenbestimmung zeigte keine signifikanten Unterschiede zwischen den Gruppen. In den immunhistochemischen Untersuchungen waren ebenfalls keine signifikanten Unterschiede zwischen der Kontrollgruppe und den silberbeschichteten Gefäßprothesen nachweisbar. **Schlussfolgerungen:** Ein Nachteil durch die Silberbeschichtung in Bezug auf Einheilung und Offenheit konnte nicht nachgewiesen werden. Ein möglicher Vorteil durch die antibakterielle Wirkung der Silberbeschichtung muss in der klinischen Anwendung untersucht werden.

Schlüsselwörter
Silberbeschichtete Gefäßprothese · Polyestergefäßprothese · Einheilungsverhalten

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Zentralbl Chir 2005; 130: 71–76 · © Georg Thieme Verlag KG Stuttgart · New York
DOI 10.1055/s-2004-836244
ISSN 723-7065

Polyester and Polytetrafluoroethylene have become widely accepted as the vascular prosthetic materials for bypass purposes [17]. The properties of vascular prostheses have been optimised through the use of a variety of coatings and fabrication processes. Major negative aspects associated with alloplastic biomaterials continue to be thrombogenicity, neo-intimal hyperplasia and the susceptibility of the prosthetic bed to infection. Before they can be used in humans, newly developed vascular prostheses and their healing characteristics first have to be investigated in animal experiments – at the present time, alternative biological test systems are not available. In the field of reconstructive vascular surgery, graft infection is a rare (1–2.6%) but serious complication with a major amputation rate of 50% and a mortality rate of 25% [3, 10, 11]. The bacteriostatic and bactericidal effects of silver, as well as its biocompatibility are well documented in the literature [5, 9, 15]. This has prompted the development of vascular prostheses coated with silver. A number of investigations have confirmed their antimicrobial efficacy [5, 15], but no reports have so far been published on tissue reaction over the long term investigated in the animal model, and its relevance to the human situation.

The aim of the present investigation was to analyse – using quantified immunohistochemistry – the intraluminal and extraluminal healing characteristics of a new metallic silver-coated, gelatine impregnated vascular prosthesis in comparison with conventional gelatine impregnated prostheses made of polyester of identical fabrication.

Material and Methods

Animals: Female domestic pigs approximately 3 months of age with an average body weight of 34.9 kg (range 27–42 kg) were chosen. The average diameter of the infrarenal aorta was 8 mm. Approval of an experimental study taking the form of a survival study was given by the Thuringian Office for Food Safety and Consumer Protection Weimarplatz 4 in 99423 Weimar (Germany) under the Registration No. 08-61/02.

Vascular prostheses: Test samples of the commercially available Uni-Graft® K DV (B/BRAUN, Aesculap) were compared with a new silver coated, gelatine impregnated polyester vascular graft. Silver coating consists of a dense layer of metallic silver (average thickness 1200 Å) which is deposited by a physical vapour deposition process (PVD) on the surface of the polyester of the graft. The coating is designed to inhibit attachment, colonization and biofilm formation of microorganisms to the graft surface. To guaranty blood permeability at the time of implantation the graft is impregnated by gelatine (B/BRAUN, Aesculap) after silver coating process.

The diameter of the grafts of both group, control and test group was 8 mm.

Operative technique: Prior to surgery, the animals were fasted for 8 hours but had free access to drinking water. As premedication, a single subcutaneous injection was administered (azeparon 1–2 mg/kg body weight (BW)) and atropine (0.05 mg/kg BW). Following sedation with ketamine and xylazine, the animals were intubated. Intra-operatively in addition, fentanyl (0.005 mg/kg BW) for analgesia, pancuronium (0.1 mg/kg BW) for muscle relaxation, and droperidol (0.2 mg/kg BW) and a ketamine/diazepam continuous infusion were administered. Perioperative antibiotic cover was provided by 1 × 2.25 g piperacillin/tazobactam. After performing a median laparotomy, the retroperitoneum was then incised and the infrarenal aorta exposed. The renal arteries and the inferior mesenteric artery were preserved and a lumbar artery was regularly ligated. Following systemic heparinization (1000 IU heparin) the aorta was clamped and a segment resected. An alloplastic vascular prosthesis (40 mm in length) was then interposed using a continuous suturing technique (prolene 5 × 0). At the end of the experiments after 3 and 6 months, the animals were sacrificed and the prostheses removed en bloc together with the adjacent tissue.

Randomisation: 24 domestic pigs were randomized to 4 groups of 6 animals each – 2 control and two experimental groups by drawing lots (Table **1**). The histological work-up of the specimens was carried out by an independent, blinded pathologist.

Test parameters: A specimen of tissue (prosthesis together with neo-intima and surrounding tissue, including the anastomosis), was photodocumented, fixed in 4% formaldehyde solution (pH 7.2) and embedded in paraffin. Evaluation covered the macroscopic appearance and histological and immunohistochemical analyses of the specimens.

Macroscopically, the parameters patency, neo-intima formation and incorporation were assessed with the aid of a score (Prosthesis patent: 1 – yes, 2 – no; Neo-intimal formation: 1 – complete, 2 – incomplete; Incorporation: 1 – complete, 2 – partial, 3 – not incorporated).

Conventional histology was carried out using H&E staining and a connective tissue stain (Goldner). The thickness of the neo-intima as a sign of proliferation was measured in µm.

For the immunohistochemical analysis three tissue regions were assessed. The proximal anastomosis was investigated intraluminally and the region in the middle of the prosthesis both intraluminally and extraluminally. The immunohistochemical analysis

Table **1** Randomisation

groups	*group designation*	*prosthesis*	*observation period*	*No. of animals*
control group 1	3U	UNI-GRAFT® K DV	3 months	6 animals
control group 2	6U	UNI-GRAFT® K DV	6 months	6 animals
experimental group 1	3S	metallic silver coated, gelatine impregnated vascular graft	3 months	6 animals
experimental group 2	6S	metallic silver coated, gelatine impregnated vascular graft	6 months	6 animals

Groups investigated n = 4, animals n = 24

Table **2** Macroscopic and microscopic findings

		macroscopy			*microscopy*	
animal	***group***	***patency***	***Neo-intima***	***Incorp.***	***NI-prox. A.***	***NI-Middle***
1	3U	patent	1	2	1317	793
3	3U	patent	1	1	2756	1936
14	3U	patent	1	1	1314	1037
16	3U	occluded	1	3	2315	2084
17	3U	patent	1	2	306	830
22	3U	patent	1	2	1373	1345
	mean		1.0	1.8	1563.5	1337.5
	SD		0.0	0.8	863.4	558.5
11	3S	patent	1	3	1219	1206
18	3S	patent	1	2	873	1111
19	3S	patent	1	1	423	568
20	3S	patent	1	1	329	984
21	3S	patent	1	1	1150	555
23	3S	patent	1	1	967	1168
	mean		1.0	1.5	826.8	932.0
	SD		0.0	0.8	371.7	296.7
2	6U	occluded	1	2	1643	520
5	6U	patent	1	1	571	552
12	6U	occluded	1	1	1991	1982
13	6U	patent	1	1	393	410
15	6U	patent	1	1	1628	1890
24	6U	patent	1	1	1484	1069
	mean		1.0	1.2	1285.0	1070.5
	SD		0.0	0.4	646.4	708.6
4	6S	occluded	1	1	2143	2593
6	6S	patent	1	1	486	562
7	6S	patent	1	3	330	720
8	6S	patent	1	1	315	454
9	6S	occluded	1	1	340	2351
10	6S	occluded	1	1	1524	1639
	mean		1.0	1.3	856.3	1386.5
	SD		0.0	0.8	784.2	942.7

no significant differences between the groups
SD: standard deviation
Neo-intima: Neointima formation 1 – complete, 2 – incomplete
Incorp.: Incorporation 1 – complete, 2 – partial, 3 – not incorporated
NI-prox. A.: Neo-intima thickness at the proximal anastomosis in μm
NI-Middle.: Neo-intima thickness in the middle of the prostheses in μm

was used to quantitatively analysis intraluminal and extraluminal changes.

Extraluminal investigations: The proliferation behaviour and inflammatory reaction were investigated for 350 μm around the middle portion of the vascular prostheses to evaluate healing behaviour. The proliferation marker employed was anti-Ki67 (clone MIB-1, DAKO Cytomation, Hamburg). The evaluation was effected as a percentage of the Ki67-positive mesenchymal extravascular cells in relation to the total number of mesenchymal extravascular cells, inflammatory cells being excluded. The T-lymphocyte marker anti-CD3 (polyclonal antibodies, DAKO Cytomation, Hamburg) was used to quantify the periprosthetic cellular inflammatory reaction (cells/mm^2). The evaluation was effected by determining the determination of the numerical density of the extraluminal CD3-positive T-cells in the middle section of the prosthesis.

Intraluminal investigations: The number of actin-positive cells in the intraluminal surface was determined to quantify the smooth muscle cells as a major constituent of the neo-intima. The volume density of actin-positive cells (monoclonal antibodies 1A4, DAKO Cytomation, Hamburg) in the neo-intima of the proximal anastomosis and the mid-section of the prosthesis was determined by grid counting and computed stereologically (cells per volume-unit), described by Gundersen et al. [6]. For the evaluation of the cellular proliferation behaviour the proliferation in-

Table **3** Findings of Immunhistochemistry

		Immunhistochemistry					
		extraluminal		*intraluminal*			
animal	*group*	*Ki67-Ex*	*CD 3*	*A.pos. C.-M.*	*Ki67-In*	*v. W.F.*	*A.pos. C.-A.*
1	3U	36.6	22.6	28.0	6.0	3.2	40.2
3	3U	27.5	11.8	65.6	5.9	8.6	55.8
14	3U	33.1	39.8	70.0	11.0	1.8	54.2
16	3U	32.8	71.8	69.8	7.5	6.2	67.6
17	3U	32.8	46.8	62.4	4.8	3.6	42.8
22	3U	9.4	23.6	50.8	0.8	7.8	40.6
	mean	28.7	36.1	57.8	6.0	5.2	50.2
	SD	9.9	21.6	16.2	3.3	2.7	10.9
11	3S	30.4	77.2	10.0	20.1	7.2	66.8
18	3S	18.0	33.4	51.4	6.2	1.6	48.2
19	3S	16.0	11.4	50.4	5.5	1.2	62.8
20	3S	15.8	15.8	57.6	6.6	0.8	51.2
21	3S	14.1	13.4	59.0	11.1	2.6	59.6
23	3S	23.3	25.2	51.6	3.9	7.2	58.4
	mean	19.6	29.4	46.7	8.9	3.4	57.8
	SD	6.2	24.8	18.3	6.0	3.0	7.0
2	6U	3.2	52.0	52.8	8.4	9.0	55.0
5	6U	4.9	13.2	69.2	3.6	3.4	29.0
12	6U	10.8	22.6	63.6	3.6	8.6	8.8
13	6U	3.1	10.8	47.4	0.0	3.4	27.4
15	6U	6.5	12.4	38.6	0.8	3.8	31.8
24	6U	4.8	35.0	65.6	3.9	1.4	39.0
	mean	5.6	24.3	56.2	3.4	4.9	31.8
	SD	2.9	16.3	11.9	3.0	3.1	15.1
4	6S	5.6	81.4	72.0	2.5	3.6	75.6
6	6S	4.3	24.4	38.2	2.8	1.4	55.6
7	6S	2.3	85.0	47.8	1.6	0.2	46.6
8	6S	2.7	16.6	72.6	3.8	1.2	45.2
9	6S	5.3	28.4	48.8	13.4	4.6	42.6
10	6S	5.8	25.0	60.0	5.7	4.6	4.6
	mean	4.3	43.5	56.6	5.0	2.6	45.0
	SD	1.5	31.0	14.0	4.4	1.9	23.2

no significant differences between the groups
SD: standard deviation
Ki67-Ex: Percent of Ki67-positive cells 350 μm periprosthetic at the middle of the prostheses
CD 3: Number of CD3-positive T-cells 350 μm periprosthetic in cells/mm^2
A.pos. C.-M.: Number of actin positive cells in the middle of the prostheses (cells per volume-unit)
Ki67-In: Percent of Ki67-positive cells at the proximal anastomosis
v. W.F.: Number of microvessels at the proximal anastomosis, surface density of neo-intimal microvessels per mm^2
A.pos. C.-A.: Number of actin positive cells at the proximal anastomosis (cells per volume-unit)

dex was determined at the proximal anastomosis (on the basis of Ki67 as described for the extraluminal method). For the quantification of neo-vascularisation (number of microvessels) within the neo-intima, the endothelial marker, von Willebrand factor (clone F8/86, DAKO Cytomation, Hamburg), was applied. The evaluation was done as the surface density of neo-intimal microvessels per mm^2.

Statistics: The statistical analysis was carried out using the Student T-test (significance $p < 0.05$). For the macroscopic findings a descriptive analysis was applied.

Results

Postoperatively, four pigs developed incisional hernias which, however, subsequently regressed, and the animals were not impaired in any way. Postoperative feeding was complication-free. One early postoperative death (3rd postoperative day) occurred due to a bowl perforation of uncertain genesis. This animal was excluded from the study. Nutritional status was good with all animals rapidly gaining weight – the average weight after 3 months was 88.3 kg (range 75–105 kg), and after 6 months 144.4 kg (range 137–154 kg). No clinical signs of a perfusion dis-

order of the hind legs (leg temperature, mobility) were seen in any animal receiving a silver-coated prosthesis.

Macroscopy: In the group 3U (control group 1, Uni-Graft® KDV, 3 months), one prosthesis was found to be occluded at 3 months; in the group 3S (experimental group 1, metallic silver coated, gelatine impregnated graft, 3 months) all prostheses were patent. After 6 months, two prostheses were found to be occluded in the group 6U (control group 2, Uni-Graft® KDV, 6 months) and 3 prostheses in group 6S (experimental group 2, metallic silver coated, gelatine impregnated graft, 6 months). The total patency rates were 75% in both groups after 6 months. Macroscopically, all prostheses showed a complete neointima. The incorporation score of all prostheses was similar, with no significant differences to be seen (Group 3U 1.83 ± 0.75, group 3S 1.50 ± 0.84, group 6U 1.17 ± 0.41 and group 6S 1.33 ± 0.82). Table **2** details the macroscopic findings.

Histology: The microscopic measurement of the neo-intimal thickness showed a smaller thickness in group 3S as compared with group 3U. The differences were, however, not significant. After 6 months, the differences were noticeably less. Table **2** details the neo-intimal thickness.

Immunohistochemistry: The markers employed were tested in preliminary experiments for their effectiveness in porcine tissue. No significant differences were seen in the percentage proportion of actin-positive cells in the neo-intima between the individual groups or between the proximal anastomosis and the middle part of the prosthesis. In the groups with silver-coated prostheses the proliferation behaviour (Ki67-positive cells) was not significantly increased. In contrast, the surface density of neo-intimal microvessels in the region of the proximal anastomosis was lower in the silver-coated prostheses. However, these differences were again non-significant. After 3 months, the cellular immune reaction (CD 3 T-lymphocyte marker) was smaller in the silver-coated group (non-significant). After 6 months, the periprosthetic proliferation (Ki67-positive cells) as an expression of complete incorporation was clearly reduced in both groups. Significant differences between silver-coated and non-silver-coated prostheses were not observed. Table **3** details the results of immunhistochemical investigations.

Discussion

To allow for ingrowth of connective tissue cells, a vascular prosthesis must be porous [16]. Good healing of the graft into its surroundings is a prerequisite for the prevention of infections and mechanical complications. During the further course, a neo-intima covered by a layer of endothelium should form. As a result of interactions between the material of the prosthesis and the activated inflammatory cells, extraluminal incorporation varies in accordance with the composition of the prosthesis [2, 8]. The healing characteristics (biocompatibility) of vascular prosthetic materials have been described in several animal models. In the porcine model, the intraperitoneal and retroperitoneal situations are comparable with those found in humans, and the coagulation immune system is similar to that of humans [18]. Many survival experiments were run for only 1 to 3 months [2, 8, 12]. But it is the long-term behaviour of alloplastic materials in the body that is of particular interest. With this in mind, the present study was conducted over 3 and 6 months. For evaluation of the patency rates of vascular grafts, consensus has it that the canine model is superior [1]. Since the aim of this study was to investigate not the patency rate but the biocompatibility, the porcine model was used. An advantage of the porcine model is that the animals can be obtained in sufficient numbers, standardised in terms of weight and health, and that animal management is inexpensive. For investigating vascular prostheses having a diameter of 8 mm, correspondingly large animal vessels are needed, and for this purpose the infrarenal aorta of the young pig is an appropriate model.

A number of studies have demonstrated the antimicrobial effect of silver ions [9, 14, 15]. Others have demonstrated an advantage of antibiotic-coated grafts over silver-coated grafts [5]. Silver-coated prostheses are already being used in the clinical setting, but studies on their clinical effectiveness are lacking. Our study investigated the healing behaviour of a new metallic silver coated, gelatine impregnated graft over periods of 3 and 6 months in comparison with a control group comprising conventional vascular grafts. The selected immunohistochemical markers for the demonstration of smooth muscle cells (actin), T-lymphocytes and endothelial cells (von Willebrand factor) were shown to be efficient by Ao et al. in a sheep model, although they were not quantified [2]. In the present model, the healing characteristics were assessed periprosthetically on the basis of macroscopic and immunohistochemical aspects. No significant differences were to be seen between the groups investigated. After 6 months the proliferation marker Ki67 has significantly decreased in the periprosthetic tissue as an expression of good incorporation of the grafts in both groups. Between the silver-coated and control groups, no significant differences in proliferative behaviour of the periprosthetic cells were to be seen. After 6 months, both groups showed a clear increase in intimal cell proliferation, demonstrating the need for long-term studies. However, rapid growth in the pig leads us to expect a high proliferation index. For this purpose, the adult dog model is more suitable.

Qin et al. showed that the von Willebrand factor has a mitogenic influence on smooth muscle cells [14]. In this connection, we investigated the extent of the neo-intimal microvascularisation in the region of the anastomosis by using the von Willebrand factor, and found no significant differences.

The tendency of the metallic silver-coated prostheses to show a smaller neo-intimal thickness after 3 months might be an expression of the antiproliferative action of the silver ions similar to the bacteriostatic effect in the porous vessel wall [5]. Further investigations with intraluminal coating with silver or drug-eluting substances (cytostatic agents) might act in concert with the antimicrobial effect of silver-coated vessel grafts to reduce intimal hyperplasia [7].

Conclusions

The purpose of our study was to compare the healing characteristics (biocompatibility) of a new metallic silver coated graft in comparison with a non-silver-coated prosthesis of identical structure in the porcine model before employing it in the clinical setting. The macroscopic evaluation after 3 and 6 months re-

vealed comparable healing characteristics in the silver-coated and non silver-coated vascular prostheses. The microscopic measurement of neo-intimal thickness revealed no significant differences. Nor did the immunohistochemical examinations reveal any significant differences between the silver-coated groups and the non-silver-coated prostheses. The quantification of immunohistochemical parameters for evaluating biocompatibility needs further evaluation. In terms of healing and patency, no disadvantage of the silver coating was found. A possible advantage through the antibacterial effect of the silver coating must be investigated in the clinical setting.

Acknowledgements

This study was supported financiallly by Aesculap AG & Co.KG, Postfach 40, 78501 Tuttlingen, Germany. We would also like to thank O. Kaufmann M. D. for the histopathological assessment of the grafts.

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