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Local gentamicin-collagen sponge reduces cardiovascular implantable electronic device infections and pocket hematoma

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Abstract. – OBJECTIVE: Implantation or replacement of a cardiovascular implantable electronic device (CIED) may be associated with complications, such as pocket hematomas and infections. This study aims to determine whether a lyophilized gentamycin-containing collagen implant (GCCI) reduces major CIED infections and pocket hematomas after implant.

SUBJECTS AND METHODS: A retrospective study was conducted among patients who underwent implantation or replacement of CIED at the Tor Vergata Polyclinic (Rome, Italy) between June 2007 and November 2019. The primary combined endpoint was infection and hematoma occurrence through 12 months of follow-up post-procedure. The rate of single infectious complications, pocket hematomas or both were also assessed.

RESULTS: We compared 475 patients treated with the GCCI (GCCI group) with 714 patients who did not receive it (control group). Complications occurred in 127 patients (11%); a statistically significant reduction of infections and pocket hematomas in the GCCI group was reported when compared with control patients (1% *vs*. 17%; $p<0.0001$). A total of 20 (2%) infectious events were reported, 102 (8%) patients developed a pocket hematoma, and 5 (0.4%) had both. The rate of single complications was significantly lower in GCCI group: infection 0.2% *vs*. 2.6% ($p=0.002$), pocket hematoma 0.6% *vs*. 13.8% ($p<0.001$). The association between antiplatelet/anticoagulation therapy and hematoma development was not statistically significant.

CONCLUSIONS: The GCCI is a medical device that can be used in addition to local hemostasis and prophylactic doses of systemic antibiotics with the aim of reducing infective complications and pocket hematoma after permanent CIED implantation or replacement.

Key Words:

Cardiovascular implantable electronic device, CIED, Pocket hematomas, Infections, Gentamycin-containing collagen implant, Intraprocedural antibiotics.

Introduction

It has been estimated that over 1 million patients receive cardiac implantable electronic devices (CIEDs) worldwide every year[1]. Implantation or replacement of a permanent pacemaker (PPM) and implantable cardioverter-defibrillator (ICD), although offering evident benefits, may be associated with serious complications, such as pocket hematomas and infections[2,3]. Pocket hematomas can result from inadequate hemostasis or bleeding from venous access and may increase hospitalization time and reoperation rate[4]. The estimated incidence rate of clinically significant pocket hematomas is 2-5% in patients who are not receiving any anticoagulation and 4% among patients who have interruption of oral anticoagulation without bridging[5]. The estimated infection rate of cardiac devices ranges between 1 and 2% and, despite the use of various antibiotic prophylaxis regimens and advocacy of best surgical practices, infections in most cases are the result of contamination during the procedure[6-9]. A clinically significant pocket hematoma was associated with a significantly increased risk of infection, leading to hospitalization within 1 year following CIED[10]. Consequently, strategies aimed at reducing hematomas may also decrease the long-term risk of infections.

Recently, intraprocedural antibiotics administration using an antibacterial pocket envelope or *via* an antibiotic pocket wash has been proposed to reduce CIED infection rate and preoperative antibiotics[6,7,11,12]. These strategies resulted in a lower incidence of CIED infections without a higher incidence of complications beyond the first-year post-procedure, supporting the viability and effectiveness of incremental antibiotic treatments[6,7,11,12].

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The gentamycin-containing collagen implant (COLLATAMP® EG, Schering-Plough, Stockholm, Sweden; hereafter termed GCCI) is a matrix of purified bovine collagen type I impregnated with 2.0 mg/cm^2 gentamycin sulfate[13-16]. Within GCCI, gentamycin is released by a combination of diffusion and enzymatic breakdown of the collagen matrix, giving a high local concentration for at least 72 hours; systemically, blood or plasma levels are not generally achieved[17]. Some studies[18,19] have shown the effectiveness of the GCCI to reduce the incidence of infectious complications in major heart surgery and the role of microcrystalline collagen in wound healing. Otherwise, the role of GCCI in CIED interventions was scarcely investigated.

This observational study aimed to retrospectively assess the rate of local hematoma and surgical site infection in patients treated with the GCCI inside the device pocket during CIED implantation or replacement compared with patients treated with the conventional preoperative antibiotic regimen.

Subjects and Methods

Study Design and Setting

This was a retrospective observational study carried out between June 2007 and November 2019 at the Policlinico Tor Vergata (Rome, Italy). Clinical data of consecutive patients undergoing successful CIED implantations or CIED replacements were used. One procedure for each patient was considered; device revision or replacement cases for reasons other than end-of-life battery were not considered. Patients with mechanical cardiac prosthesis were excluded. Indications for the treatment with the GCCI were based on the hemorrhagic risk (dual antiplatelet therapy/anticoagulant therapy), the infectious risk (age, diabetes, chronic kidney disease, >2 leads, or immunosuppressed patients) and the availability of the GCCI device in the hospital. Pregnant, breastfeeding patients and patients with chronic kidney disease with glomerular filtration rate (GFR) ≤15 mL/min were excluded because of the contraindications to the study product as reported in manufacturer's guidelines[20].

The study was conducted in accordance with the ethical standards as laid down in the Declaration of Helsinki and its later amendments and was notified to the Ethics Committee of Policlinico Tor Vergata (Rome, Italy) on 15 February 2022. All the participants signed an informed consent form.

Study Measures

The primary composite endpoint was CIED infection complications and pocket hematoma within 12 months after the procedure, according to the treatment with the GCCI. CIED infection was defined as the presence of local and systemic signs and symptoms (surgically site pain, redness or swelling of the wound, dehiscence with or without drainage of pus, fever) and confirmed by laboratory results[21]. The hematoma was defined as a blood collection inside the prepectoral pocket that required monitoring/revision of the implant. Occurrence of infection or pocket hematoma individually was also assessed as secondary endpoints, along with the impact of antiplatelet/anti-coagulant therapies in developing a pocket hematoma.

Gentamycin-Containing Collagen Implant

The GCCI consists of a matrix of purified bovine collagen type I impregnated with 2.0 mg/cm^2 gentamicin sulfate[15,16]. The collagen matrix is fully resorbed within 1-7 weeks, depending on the location (well-vascularized tissues versus bone cavities), making its removal unnecessary. The GCCI is available in different sizes (10×10 cm, 5×5 cm or 5×20 cm) and can be applied entirely or partially cut into small strips, according to the size of the pocket, into the surgical wound during implantation or replacement.

Statistical Analysis

Data were described and summarized using means with standard deviation and proportions. The χ^2 test was applied to compare the influence of the categorical variables. $p<0.05$ was considered statistically significant.

Results

Overall, 1.250 subjects were enrolled. Due to the lack of follow-up data and the consequent exclusion from the study, 1,189 patients were included. Baseline characteristics of included patients were listed in Table I; device characteristics were summarized in **Supplementary Table I**.

All patients underwent antibiotics prophylaxis with cefazolin or vancomycin/gentamicin, and

Table I. Patients' characteristics (n=1,189).

Characteristics	Patients, n (%)
Age (years), mean (SD)	76 (10)
Males	764 (64)
NYHA class:	
• I	610 (51)
• II	507 (43)
• III	64 (5)
• IV	8 (1)
AF/AFL	460 (39)
CAD	235 (20)
CMP:	
• Genetic	3 (0.2)
• Acquired	1 (0.08)
• Secondary	1 (0.08)
Hypertensive cardiopathy	483 (41)
Valvulopathy (>++)	334 (28)
Arterial hypertension	982 (83)
Diabetes	155 (13)
CKD	144 (12)
eGFR <30 mL/min (>15 mL/min)	16 (1)
LVEF >55%	747 (63)
LVEF, mean (SD)	44 (7)
Antiplatelet	
• Single	499 (42)
• DAPT	116 (10)
Anti-coagulant	339 (29)
β-blockers	439 (37)
Calcium channel blockers	442 (38)
Diuretic drugs	629 (53)
ACE-Inhibitors/sartans	777 (65)
IC/amiodarone	159 (13)
Digitalis	29 (2)
Rhythm at the implant:	
• AF	270 (23)
• Sinus rhythm	610 (51)
• Junctional	309 (26)
Heart rhythm/VRR < 40 bpm	526 (44)
Asystole > 3 seconds (> 5 seconds if AF)	292 (25)
SND	197 (17)
AV block	625 (53)
Alternant BBB	86 (7)
Syncope	296 (25)
TAVI	62 (5)
Fluoroscopy time (minutes), mean (SD)	7 (18)
Procedure time skin-to-skin (minutes), mean (SD)	69 (26)

ACE: Angiotensin-converting enzyme; AF: Atrial fibrillation; AFL: Atrial flutter; CAD: Coronary artery disease; CKD: Chronic kidney disease; CMP: Cardiomyopathy; DAPT: Dual antiplatelet therapy; eGRF: Estimated glomerular filtration rate; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association; SND: Sinus node disfunction; TAVI: Transcatheter aortic valve implantation; VRR: Ventricular rate response.

475 (40%) were additionally treated with the GCCI (GCCI group). The remaining 714 (60%) patients who did not receive the additional GCCI treatment were considered a control group. Baseline characteristics of GCCI and control patients were not statistically different **(Supplementary Table II)**. The distribution of patients according to the type of procedure (implant or replacement) and the type of electronic device (PPM or ICD) is shown in Table II.

Infection Complications and Pocket Hematoma

Infection and pocket hematoma occurred in 127 patients (11%). Of them, 4 were treated with the GCCI (3%), and 123 were controls (97%). Thus, a statistically significant reduction of infection and pocket hematoma in the GCCI group was reported if compared to control patients (1% *vs.* 17%: $p<0.0001$).

According to the type of electronic device, infection and pocket hematoma occurred in 0.4% (n=2) of GCCI-PPM patients *vs.* 20% (n=90) of control-PPM patients ($p<0.05$) and in 9% (n=2) of GCCI-ICD patients *vs.* 12% (n=32) of control-ICD patients ($p<0.05$).

Secondary Endpoints

The occurrence of single infectious complications, pocket hematoma or both according to the type of procedure and the type of electronic device is reported in Tables III, IV and V, respectively.

A statistically significant higher occurrence of infective complications in patients undergoing ICD implant or replacement (n=12 out of 286) compared to PPM implant or replacement (n=8 out of 903) was reported (4% *vs.* 0.8%: $p<0.05$). Otherwise, the type of electronic device was not related to a statistically different occurrence of pocket hematoma (n=80 out of 903; 9%, ICD implant *vs.* n=22 out of 286; 8%, PPM implant; $p>0.05$).

Pocket Hematoma Among Patients Treated With Antiplatelet/ Anti-Coagulant Therapy

The impact of antiplatelet/anti-coagulant therapy was evaluated within the 107 patients that developed a pocket hematoma. Among them, 8 (7%) received an antiplatelet associated with oral anti-coagulant (DOACs or anti-vitamin K agents), 12 (11%) dual antiplatelet therapy, 5 (5%) received a single antiplatelet and 18 (17%) an oral anti-coagulant. No one patient had international normalized ratio >2 at the time of intervention. The association between antiplatelet/anti-coagu-

Table II. Distribution of GCCI and control patients according to the type of procedure (de novo implant or replacement) and the type of electronic device.

	De novo implants, n (%)	Replacement, n (%)	Total (n)
GCCI			
All devices	388 (82.0)	87 (18.0)	475
PPM	371 (82.0)	82 (18.0)	453
ICD	17 (77.0)	5 (23.0)	22
Control			
All devices	682 (95.5)	32 (4.5)	714
PPM	425 (94.4)	25 (5.6)	450
ICD	257 (97.3)	7 (2.7)	264

ICD: Implantable cardioverter-defibrillator; PPM: Permanent pacemaker.

Table III. Infective complications in GCCI and control group, according to the type of implant and type of intervention.

	GCCI group, n (%)	Control group, n (%)	*p*-value
Total	1 (0.3)	19 (2.7)	0.002
PPM:	1 (0.3)	7 (1.4)	0.21
• De novo implant	1 (0.3)	6 (1.3)	0.31
• Replacement	0 (0)	1 (0.2)	0.83
ICD:	0 (0)	12 (4.5)	0.01
• De novo implant	0 (0)	9 (3.5)	0.03
• Replacement	0 (0)	3 (1.1)	0.40

GCCI: Gentamycin-containing collagen implant; ICD: Implantable cardioverter-defibrillator; PPM: Permanent pacemaker.

Table IV. Pocket hematoma in GCCI and control group, according to the type of implant and type of intervention.

	GCCI group, n (%)	Control group, n (%)	*p*-value
Total	3 (0.3)	99 (18.5)	< 0.0001
PPM:	1 (0.3)	79 (17.0)	< 0.0001
• De novo implant	1 (0.2)	56 (12.0)	< 0.0001
• Replacement	0 (0)	23 (5.0)	0.0001
ICD:	2 (5.8)	20 (8.0)	0.005
• De novo implant	1 (4.5)	17 (6.2)	0.005
• Replacement	1 (4.5)	3 (1.1)	0.9

GCCI: Gentamycin-containing collagen implant; ICD: Implantable cardioverter-defibrillator; PPM: Permanent pacemaker.

Table V. Concomitant pocket hematoma and infectious complications in GCCI and control group, according to the type of implant and type of intervention.

	GCCI group, n (%)	Control group, n (%)	*p*-value
Total	0 (0)	5 (0.7)	0.17
PPM:	0 (0)	3 (0.6)	0.4
• De novo implant	0 (0)	2 (0.4)	0.6
• Replacement	0 (0)	1 (0.7)	0.8
ICD:	0 (0)	2 (0.6)	0.6
• De novo implant	0 (0)	1 (0.3)	0.8
• Replacement	0 (0)	1 (0.3)	0.8

GCCI: Gentamycin-containing collagen implant; ICD: Implantable cardioverter-defibrillator; PPM: Permanent pacemaker.

lant therapy and the development of hematoma was not statistically significant compared to patients who had not developed a hematoma and were on the same antiplatelet/anti-coagulant regimen (Table VI).

Discussion

Several studies[16,18,19,22] demonstrated the effectiveness of GCCI in reducing infective complications during surgical procedures and in managing soft tissue complications, wound infections or open fractures. To the best of our knowledge, this is the first study that evaluated retrospectively the reduction of the infective complications and pocket hematoma through the use of the GCCI for CIED interventions. Our findings show that the use of GCCI for CIED *de novo* implant or replacement was associated with a significantly low rate of major CIED infections and pocket hematoma in comparison to the conventional antibiotic coverage (1% *vs.* 17%; $p<0.0001$) without an increase of device-related mechanical complications, showing the effectiveness of the local gentamicin-collagen sponge and stating statistical superiority to conventional antibiotic coverage and local hemostasis. This can be explained by attaining a high level of antibiotic and hemostasis factors in situ and their slow washout.

A statistically significant reduction of infective complications and pocket hematoma in PPM-GCCI patients and ICD-GCCI patients was demonstrated compared to PPM-control and ICD-control patients (0.4% *vs.* 20%; $p<0.05$ and 9% *vs.* 12%; $p<0.05$, respectively).

The study also states a statistically significant higher incidence of infective complications in patients undergoing ICD implant or replacement than PPM implant or replacement (4% *vs.* 0.8%: $p<0.05$), probably due to the larger hardware size and the lifetime of devices.

A statistically significant reduction was observed in the incidence of single pocket hematoma (0.6% *vs.* 14%; $p<0.0001$) in GCCI-group compared to control patients. A significant reduction of this parameter was also observed in the PPM-GCCI group compared to the PPM-control patients (0.2% *vs.* 17%; $p<0.0001$). This is in line with several studies[23-25], which demonstrated the favorable role of GCCI during hemostasis, thanks to the activation of the extrinsic coagulation pathway triggered by blood contact with the renaturated collagen fibers of GCCI, thanks to its spongy structure which allows it to stabilize the clot, promote the formation of granulation tissue and the re-epithelialization process[23-25]. The overall effect is an improvement of the healing process.

Regarding the type of intervention, a statistically significant reduction in the incidence of infections in de novo implant or replacement-GCCI patients compared to de novo implant or replacement-control patients (0.5% *vs.* 3.5%; $p<0.05$ and 0% *vs.* 1.4%; $p<0.05$, respectively) was observed.

Similar results were demonstrated for the incidence of pocket hematoma, with a statistically significant reduction in de novo implant-GCCI patients compared to *de novo* implant-control patients (0.5% *vs.* 14%; $p<0.05$) and in replacement-GCCI patients compared to replacement-control patients (1.4% *vs.* 12%; $p<0.05$).

Regarding the development of pocket hematoma, the role of the type of antiplatelet/anti-coagulant treatment prescribed at the time of discharge has been assessed. There was no statistically significant evidence for the development of hematoma depending on the type of drug used.

Several studies[6,7,11,12] have already evaluated local devices able to reduce infectious complications and pocket hematoma in the electrophysiological field. Nevertheless, the GCCI can be easily modeled in the pocket, as it can be cut into pieces of different sizes, representing a cheaper

Table VI. Incidence of antiplatelet/anti-coagulant therapy in the development of pocket hematoma.

Therapy	Patients who developed hematoma (n = 107), n (%)	Patients who not developed hematoma (n = 1,087), n (%)	*p*-value
Antiplatelet and oral anticoagulant (DOACs or anti-vitamin K agents)	8 (7.4)	81 (7.4)	0.85
Dual antiplatelet therapy	12 (11.2)	128 (11.7)	0.97
Single antiplatelet	5 (4.6)	83 (7.6)	0.50
DOACs/anti-vitamin K agents	18 (16.8)	140 (12.8)	0.52

DOAC: Direct-acting oral anti-coagulants.

device than other products, such as the TYR-X envelope[11]. Despite some limitations, such as the retrospective monocenter nature of the study and the lack of cost analysis, our findings pave the way for further studies that will help investigate whether the GCCI has performance statistically not inferior to similar products.

Conclusions

The GCCI is a medical device that has already been proven as a useful aid in the reduction of infections and hematoma after surgical interventions; our findings suggest that this device can be safely used in addition to local hemostasis and prophylactic doses of systemic antibiotics with the aim of reducing infective complications and pocket hematoma after permanent CIED implantation or replacement.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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Availability of Data
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval
This study was notified to the Ethics Committee of Policlinico Tor Vergata (Rome, Italy) on 15th February 2022.

Consent to Participate
All the participants signed an informed consent form.

Consent for Publication
Not required as this manuscript does not include images or videos related to the participants.

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