

## ORIGINAL ARTICLE

# Gentamicin bound to the nanofibre microdispersed oxidized cellulose in the treatment of deep surgical site infections

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### Summary

The aim of this experimental *in vivo* study was to examine the effect of topically-used gentamicin bound to microdispersed oxidized cellulose (MDOC) in nanofibre form in the treatment of deep surgical site infections and to compare it with Garamycin Schwamm<sup>®</sup>. Twelve domestic swine were used in a model of a full-thickness infected dermal wound. The effectiveness of both forms of gentamicin were tested in wound infections caused by *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*. The effectiveness of gentamicin-MDOC and Garamycin Schwamm<sup>®</sup> were comparable according to microbiological culture findings, with no statistically significant differences. When macroscopically assessed, 100% of the infected wounds treated by gentamicin-MDOC were without signs of infection, compared with only 16.7% when Garamycin Schwamm<sup>®</sup> was used and this was of statistical significance. Therefore when combined with a nanofibre MDOC carrier, topically-used gentamicin is rendered more effective for the treatment of full-thickness skin infections.

**Key words:** gentamicin; microdispersed oxidized cellulose; surgical site infections; Garamycin Schwamm

## INTRODUCTION

Surgical site infections (SSI) are the second or third most frequent healthcare-associated infections and the subject of extensive research for the development of new woundcare products and technologies for wound healing (Smyth et al. 2008).

Microdispersed oxidized cellulose (MDOC), a trademark of HemCon Medical Technologies, Inc., is a random copolymer of polyanhydroglucose and polyanhydroglucuronic acid. It has been produced as SEAL-ON<sup>™</sup> (HemCon Medical Technologies, Inc., Portland, U.S.A.) for its haemostatic effect and its ability to facilitate blood clot formation. MDOC is also believed to have an influence on wound healing but no clear results have as yet been shown. Therefore we chose to examine its efficacy as a topical carrier for gentamicin in the healing of acute wound infections in comparison to Garamycin Schwamm<sup>®</sup> (Essex Chemie AG, Luzern, Switzerland). For this purpose, an experimental *in vivo* model of a full-thickness infected dermal wound in pigs was created; the wound infections caused by *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli* – the three most often cultivated

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pathogens from surgical site infections in the Teaching Hospital in Hradec Králové. All these pathogens are among the most common in SSI according to the literature within last decades (CDC NNIS 1996, Nooyen et al. 1994).

## MATERIALS AND METHODS

### *Preparation of gentamicin-MDOC*

MDOC in the form of sodium-calcium salt of polyanhydroglucuronic acid (PAGA) has several biologically useful properties (active haemostasis, immunostimulation, quick absorption, and anti-adhesion). From the physico-chemical point of view, this ionogenic polysaccharide, which functions as a carboxylate ion exchanger, is fully absorbed by the organism. But it is not a film-forming or fibre-forming substance in and of itself. Depending on its concentration, it creates salts or gels in water as colloido-dispersed systems. However in gels without a biocompatible non-toxic stabiliser the CaNaPAGA solution separates from the gel, and therefore, in order to prepare fibres from MDOC, modifying components such as biocompatible carrier-polymers, softening agents, etc. should be included in the preparation.

MDOC as a carboxylate polymer (as well as hyaluronic or alginic acid) creates intermolecular complexes (IMC) with positively-charged low-molecular substances or polymers, i.e. it can work as a carrier of substances such as basic antibiotics including gentamicin.

For the production of MDOC nanofibres ( $\varnothing$  of fibres is 50–500 nm) it is necessary to use biocompatible and absorbable fibre-forming polymers that would create nanofibres together with MDOC or be used as a binding material for the preparation of nanofibres. Medicinal glycerine, which has an impact on the physical properties of micro or nanofibres, has been successfully used as a softening agent for these systems. The nanofibres were always fully absorbable after their application.

Gentamicin sulphate was attached to PAGA during the process. Therefore, instead of the sulphuric acid in gentamicin sulphate, the anion (polyanhydroglucuronate of gentamicine) was created by PAGA.

At the start of these studies when nanofibres were prepared, it was impossible to achieve a higher surface density than the max. amount of 15 g/m<sup>2</sup>. This meant that, upon a concentration of 14.3% w/w of gentamicin in the MDOC nanofabrics, the content of gentamicin sulphate per 100 cm<sup>2</sup> of the area was a maximum of 21.45 mg, a concentration insufficient

for its intended effect. It is noted that Garamycin Schwamm<sup>®</sup> contains 130 mg of gentamicin for the same area. Therefore, microfibres were prepared from long-fibrous medicated cotton-wool. These microfibres were transferred to raw cellulose through nitrogen oxides in the HNO<sub>3</sub> medium, followed by hydrolysis of the cellulose in the medium of H<sub>2</sub>O<sub>2</sub> and Ca salts. After hydrolysis, gentamicin sulphate was added to the reaction mixture during homogenization at a temperature of 20 °C. The suspension of fibres was filtered through a filter divider. The fibres were created by being washed with aqueous alcohol and dehydrated using concentrated ethylalcohol. Afterwards, they were dried in a laminar box to a constant weight.

The technology for the production procedure for MDOC nanofabrics with a surface density of up to 150 g/m<sup>2</sup> was developed and controlled. Thus, a uniform concentration of gentamicin in an amount up to 150 mg on an area of 100 cm<sup>2</sup> was achieved; i.e. a concentration comparable to Garamycin Schwamm<sup>®</sup>.

### *Experimental design and treatment*

Twelve female domestic swine (35–45 kg of weight) were used in this study; each experiment taking seven days. After intramuscular premedication by ketamine 30 mg/kg (Narkamon<sup>®</sup>, Zentiva, Czech Republic), azaperone 40 mg/kg (Stressnil<sup>®</sup>, Janssen Pharmaceutica, Belgium) and atropine 0.5 mg (Atropin Biotika A.U.V.<sup>®</sup>, Biotika, Slovakia) the animal was put under general intravenous anaesthesia and maintained with ketamine. After preparation of the operation field, eight full-thickness dermal defects 5 cm long with side incisions and fascial injury were created in the paravertebral area (four wounds on each side – on the left marked L1 to L4, on the right marked R1 to R4). Contusion of skin margins using Pean forceps was performed to imitate the most common wound type in routine practice. After that, 0.5 ml of the microbiological agent suspension in a density of 10<sup>8</sup> CFU/ml was injected into seven wounds, the last one left clean without infection (always marked R4) as a control. The comparative effectiveness of gentamicin-MDOC and Garamycin Schwamm<sup>®</sup> was tested against each microbiological agent infection separately in two animals (also in 12 treated infected wounds). In every animal there were 2 controls – one infected non-treated wound (marked L1) and one clean wound without infection (marked R4). After 45 minutes, pieces of gentamicin-MDOC or Garamycin Schwamm<sup>®</sup> (5×1.6 cm size containing 10.83 mg of gentamicin) were always placed into six infected wounds (L2 to L4 and R1 to R3). The entire operation area was covered by gauze and a surgical towel. After 24, 48 and 168 hours, swabs were made

for cultivation on blood agar, macroscopic assessment of wounds divided in 3 groups according to the absorption of the carrier and the presence of signs of local infection was performed and photo-documentations were carried out. A very similar experimental design has already been used in an experimental study performed by Plodr (2004).

Presence of pus in the wound bed was considered to be an indicator of local infection. At the end of the experiment the animals were sacrificed by intravenous application of T-61® (Intervet Canada Ltd., Canada). During the experiment, the animals received humane care according to the criteria outlined in the "Guide for the Care and Use of Laboratory Animals". The animals were kept in specific boxes (each animal separately) during the whole experiment with unrestricted access to water and were fed by mixture A1 for laboratory animals.

Statistical analysis was carried out using Fisher's exact test, at the significance level  $2\alpha=0.05$ .

## RESULTS

The results of cultivations (on blood agar) of microbiological swabs from the wounds taken at 24, 48 and 168 hours were compared. No significant differences in *E. coli* and *P. aeruginosa* – infected wounds were noted. In *S. aureus* infections, 50% of the wounds treated by nanofibre gentamicin-MDOC were negative compared with only 8.3% treated by Garamycin Schwamm®, but the difference was not statistically significant (Table 1).

All the infected controls had a positive cultivation finding at the end of the experiment. Approximately half of the clean controls were found to be secondarily contaminated, mostly with *Staphylococcus epidermidis*. Microbiology observations showed similar results with the two sources of gentamicin used, with the exception of the *S. aureus* infections. However, macroscopic assessments showed big differences between the wounds treated with the forms of gentamicin.

Macroscopic assessment is allowed for the diagnosis of wound infection. According to the CDC definition of SSI the diagnosis can be made by a surgeon or attending physician, with no necessity for having a positive cultivation finding, and is a matter of subjectivity. Bruce et al. (2001) published a meta-analysis of 90 studies pertaining to the definition of SSI; in most of them diagnosis of the wound infection is made only by macroscopic assessment. And more, positive cultivation can be due

to colonization or contamination only – it is not a sign of infection without further symptoms.

Nanofibre gentamicin-MDOC was fully absorbed in 94.4% of the treated wounds at 48 hours and in 100% of those at 168 hours. All the wounds were macroscopically clean, healed with a crust and at 48 hours and 168 hours showed no signs of local infection (presence of pus). Garamycin Schwamm® was fully absorbed in 5.6% of wounds at 48 hours and in 16.7% at 168 hours. Additionally, 25% of the wounds at 48 hours and 83.3% at 168 hours showed local signs of infection, especially if the collagen carrier of Garamycin Schwamm® was not fully absorbed. All these differences were statistically significant (Table 2).

Macroscopic assessment of the infected wounds treated with gentamicin-MDOC showed, in all cases, similar results to the uninfected control wounds, *i.e.* absence of any evidence of local infection, or presence of pus.

## DISCUSSION

Surgical site infections (SSI) lead to increased morbidity, mortality, longer hospital stays and higher hospital costs. Antibiotic prophylaxis is generally recommended for all clean-contaminated, contaminated and dirty procedures, mostly by systemic administration. Topical administration of antibiotics for prophylaxis is recommended for both contaminated and clean wounds (Diehr et al. 2007). Topical antimicrobials can be used in the treatment of secondarily-infected wounds, and the treatment is found to be as effective as the systemic administration of antibiotics in the case of minor infected wounds (Kraus et al. 1998). More importantly, there is a clear role for the topical administration of antibiotics in the treatment of chronic wounds (O'Meara et al. 2001).

One of the most common topically-used antibiotics in surgery is gentamicin. This is probably due to its effectiveness on a broad spectrum of gram positive and gram negative bacteria and, when used topically, its efficacy against methicillin-resistant *S. epidermidis* (MRSE) and methicillin-resistant *S. aureus* (MRSA) (Eklund 2007, Friberg et al. 2007). Other advantages of topical administration of gentamicin are its high concentration in the wound and minimal concentration in the serum. High local gentamicin levels, about 75–200 times higher than minimum inhibition concentration (MIC), 4mg/l, were observed in wound fluid compared to that in the serum 1–4 mg/l after 24 hours), both levels being

Table 1. Microbiological cultivation – counts and percentage of treated wounds with negative cultures.

	<i>E. coli</i>			<i>S. aureus</i>			<i>P. aeruginosa</i>		
	24 h	48 h	168 h	24 h	48 h	168 h	24 h	48 h	168 h
Garamycin Schwamm	12/12 100%	12/12 100%	12/12 100%	12/12 100%	0/12 0%	1/12 8.30%	12/12 100%	12/12 100%	8/12 66.70%
nanoMDOC	12/12 100%	12/12 100%	12/12 100%	12/12 100%	12/12 100%	6/12 50%	12/12 100%	12/12 100%	6/12 50%

For both the tested materials – in the first line in fraction number of wounds with negative cultures findings to all treated wounds, in the second row the ratio expressed as a percentage.

Table 2. Macroscopic assessment of the wounds at 7 days – counts and percent of wounds.

	<i>E. coli</i>			<i>S. aureus</i>			<i>P. aeruginosa</i>		
	I	II	III	I	II	III	I	II	III
Garamycin Schwamm	0/12 0%	0/12 0%	12/12 100%	3/12 25%	0/12 0%	9/12 75%	2/12 16.70%	0/12 0%	10/12 83.30%
nanoMDOC	12/12 100%	0/12 0%	0/12 0%	12/12 100%	0/12 0%	0/12 0%	12/12 100%	0/12 0%	0/12 0%

For both the tested materials – in the first line in fraction number of wounds classified in each group according to the presence of infection and complete/incomplete resorption to all treated wounds, in the second row the ratio expressed in percentage.

group I – clean wound, tested material fully absorbed;

group II – clean wound, tested material not fully absorbed;

group III – wound with signs of infection, tested material not absorbed.

Table 3. Resorption of the carrier – counts and percent of wounds.

	Complete resorption			Incomplete resorption		
	24 h	48 h	168 h	24 h	48 h	168 h
Garamycin Schwamm	2/36 5.6%	2/36 5.6%	6/36 16.7%	34/36 94.4%	34/36 94.4%	30/36 83.3%
nanoMDOC	21/36 58.3%	34/36 94.4%	36/36 100%	15/36 41.7%	2/36 5.6%	0/36 0%

For both the tested materials – in the first line in fraction number of wounds with complete/incomplete resorption of the carrier to all infected treated wounds with specific material (3×12 wounds with *S. aureus*, *P. aeruginosa* and *E. coli* infection), in the second row the ratio expressed in percentage.

safely below the toxic threshold of 10 mg/l (Leyh et al. 1999, Friberg et al. 2003, Eklund et al. 2005, Eklund 2007).

Most published articles involving topically-administered gentamicin with a collagen carrier describe the results of the prophylaxis of SSI in cardiac surgery (Leyh et al. 1999, Friberg et al. 2003, 2007, Eklund et al. 2005, Eklund 2007, Friberg 2007, Schersten 2007). Gentamicin-collagen implants with various brand names (Collatamp-G®, Gentacoll®, Sulmycin Implant®), containing 130 mg of gentamicin and 280 mg of collagen are placed underneath the sternum or between its edges before sternotomy closure. In some studies, more than one implant of gentamicin-collagen was applied (Leyh et al. 1999, Friberg et al. 2005, Friberg 2007).

In the first randomized controlled study published by Friberg et al. in 2005, the sternal wound infection rate was 4% in the gentamicin group and 5.9% in the control group, this was not statistically significant. The data presented showed a slight reduction in infection rate in gentamicin-collagen groups, but the study population was too small to make a statistically reliable conclusion.

In the next randomized control study, the incidence of SSI in 2000 patients undergoing open-heart surgery was significantly reduced from 9% to 4.3% in the gentamicin group, but without effect as to the occurrence of osteitis or mediastinitis (Friberg et al. 2005). The difference in all groups involving deep SSI was not of statistical significance, except in groups of patients with either a BMI (body mass index) >25 kg/m<sup>2</sup> or diabetes mellitus, or both (Friberg et al. 2005, Friberg 2007). On the other hand, there were significantly more reoperations for bleeding in the gentamicin-collagen group (4.0% vs. 2.3%). This result was not explained, but it can be argued that the difference may be due to bleeding from the bone marrow from a gap between the two sternum halves when two gentamicin-collagen layers were inserted (Friberg et al. 2005). A similar increase in the number of cases with postoperative bleeding with dehiscence was noted by Leyh et al. (1999). In general, topically-administered gentamicin-collagen implants are recommended for antibiotic prophylaxis in cardiac surgery.

The use of topical gentamicin as a prophylaxis is also recommended in some clean procedures in orthopaedic and general surgery. Eveillard et al. proved the effectiveness of gentamicin-impregnated cement in the prevention of deep wound infection after primary total knee arthroplasty. The infection rates were 1.21% for patients who had antimicrobial cement and 9.52% for those who had not (Eveillard et al. 2003). Musella et al. (2001) recommended the use

of gentamicin-laced collagen tampons in groin hernia patients if polypropylene mesh is inserted under aponeurosis of the external oblique muscle. In the gentamicin group, 1/301 patients (0.3%) developed a postoperative wound infection compared with 6/294 in the control group (2.0%).

In clean-contaminated and contaminated procedures, the results are ambivalent. Buimer et al. (2008) describe a significant reduction in postoperative complications (dehiscence, infection), after one week of treatment, in a group of patients treated with enclosure of gentamicin after primary excision in case of hidradenitis suppurativa (35%) compared with patients treated with primary excision only (52%). However, after 3 months, complications in both groups were comparable.

In the case of pilonidal sinus treatment, bacteriological culture findings were not statistically different when treated by excision, gentamicin-collagen implantation and primary closure, or open treatment alone (Holzer et al. 2003). This study indicates that the use of gentamicin-collagen shortens the time of wound healing in patients with a primary closure.

In the case of repair of an anal fistula, using an advancement flap, gentamicin-collagen did not decrease the infection rate, and there was no difference in the recurrence rate (Gustafsson et al. 2006). A number of studies evaluate the effectiveness of topical administration of gentamicin in colorectal surgery procedures. Wounds after stoma closure, and perineal wounds after abdominoperineal excisions, were contaminated and the incidence of SSI was high. Haase et al. did not find any differential effect between subcutaneously-used gentamicin implants with regard to the prevention of wound infections after loop-ileostomy closure (Haase et al. 2005). However, very good results were achieved with the topical administration of gentamicin in randomized controlled studies (Rosen et al. 1992, Gomez et al. 1999, Grüssner et al. 2001). Grüssner et al. (2001) found a reduction of pathogens in cultures and a lower infection rate in perineal wounds after abdominoperineal excisions. In total, the bacteriological efficacy amounted to 83.7% in the treated group vs. 60.4% in the controls. The difference in infection rates was also significant; 6% vs. 20.8%. Similar results were reported in the studies of Rosen et al. (1992) and Gomez et al. (1999) – though with a significantly higher percentage of primary wound healing in the gentamicin treated group, 87% vs. 46% for the control group, and an infection rate of 9% vs. 44%, respectively.

In our study reported here, we used a new biodegradable carrier formed by microdispersed oxidized cellulose in nanofibre form. This cellulose has a good haemostatic effect and facilitates blood clot formation, in agreement with previous tests of product SEAL-ON™ (HemCon Medical Technologies, Inc., Portland, USA).

The collagen matrix is fully biodegradable and resorbed within 1 to 8 weeks, depending on the vascularization of the tissue (Gustafsson et al. 2006, Buimer et al. 2008). In contrast, microdispersed oxidized cellulose is fully resorbed within the first 48 hours in 94% of wounds (Table 3). When gentamicin is attached to the carrier (gentamicin-MDOC, 130 mg gentamicin/100 cm<sup>2</sup>), we found superior inhibition of infection by comparison to the topical administration of gentamicin (Garamycin Schwamm®). In this study, Garamycin Schwamm® was not fully absorbed in 83.3% of the wounds at 7 days, and, like a foreign body in the wound bed, could increase the rate of SSI. In agreement with previously published data we found no adverse effects due to treatment with gentamicin.

There were no macroscopic differences between infected treated wounds with nanofibre MDOC and infected and clean controls. To conclude, no treatment has similar macroscopic results as the treatment with MDOC, but the advantage of nanofibre MDOC with gentamicin is in the better cultivation results compared to the infected controls. We proved quicker resorption of MDOC than collagen-gentamicin in Garamycin Schwamm.

So, when gentamicin is attached to the carrier formed by MDOC in comparable amount (130 mg/100 cm<sup>2</sup>), we find this superior for administration.

## CONCLUSIONS

Topically-used gentamicin, attached to nanofibrous microdispersed oxidized cellulose is effective in the treatment of soft tissue infections, due to its antimicrobial activity, excellent resorption of the MDOC carrier in comparison to collagen, and its promotion of blood clot formation.

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