Microbial sealant to reduce surgical site infections following coronary artery bypass graft

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This brief was prepared by Arlene Vogan from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S).
**TECHNOLOGY BRIEF**

**Register ID**
WP102

**Name of technology**
InteguSeal® microbial sealant

**Purpose and target group**
Reduction of surgical site infection following coronary artery bypass graft surgery

**Stage of development in Australia**

- [ ] Yet to emerge
- [ ] Experimental
- [x] Established
- [ ] Established but changed indication or modification of technique
- [ ] Investigational
- [ ] Nearly established
- [ ] Should be taken out of use

**Australian Therapeutic Goods Administration approval**

- [x] Yes
- [ ] No
- [ ] Not applicable

**ARTG number**
131323

**International utilisation**

<table>
<thead>
<tr>
<th>Country</th>
<th>Trials underway or completed</th>
<th>Limited use</th>
<th>Widely diffused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
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<tr>
<td>United Kingdom</td>
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<td>Brazil</td>
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<tr>
<td>Netherlands</td>
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</tbody>
</table>

**Impact summary**

Kimberly-Clark Worldwide Inc. (Roswell, GA, USA) provides InteguSeal®, a cyanoacrylate-based microbial sealant with the aim of reducing surgical site infections in a wide range of surgical procedures, including coronary artery bypass graft (CABG) surgery. Upon application, InteguSeal® forms a continuous barrier that immobilises bacteria that persist after skin sterilisation and prevents bacterial migration to the surgical site. The technology would be made available through
hospitals, and would be incorporated into standard pre-operative skin preparation protocols. The sealant is registered on the ARTG; however, diffusion of use in Australia is unknown. One surgical hospital has reported the integration of the technology into standard pre-operative treatments for cardiac surgery indications.

Background

Surgical site infections (SSIs) are a predominant cause of postoperative morbidity and mortality, and can range from superficial infections, where skin and subcutaneous tissue are affected; to deep tissue or systemic infections and sepsis. \(^2,3\) SSIs occur within 30 days of surgery and manifest as pus, or swab with >10\(^6\) colony forming units (CFU) per mm\(^3\) tissue. Symptoms include pain, localised swelling, redness or heat. Most SSIs are caused by the endogenous bacterial microorganisms of the skin’s natural flora, such as *Staphylococcus aureus*, coagulase-negative staphylococci, *Escherichia coli* and *Klebsiella* spp.\(^4\)

SSIs are the third most frequently reported hospital acquired infection (HAI), and are the most commonly acquired in surgical patients.\(^2,5\) A number of factors that relate to the patient, procedure and the clinical environment contribute to the overall risk.\(^3,4\) The level of bacteria at the surgical site is one of the most important factors in determining the risk of SSI, and the incidence varies based on the type of surgery. Table 1 summarises surgery by type and subsequent risk of SSI. Patient specific risk factors for SSI include obesity, smoking and alcohol consumption.\(^2\)

Table 1  Surgery type by risk of surgical site infection

<table>
<thead>
<tr>
<th>Surgery type</th>
<th>Description</th>
<th>Risk of SSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clean</td>
<td>Generally elective surgery, where the respiratory, alimentary, genitourinary tracts or the oro-pharyngeal cavity are not entered. Cases are primarily closed and drained with a closed drainage system when required.</td>
<td>2.1%</td>
</tr>
<tr>
<td>Clean-contaminated</td>
<td>Surgery in which the respiratory, alimentary, genital or urinary tract is entered under controlled conditions and without unusual contamination.</td>
<td>3.3%</td>
</tr>
<tr>
<td>Contaminated</td>
<td>Surgery on fresh, accidental wounds, or operations with major breaks in sterile technique or gross spillage from the gastrointestinal tract, and incisions in which acute, non-purulent inflammation is encountered.</td>
<td>6.4%</td>
</tr>
<tr>
<td>Dirty</td>
<td>Old traumatic wounds with retained devitalised tissue and those that involve existing clinical infection or perforated visera. (This definition suggests that organisms causing postoperative infection were present in the operative field before the operation.)</td>
<td>7.1%</td>
</tr>
</tbody>
</table>

Adapted from Wilson (2008)\(^6\) and Lipp et al (2010)\(^7\)
InteguSeal® (Kimberly-Clark Worldwide Inc., Roswell, Georgia, USA) is a cyanoacrylate-based microbial sealant that may further decrease rates of SSI incidence. The sealant can be incorporated into current pre-operative skin preparation practices, with application following standard skin sterilisation methods using a ready-to-use applicator that is available in three sizes.8 Cyanoacrylates were initially synthesised in 1949, and in their basic form, are a low-viscosity liquid. On contact with anionic substances, such as moisture and proteins on the outermost layer of the epidermis, the cyanoacrylates polymerise into long chains and form a solid film. Upon application, InteguSeal® forms a continuous, yet breathable barrier that immobilises the bacteria that survive pre-operative preparation, and subsequently prevent migration of microbes into the incision site.3, 9, 10 In its polymerised form, InteguSeal® is able to seal micro-abrasions on the skin and can prevent potential pathogen recolonisation.4 In addition, it can inhibit the ‘greenhouse effect’ caused by unbreathable surgical drapes, whereby bacterial proliferation can occur in the warm, moist environment underneath.3 Due to the properties of InteguSeal®, the technology can be used without further encouraging the development of bacterial resistance.6 InteguSeal® received CE mark, FDA and TGA approval in 2006. The product is gradually exfoliated over five to seven days or can be removed more rapidly using soapy water, mineral oil or acetone.11

Clinical need and burden of disease

SSIs are the most commonly reported HAI in surgical patients, and account for 25-38 per cent of HAIs.2, 5 It has been estimated that 2-5 per cent of all patients who undergo surgery will develop an SSI. When compared to patients who do not develop an SSI, the added morbidity associated with these infections includes prolonged hospitalisation, a five-fold increase in the risk of re-hospitalisation and a two-fold increase in the risk of death.5

New South Wales surveillance data between 2008 and 2010 identified the average incidence of SSIs in CABG procedures at 2.56 per 100; as compared to hip and knee replacements where the average incidence was 1.35 per 100 and 1.15 per 100, respectively.12 Victorian SSI monitoring data has estimated the crude mortality rate for patients with an SSI at five per cent.13

Diffusion of technology in Australia

InteguSeal® was registered with the TGA in September 2006.14 There is an indication that it has been integrated into existing routine pre-operative procedures in at least one surgical centre (Fremantle Hospital, Fremantle, Western Australia).1
Comparators

Standard surgical pre-operative care includes hair removal and preparation of the surgical site with an appropriate antiseptic such as chlorhexidine or povidone-iodine alcohol-based solutions. This sterilisation process can reduce bacterial counts by approximately 80 per cent; however, some organisms that are buried deep in hair follicles or sweat glands may persist after preparation. After the alcohol solutions have dried, iodine-impregnated drapes can additionally be used for further prevention of bacterial contamination. Complete skin sterilisation is essentially not possible.

Safety and effectiveness

Included are two randomised controlled trials (RCTs) that assess the safety and effectiveness of InteguSeal® use in CABG for the prevention of SSIs.

von Eckardstein et al (2011)

Study description

This multi-centre, parallel group, open-label RCT (level II evidence) at five sites on three continents enrolled 293 participants between April 2006 and February 2009 (ClinicalTrials.gov NCT00467857). Participants were scheduled to undergo elective CABG surgery, with the saphenous vein or radial artery used as one of the graft sites. Major exclusion criteria included patients undergoing an additional surgical procedure; morbid obesity; known allergy to cyanoacrylate, isopropyl alcohol, iodine or tape; an abnormal skin condition around the surgical incision site; chemotherapy, immunosuppressive therapy or steroid therapy; use of antibiotics for an active infection; and a hospital stay of greater than 14 days. Patients were randomised 1:1 to the intervention group (n=146), to receive standard skin preparation followed by the use of the InteguSeal® microbial sealant, or the control group (n=147), to receive standard skin preparation alone. Prophylactic antibiotics were administered at the discretion of the surgeon and according to hospital protocol. The sternal and graft surgical sites were prepared with standard preparations. After standard skin preparation, the sealant was applied to both sites of patients in the intervention group. After approximately three minutes, when the sealant had formed a film on the skin, it was considered dry and the surgery commenced. Microbiological samples were collected from both incision sites at three points during the procedure: pre-skin preparation, post-incision (immediately after incision through the skin, but before opening of the fascia), and at the end of the CABG procedure. Samples were assessed for total bacterial burden, with results calculated using per-protocol analysis. Vital signs, surgical wound status and adverse events were monitored in all patients during hospitalisation and 30 days after the procedure; while rates of SSIs and other adverse events were calculated on an intention-to-treat analysis. Baseline
characteristics of the treatment groups were similar; however, a significantly greater number of obese patients were randomised to the intervention group (intervention n=40; control n=20; \( p=0.003 \)), and neither the mean duration of surgery nor the mean duration of mechanical ventilation significantly differed between the intervention and control groups. There were 15 out of 146 participants (10.3%) from the intervention group and nine of 147 (6.1%) from the control group that were ineligible for inclusion in the per-protocol analysis. Microbiological data were only available for 121 patients (83%) in the intervention group and 132 participants (90%) in the control group.

**Safety**

Adverse events were experienced in 11 of the 146 (7.5%) participants in the intervention group, and 16 of the 147 (10.9%) in the control group. Most events were related to SSIs. Four deaths were observed; however, none were considered to be related to the study treatment.

**Effectiveness**

The average bacterial counts were highest in the pre-skin preparation samples, and lowest in the post-incision samples for both treatment groups, with no significant between-group differences. There was a significant difference observed between the intervention and the control group in the post-CABG samples at the sternal site (intervention 0.58 CFU/mL, control 0.83 CFU/mL, \( p=0.039 \)), with a trend observed at the graft site (intervention 0.19 CFU/mL, control 0.34 CFU/mL, \( p=0.057 \)). Mean bacterial counts in both groups increased from post-incision to post-CABG; however, the increase observed in the intervention group was significantly less than that in the control group at both incision sites (sternal site: intervention 0.37 CFU/mL, control 0.57 CFU/mL, \( p=0.047 \); and graft site: intervention 0.09 CFU/mL, control 0.27 CFU/mL, \( p=0.037 \)).

SSIs developed in nine of 146 patients (6.2%) in the intervention group and 14 of 147 patients (9.5%) in the control group; however, these differences were not statistically significant. The majority of SSIs were superficial infections. Interestingly, while all patients with risk factors of obesity, alcohol or tobacco use were significantly more likely to acquire an SSI (\( p=0.024 \)), obese participants in the intervention group were significantly less likely to acquire an SSI than their counterparts in the control group (intervention 1/40; control 3/20, \( p=0.015 \); relative risk reduction 83%).
Study description

This trial enrolled participants undergoing CABG surgery who required three or more lengths of long saphenous vein involving both legs to achieve revascularisation. In this RCT (level II evidence), patients (n=47; 94 legs) served as their own controls. The InteguSeal® microbial sealant was applied to one randomly selected leg per patient after standard pre-operative preparation. The other leg acted as a matched control, and received standard preparation alone. The sealant was not used for the sternal incision. Patient wounds were examined daily, with a wound swab taken on the fourth postoperative day from the skin incision site (or infected region if there was evidence of an infection). Patients were followed up at four weeks post-discharge and wounds were examined by blinded observers. No patients were lost to follow-up.

Safety

No cases of skin sensitivity or other reactions were reported after the application of the microbial sealant. All reported adverse events were related to SSIs. One of 47 treated legs (2.1%) developed a severe infection and required incision and drainage. Twelve of the 47 control legs (25.5%) developed infections with four requiring incision and drainage and one requiring debridement. No long-term consequences resulted.

Effectiveness

As reported above, of the 47 legs prepared with the microbial sealant, one developed a severe infection (2.1%). The untreated leg in that same patient had no infection. No other infections were observed in the other 46 legs that received the intervention. Microbiological wound swabs from each of the treated legs resulted in 13 positive cultures (27.7%). Evidence of infection was observed in 12 of 47 control legs (25.5%), and ranged in severity from serous fluid oozing to severe infection. There were 22 positive cultures in total from microbiological sampling of the untreated surgical site (46.8%). The difference in the proportion of control legs that presented with infection was significantly different to the legs treated with the intervention (95% CI [-0.374, -0.0945], \( p = 0.0011 \)).

Cost impact

Hospital acquired infections have been estimated to cost the Australian health care system approximately $40 million per year. \(^{13}\) Surgical wound infections after CABG surgery add an estimated average of A$12,419 per procedure and A$31,597 if the infection is a deep sternal wound. \(^{16}\) The majority of these costs are due to added
length of stay. The costs associated with patients who require readmission are additionally higher.\textsuperscript{1}

InteguSeal\textsuperscript{®} is manufactured in single-use applicators of three varying sizes, depending on the coverage area required for surgery. One applicator of median size to cover an area 25cm x 25cm is A$30.\textsuperscript{1}

**Ethical, cultural or religious considerations**

No ethical, cultural or religious considerations were raised.

**Other issues**

One of the studies included in this brief, von Eckardstein et al (2011),\textsuperscript{15} was sponsored by the manufacturer. No conflicts-of-interest were declared by Iyer et al (2011).\textsuperscript{1}

Side-effects of the sealant are rare, but can include allergic reaction or skin irritation.\textsuperscript{5} No adverse effects of the sealant were reported in the included studies.

A large industry-sponsored, single-blind (patient) RCT investigating the use of InteguSeal\textsuperscript{®} in arterial bypass surgery on lower extremities has been registered in the Netherlands (NCT00940979). This study has an estimated enrolment of 450 participants, although it is not yet recruiting.\textsuperscript{17} The primary outcome measure will be postoperative wound infection rates with the secondary outcomes of cost and complication rate.

**Summary of findings**

The application of InteguSeal\textsuperscript{®}, in combination with standard pre-operative practices, appears to be safe, with no adverse events related to the application of the technology reported in the included studies. It appears effective at reducing the amount of bacteria present at the surgical site when compared to standard preparation; however, it is uncertain whether this translates into significant decreases in the incidence of SSIs. The technology is designed to be used in conjunction with standard procedures, and as such, its use would pose a small additional cost; however, the cost and patient benefits from preventing an SSI may justify such expenditure. There may be an enhanced beneficial effect in obese patients, with one study showing a significant reduction in SSI incidence in patients pre-treated with the microbial sealant.

**HealthPACT assessment:**

Based on the outcomes, the quality of available evidence and the potential diffusion of use in Australia, HealthPACT recommended that the technology be monitored for 24 months.
**Number of studies included**

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the [HealthPACT web site](http://www.health.nsw.gov.au/hospitals/hai/index.asp).

Total number of studies 2
Total number of level II studies 2

**References**


**Search criteria to be used**

Microbial sealant

InteguSeal®

Surgical site infection